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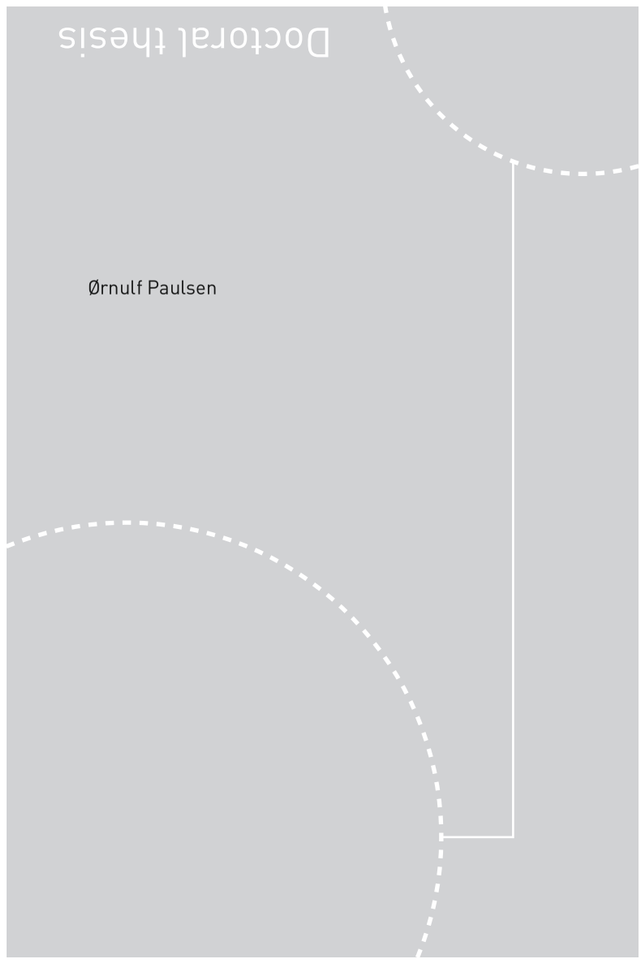
Ørnulf Paulsen

Corticosteroids for Cancer Pain



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Thesis for the Degree of
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and Molecular Medicine

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Trondheim, May 2017

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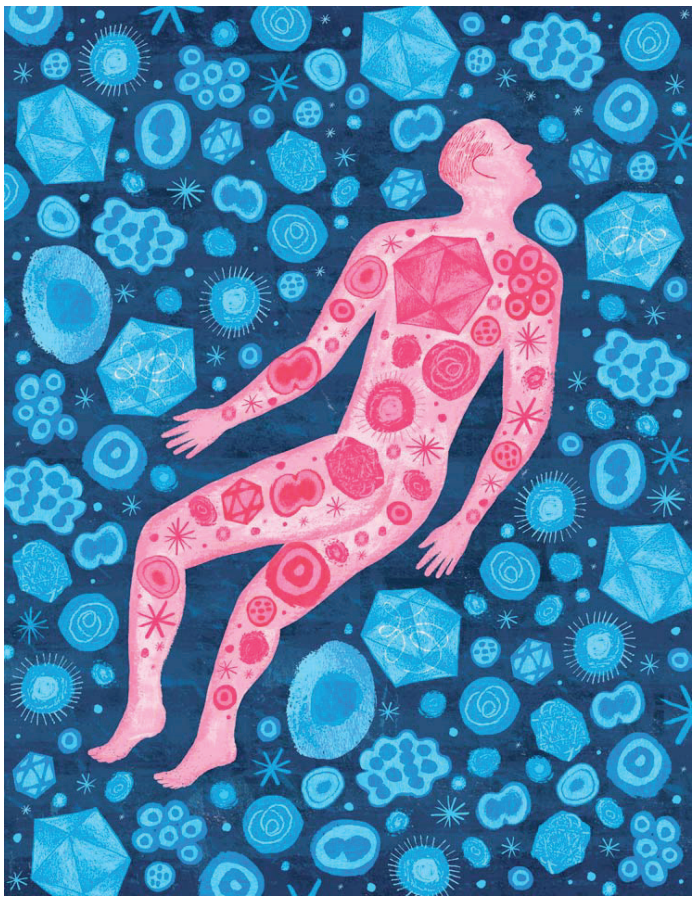

Inflammation ©James O'Brian

Doktorgradsprosjekt «Kortikosteroider for kreftsmerte»

De fleste kreftpasienter vil oppleve kreftrelaterte symptomer i løpet av sykdommen. Smerte er et av de mest fryktede symptomene. Appetittløshet og fatigue (trøtthet) er andre vanlige symptomer. Smerte, appetittløshet og fatigue forekommer hyppig hos alvorlig syke kreftpasienter og gir mye plager og redusert helserelatert livskvalitet.

Kortikosteroider blir hyppig brukt for å lindre symptomer hos kreftpasienter. Lindring av kreftrelatert smerte er en av indikasjonene for kortikosteroider, også i følge anbefalinger i publiserte retningslinjer.

I doktorgradsavhandlingen «Kortikosteroider for kreftsmerte» har Ørnulf Paulsen og medarbeidere undersøkt det vitenskapelige grunnlaget for denne praksisen. I en systematisk studie av publisert litteratur konkluderte de med at kortikosteroider kan ha en moderat smertelindrende effekt hos kreftpasienter, men faktagrunnlaget ble bedømt som svært svakt. Det var få studier som hadde undersøkt om kortikosteroider gir lindring av kreftsmerte.

Videre viste de i en tverrsnittsstudie blant europeiske kreftpasienter at både kortikosteroider og ikke-opioide smertelindrende medikamenter ble hyppig brukt. Begge medikamentgruppene ble brukt av rundt 50 % av pasientene.

Forskerne gjennomførte en randomisert, dobbelblindet studie hos pasienter med avansert kreftsykdom og kreftrelatert smerte. Studien viste ingen smertelindrende effekt av kortikosteroider (metylprednisolon 32 mg daglig). Alle pasientene brukte smertelindrende morfin-preparater. Doktorgradsavhandlingen fant ikke holdepunkter for at kortikosteroider har en smertelindrende effekt ved kreftsmerter. Dette tilsier at man ikke generelt bør anbefale kortikosteroider for lindring av kreftsmerte.

Den randomiserte studien fant imidlertid signifikant bedring av appetitt og mindre fatigue etter behandling med kortikosteroider. Avhandlingen indikerer således at kortikosteroider gir bedre appetitt og mindre kreftrelatert fatigue hos alvorlig syke kreftpasienter. Imidlertid må videre forskning vise om behandlingen bør brukes lenger enn en til to uker.

Til slutt viste forskerne i en eksplorativ analyse at appetittløshet og fatigue var relatert til betennelses-markører i blod (inflammasjon). Avhandlingen indikerer at det er sammenheng mellom systemisk inflammasjon, og appetittløshet og fatigue hos alvorlig syke kreftpasienter.

"The nonspecific effect of steroids in producing euphoria,

stimulating the appetite, and creating a sense of well-being have made them

invaluable in the management of the terminal patient.

… Narcotic requirements are frequently decreased by their administration."

- Harold W. Schell, Uncas-on-Thames Hospital, 1972

Corticosteroids for Cancer Pain

Name of candidate: Ørnulf Paulsen

Department: Institutt for kreftforskning og molekylærmedisin /

European Palliative Care Research Centre

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Funding: Helse Sør-Øst / The South-Eastern Norway Regional Health Authority

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Main supervisor: Professor Stein Kaasa

Co-supervisors: Professor Pål Klepstad, Professor Nina Aass

Ovennevnte avhandling er funnet verdig til å forsvares offentlig

for graden Doctor Philosophiae

Disputas finner sted i Medisinsk-teknisk forskningssenter, fredag 12.05 kl 12.15

This thesis has been assessed to be worthy of being defended

For the degree of PhD in palliative care

The public defence takes place in the Medical Technical Research Centre Friday 12.05 at 12.15 pm

Table of content

Acknowledgements

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First of all, I want to thank the patients who, despite their difficult situation in life, spent precious time participating in the studies.

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To me, clinical palliative care, as well as palliative care research, is a matter of two main values:

- *You matter because you are you, and you matter to the end of your life* Cicely Saunders
- *Vet du det ikke, eller har du ikke hørt det? Herren er den evige Gud som skapte jordens ender. Han blir ikke trett, han blir ikke utmattet, hans forstand er uransakelig. Han gir den trette kraft, og den som ingen krefter har, gir han stor styrke.* Jesaja 40; 28-29

Skien, December 2016

Ørnulf Paulsen

x

Summary in English

Most cancer patients will experience cancer related symptoms through their disease trajectory. Pain is among the most feared symptoms. Cancer related anorexia and fatigue are also common symptoms; all are frequently encountered in patients with advanced cancer and cause suffering and reduced health related quality of life.

Corticosteroids are often prescribed for symptom control in patients with cancer. Supported by published guidelines, cancer pain is one indication for the use of corticosteroids. The empirical evidence for this clinical practice is however limited.

The primary aim of this thesis was to assess the analgesic efficacy of corticosteroids on cancer pain; second, to provide evidence for the use of corticosteroids to improve cancer related fatigue and appetite.

A systematic literature review was conducted to assess the published evidence for the analgesic effects of corticosteroids on cancer pain. The review concluded that corticosteroids, i.e. methylprednisolone 32 mg daily or similar, may have a moderate analgesic effect in cancer patients. Few published trials were identified and the evidence was graded “very low”.

A cohort of European cancer patients using opioids was explored to assess the use of non-opioid analgesics and corticosteroids, the use of unnecessary drugs, and possible drug-drug interactions. The study showed that corticosteroids and non-opioid analgesics (paracetamol and/or NSAIDs) were used by fifty percent of the patients and that the patterns of use differed substantially between countries. Furthermore, many patients used unnecessary drugs and were at risk of experiencing serious drug-drug-interactions.

To assess the analgesic efficacy of corticosteroids on cancer pain, the randomized, double-blinded and placebo-controlled trial “Corticosteroids for cancer pain” was performed, which included cancer patients receiving opioids. Fifty patients with cancer pain were recruited and received methylprednisolone 16 mg or placebo twice daily for seven days. The trial found no evidence of an analgesic effect from corticosteroids on cancer pain.

Appetite and fatigue were secondary endpoints in the trial, both symptoms improved significantly in the corticosteroid-group.

An exploratory analysis showed that the patients included in the “Corticosteroids for cancer pain” trial had increased serum concentrations of inflammatory biomarkers. Furthermore, specific biomarkers were associated with loss of appetite, fatigue and the role function domain in the quality of life scale EORTC QLQ-C30.

This thesis does not find evidence of an analgesic effect from corticosteroids on cancer pain. This argues against recommending a general use of corticosteroids in the treatment for cancer pain. In contrast, the thesis indicates that corticosteroids improve cancer related fatigue and anorexia in patients with advanced cancer. However, further research has to provide evidence for the use beyond one to two weeks. Finally, this thesis supports the hypothesis that systemic inflammation is a common causal factor in loss of appetite and cancer related fatigue in cancer patients with advanced disease.

Norsk sammendrag

De fleste kreftpasienter vil oppleve kreftrelaterte symptomer i løpet av sykdommen. Smerte er et av de mest fryktede symptomene. Appetittløshet og fatigue (trøtthet) er andre vanlige symptomer. Smerte, appetittløshet og fatigue forekommer hyppig hos alvorlig syke kreftpasienter og gir mye plager og redusert helserelatert livskvalitet.

Kortikosteroider er hyppig brukt for å lindre symptomer hos kreftpasienter. Lindring av kreftrelatert smerte er en av indikasjonene for kortikosteroider, også i følge anbefalinger i publiserte retningslinjer. Det vitenskapelige grunnlaget for denne kliniske praksisen er imidlertid svak.

Hovedmålsetningen i denne doktorgradsavhandlingen var å undersøke den smertelindrende effekten av kortikosteroider ved kreftrelatert smerte. Videre ville vi undersøke effekten av kortikosteroider ved kreftrelatert fatigue og appetittløshet.

En systematisk studie av publisert litteratur ble gjennomført for å vurdere det vitenskapelige grunnlaget for kortikosteroiders smertelindrende effekt ved kreftsmerte. Oversikten konkluderte med at kortikosteroider, f eks methylprednisolon 32 mg pr dag eller tilsvarende, kan ha en moderat smertelindrende effekt hos kreftpasienter. Studien fant imidlertid få publikasjoner som undersøkte denne problemstillingen, og faktagrunnlaget ble bedømt som «svært svakt».

I en studie med europeiske kreftpasienter som brukte opioider, undersøkte vi hvor hyppig ikke-opioide smertelindrende medikamenter og kortikosteroider ble brukt. Studien undersøkte også hvor hyppig pasientene brukte unødvendige legemidler samt risikoen for interaksjoner mellom legemidler. Studien viste at både kortikosteroider og ikke-opioide smertelindrende medikamenter (paracetamol og/eller NSAIDs) ble brukt av femti prosent av pasientene, og at bruksmønsteret varierte i stor grad mellom de ulike landene. Mange pasienter brukte unødvendige legemidler, og mange hadde økt risiko for alvorlige legemiddelinteraksjoner.

For å undersøke om kortikosteroider har smertelindrende effekt ved kreftsmerte, ble den randomiserte, dobbelt-blindete og placebo-kontrollerte studien «Corticosteroids for cancer pain» gjennomført. Femti pasienter ble inkludert og fikk metylprednisolon 16 mg eller

placebo to ganger daglig i syv dager. Studien fant ikke holdepunkter for at kortikosteroider har smertelindrende effekt hos kreftpasienter.

Appetitt og fatigue var sekundære endepunkter i studien og begge symptomene ble signifikant forbedret i gruppen som fikk kortikosteroider.

En eksplorativ analyse viste at deltagerne i «Corticosteroids for pain»-studien hadde forhøyede serumkonsentrasjoner av inflammatoriske biomarkører. Spesifikke biomarkører var relatert til appetittløshet og fatigue samt til rollefunksjon, en av dimensjonene i livskvalitetsinstrumentet EORTC QLQ-C30.

Doktorgradsavhandlingen fant ikke holdepunkt for at kortikosteroider har en smertelindrende effekt ved kreftsmerter. Dette tilsier at man ikke generelt bør anbefale kortikosteroider for lindring av kreftsmerte. Avhandlingen indikerer videre at kortikosteroider gir bedre appetitt og mindre kreftrelatert fatigue hos alvorlig syke kreftpasienter. Imidlertid må videre forskning vise om behandlingen bør brukes lenger enn en til to uker. Doktorgradsavhandlingen støtter teorien om at systemisk inflammasjon er en felles etiologisk faktor for appetittløshet og fatigue hos alvorlig syke kreftpasienter.

List of papers

Paper I

Do Corticosteroids Provide Analgesic Effects in Cancer Patients? A Systematic Literature Review

Ørnulf Paulsen, Nina Aass, Stein Kaasa, and Ola Dale

Journal of Pain and Symptom Management 2013;46(1):96-105

Paper II

Polypharmacy in Patients with Advanced Cancer and Pain: A European Cross-sectional Study of 2282 Patients

Aleksandra Kotlinska-Lemieszek, Ørnulf Paulsen, Stein Kaasa, and Pål Klepstad

Journal of Pain and Symptom Management 2014;48(6):1145-59

Paper III

Efficacy of Methylprednisolone on Pain, Fatigue, and Appetite Loss in Patients with Advanced Cancer Using Opioids: A Randomized, Placebo-Controlled, Double-Blind Trial

Ørnulf Paulsen, Pål Klepstad, Jan Henrik Rosland, Nina Aass, Eva Albert, Peter Fayers, and Stein Kaasa

Journal of Clinical Oncology 2014;32(29):3221-8

Paper IV

The Relationship between Pro-Inflammatory Cytokines and Fatigue, Loss of Appetite and Pain in Patients with Advanced Cancer

Ørnulf Paulsen, Barry Laird, Nina Aass, Tor Lea, Peter Fayers, Stein Kaasa * and Pål Klepstad*

*Joint senior authors

Submitted October 2016

Abbreviations

BMI	Body mass index
BPI	Brief Pain Inventory
CI	Confidence interval
CRP	C-reactive protein
DED	Dexamethasone equivalent dose
DDI	Drug-drug interaction
EAPC	European Association for Palliative Care
ECOG	Eastern Cooperative Oncology Group
ELISA	Enzyme-linked immunosorbent assay
EORTC QLQ	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
PRC	European Palliative Care Research Centre
EPOS	European Pharmacogenetic Opioid Study
ESAS	Edmonton Symptom Assessment System
ESR	Erythrocyte sedimentation rate
FACIT-F	Functional Assessment of Chronic Illness Therapy - Fatigue
GR	Glucocorticoid receptor
GRADE	Grading of Recommendations Assessment, Development and Evaluations
HRQoL	Health related quality of life
IASP	International Association for the Study of Pain
ICD	International Classification of Diseases
IQR	Interquartile range
IL	Interleukin
INF	Interferon
JAK	Janus kinase
KPS	Karnofsky Performance Status scale
LASA	Linear Analog Scale Assessment
MCP	Monocyte chemoattractant protein
mGPS	Modified Glasgow Prognostic Score

MIF	Macrophage migration inhibitory factor
MIP	Macrophage inhibitory protein
MMSE	Mini Mental State Examination
NCCN	National Comprehensive Cancer Network
N	Number
NF	Nuclear factor
NMDA	N-methyl-D-aspartate
NRS	Numeric rating scale
n.s.	Not significant
NSAID	Non-steroidal anti-inflammatory drug
NTNU	Norwegian University of Science and Technology
OME	Oral morphine equivalents
OPG	Osteoprotegrin
PROMs	Patient reported outcomes measures
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomized controlled trial
RR	Relative risk
rECS-CP	The Revised Edmonton Classification System for Cancer Pain
SAE	Serious adverse event
SD	Standard deviation
sTNF-R1	Soluble receptor 1 for tumour necrosis factor
SPSS	Statistical Package for the Social Sciences
TNF	Tumor necrosis factor
TGF	Transforming growth factor
VRS	Verbal rating scale
WHO	World Health Organization

Foreword

When starting this research project in 2007, I had a general interest in the corticosteroid group of drugs. At this time, my experience of corticosteroids was informed from using them in palliative medicine, pulmonary medicine, and rheumatology. I observed that this class of drugs had an extraordinary place in treating debilitating illnesses through providing a general improvement in patients' overall condition and symptoms. I can still remember my tutor, Jan Thomas Lien (1940 – 2005), and how he enthusiasticly taught me about the "roborating effects of corticosteroids in patients with advanced lung cancer". I found the corticosteroids useful in my clinical practice, and noted my colleagues used them very frequently in advanced cancer disease.

Corticosteroids have some apparent positive clinical effects, which probably also have supported their frequent use. However, this emerged as a paradox when I discovered that the empirical basis for their use in palliative care seemed to be rather weak. Many important research questions regarding their use are unanswered: What is the efficacy of corticosteroids in cancer pain management? When should corticosteroid treatment be started? How long are corticosteroids effective in symptom management? What is the most effective corticosteroid dose? What are the most common adverse effects from corticosteroids in cancer patients?

Previous research in the use of corticosteroids for symptom control in palliative medicine supported the use of corticosteroids for cancer related anorexia. In contrast, although corticosteroids were often used, there was little evidence to support their use in cancer related fatigue: "anecdotal observation and very limited data from controlled trials support the use of low-dose corticosteroids in fatigued patients with advanced disease and multiple symptoms" (Radbruch, Strasser et al. 2008). Evidence supporting corticosteroids as an adjuvant analgesic for cancer pain was limited, based mainly on small trials assessing many endpoints. Furthermore, there were no high-quality trials assessing the analgetic properties of corticosteroids in patients with cancer receiving opioids. These observations, my clinical experience, combined with the desire to examine this area, informed my choice of thesis: "Corticosteroids for cancer pain".

The starting point in this research project was the “Corticosteroids for Cancer Pain” trial. This multicentre, double blinded, randomized placebo-controlled trial was planned and conducted as a part of this thesis. It examined the role of corticosteroids for the treatment of pain in patients with advanced cancer, and crucially explored the role of corticosteroids in combination with opioid analgesia. Secondary endpoints explored appetite and fatigue.

Secondly, to evaluate the existing evidence systematically, we performed a systematic review assessing the analgesic properties of corticosteroids, applying the same protocol as used in the evidenced-based EAPC recommendations (Caraceni, Hanks et al. 2012). In this publication, corticosteroids as adjuvant analgesics were not discussed. The work from this thesis will be included in the revised evidence-based recommendations on the use of opioid analgesics from the EAPC.

To further inform the thesis, I was allowed access to a large dataset from our research-group. This was data from the EPOS study, which included more than 2000 opioid –treated patients from seventeen centres in Europe. The dataset was explored to assess the frequency of the use of corticosteroids and non-opioid analgesics in this population.

This thesis also examines the relationship between cytokines and symptoms. In the “Corticosteroids for Cancer Pain”- data we could use the dataset to explore associations between biomarkers of inflammation, symptoms, and if possible, associations with response to corticosteroids.

Palliative care is striving to be evidence-based. Cicely Saunders, its founder, strongly disapproved of palliative care being categorized as “tender loving care” (Twycross 2009). High quality evidence is needed to inform clinical practice. Thus, this thesis aims to add high quality evidence for the use of corticosteroids in pain, loss of appetite and cancer related fatigue in patients with advanced cancer.

1. Introduction

1.1 Cancer:

The number of persons living with cancer is increasing, due to a combination of increased incidence of cancer and increased life expectancy. In 2012, there were altogether an estimated 3.45 million new cases of cancer in the 40 European countries (Ferlay, Steliarova-Foucher et al. 2013), and in Norway 31.651 new cases in 2014 (Cancer Registry of Norway 2015). Due to improved diagnostics, earlier diagnosis and more treatment options, death rates have declined for all cancers since the early 1990s; in USA a decrease of 1.8 % for men and 1.4 % for women per year from 2002 to 2011 (National Cancer Institute). Similar trends have been seen in Norway, where for instance the estimated five year relative survival increased by six percent for women with lung cancer, and eight percent for rectal and prostate cancers in men in the period 2010-2014, as compared to the five-year period 2000-2004 (Cancer Registry of Norway 2015). Also patients with incurable cancer disease live longer. Hence, some cancers that previously were rapidly fatal have become a chronic disease with patients surviving for years. Still, a substantial proportion of patients will die from their cancer. Cancer accounted for an estimated 1.75 million deaths in the 40 European countries in 2012 (Ferlay, Steliarova-Foucher et al. 2013), and 10 971 people died from cancer in Norway in 2014 (Cancer Registry of Norway 2015).

1.2 Palliative care:

Palliative care is a systematic approach aiming to maintain or improve the individual's quality of life and symptom control, and is defined as "the active, total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of social, psychological and spiritual problems is paramount. The goal of palliative care is achievement of the best possible quality of life for patients and their families" (WHO 1990) Palliative care encompasses both patients and their families in its scope. The discipline originated from the hospice movement in England.

Palliative care traditionally focused on patients with advanced or end-stage disease. It is currently a priority to facilitate integration of palliative care earlier in the disease trajectory. This is supported by the WHO, stating that palliative care "is applicable early in the course of

illness, in conjunction with other therapies that are intended to prolong life" (WHO 2011). Moreover, palliative care is an inexpensive health service, considered by the WHO to be an integral component of cancer care.

Studies have demonstrated improved outcomes associated with palliative care, such as lower symptom distress, improved health related quality of life (HRQoL) and patient and family well-being, higher proportions of patients dying at home, and satisfaction with care (Jordhoy, Fayers et al. 2000, Ringdal, Jordhoy et al. 2002, Yennurajalingam, Urbauer et al. 2011, Zimmermann, Swami et al. 2014). Early referral to palliative care is associated with improvement in quality of life and mood, as well as less aggressive treatment at the end of life, and longer survival (Temel, Greer et al. 2010).

1.3 Symptoms in patients with cancer

Cancer patients experience several distressing symptoms. Upon referral to a palliative care clinic, the median number of symptoms per patient was 11 (range 1-27), using a study tool covering 38 specific symptoms. The five most frequent symptoms were pain, fatigue, weakness, anorexia, and lack of energy, with prevalences ranging from 60 to 84 percent (Walsh, Donnelly et al. 2000). This coincides with a review of published data from patients with incurable cancer (Teunissen, Wesker et al. 2007). The prevalence of symptoms increased significantly with stage of disease; lowest in patients receiving curative treatment, intermediate in those receiving palliative chemotherapy, and highest in patients for whom anticancer treatment no longer was feasible (van den Beuken-van Everdingen, de Rijke et al. 2009) . Fatigue, loss of appetite, constipation, dry mouth, depression, and anxiety all had an independent, negative influence on HRQoL (van den Beuken-van Everdingen, de Rijke et al. 2009). In addition to pain, two other symptoms are studied more in detail in this thesis: cancer related fatigue and loss of appetite.

1.4 Cancer pain

Pain is a subjective experience, defined by the International Association for the Study of Pain, IASP, as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"(IASP 1994). To try to describe the all-encompassing nature of pain, Dame Cecily Saunders, the founder of the

hospice movement, introduced the concept “total pain”, which included the physical, psychological, social, and spiritual components of pain (Saunders 1978, Richmond 2005).

Pain remains one of the most prevalent consequences of cancer, and many cancer patients suffer from insufficient pain control (Breivik, Cherny et al. 2009, Hjermstad, Aass et al. 2016). About 90 % of cancer patients will experience pain at some point during their disease trajectory (Caraceni and Portenoy 1999).

In the general public, cancer is associated with the symptom of pain, especially towards the end of life (Levin, Cleeland et al. 1985). Pain is a feared symptom among cancer patients. When asked to imagine a situation with cancer and one year left to live, pain was the top concern in a study performed in seven European countries (Bausewein, Calanzani et al. 2013). Studies also indicate that fear for pain reduces the level of functioning in cancer patients (Lemay, Wilson et al. 2011). Likewise, fear for future pain or a painful death was stated as a reason for a possible wish for euthanasia (Johansen, Holen et al. 2005). Adequate pain treatment is a human right, and it is the duty of any health care system to provide it (Daniel S Goldberg 2011).

1.4.1 Pain perception and pathophysiology

Pain is caused by the tumour in more than 90 % of cancer patients with pain, by cancer treatment in 20 % of patients, and in two percent it is classified as unrelated to both the tumour and the treatment (Caraceni and Portenoy 1999). The neurophysiology of cancer pain is complex. It involves inflammatory, neuropathic, ischemic, and compression mechanisms, which in the individual patient may occur at multiple sites, be combined, and change over time (Raphael, Ahmedzai et al. 2010).

The classic anatomic description of sensation of pain starts at the peripheral nociceptors belonging to primary sensory neurons whose cell bodies are located in dorsal root ganglia (Figure 1). Specialized receptors detect alterations in the tissue: changes in pressure, acidity, temperature, or inflammation (Falk and Dickenson 2014). Central axons of primary afferents terminate in the spinal cord dorsal horn where second-order spinal neurons project to the brain, enabling the spinal cord to fulfil its pivotal role in pain transmission. Modulation of primary afferent inputs occurs here: excitation, for instance by N-Methyl-D-aspartate (NMDA), substance P and descending serotonin release, and inhibition via Gamma-

Aminobutyric acid (GABA) interneurones, enkephalin release (opioid receptors) and descending pathways. The ascending pathways connect to the brain and are responsible for the localisation of pain and the affective symptoms (Raphael, Ahmedzai et al. 2010).

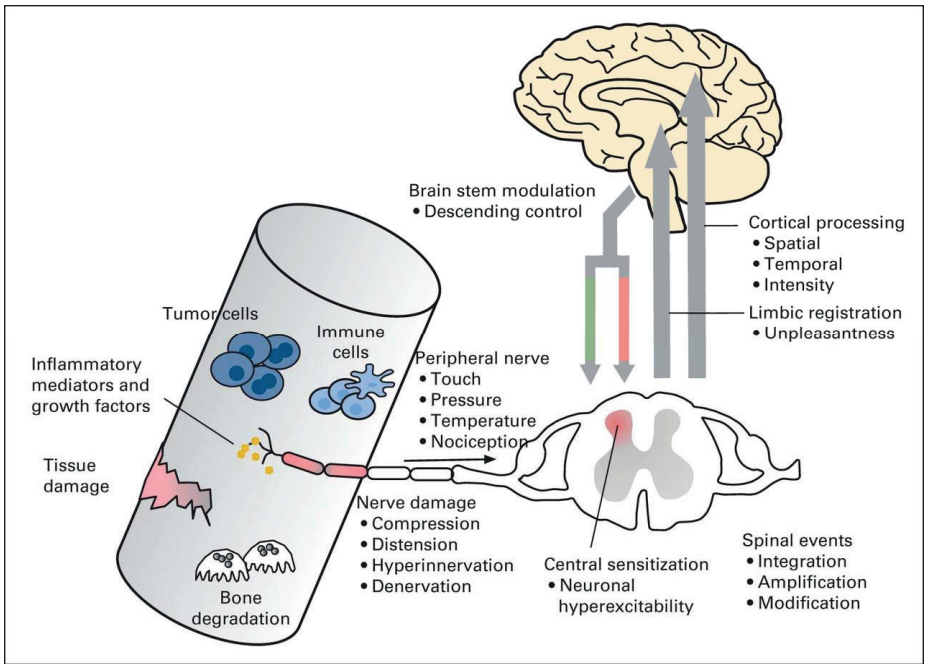

Figure 1: *Basic mechanisms of pain processes at peripheral, spinal, and suptraspinal sites and influences of various peripheral mechanisms, including tumour cell- and immune cell-mediated release of pronociceptive factors, direct tissue damage, and bone degradation through osteoclast activation. Because of peripheral events, central excitability changes are recruited. Combination of these events produces final pain experience at highest centres of brain (Falk and Dickenson 2014) (Used with permission)*

Neuropathic pain, which arises from damage to central or peripheral neurons; visceral pain, with viscera's dual-fold innervation (autonomic and spinal); cancer-induced bone pain; cancer therapy induced pain; and inflammatory pain are all different pain concepts that differ in peripheral and central mediators, and patterns of transmission and modulation, showing for instance different degrees and mechanisms of dorsal horn hyperexcitation (Figure 2) (Raphael, Ahmedzai et al. 2010).

While anatomical structures and neural centres involved in pain control are well identified, the molecular and neurochemical components of pain modulation deserve further

clarification (Mensah-Nyagan, Meyer et al. 2009). As an example, it has become evident that the neurons have capacity to change their function, chemical profile, or structure, or to trigger apoptotic processes, particularly in chronic pain states (Mensah-Nyagan, Meyer et al. 2009).

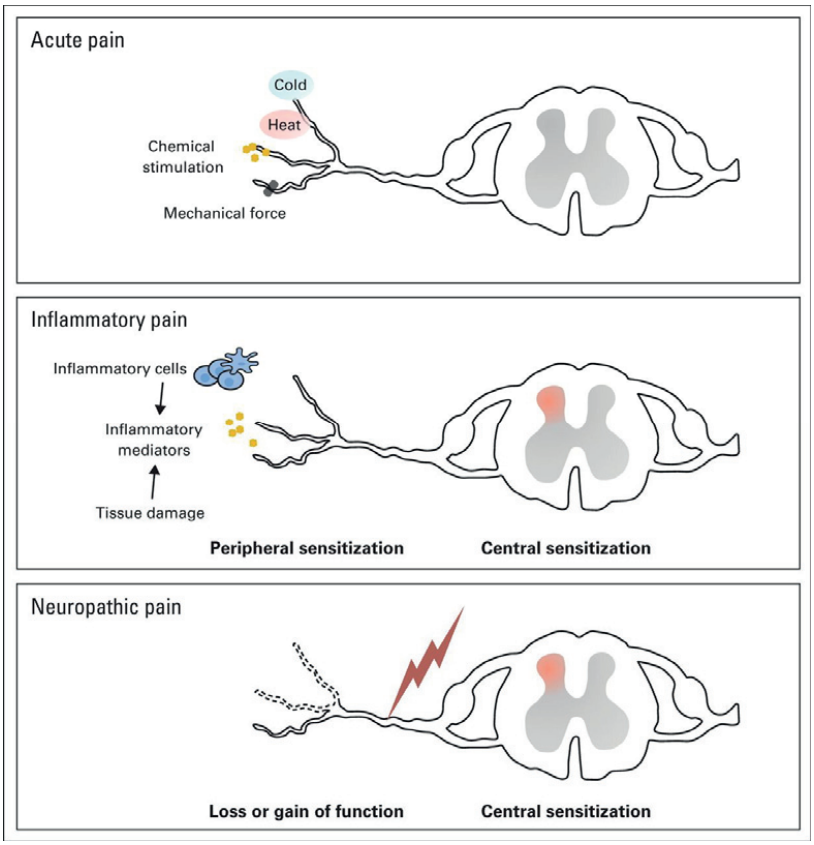

Figure 2: *Diagram of three main types of pain (Falk and Dickenson 2014) (Used with permission)*

Moreover, glia (microglia and astrocytes), which until recently were thought to be passive support cells for neurons, are now considered to be a crucial part of pain modulation (Watkins, Hutchinson et al. 2007). Research has revealed that activated immune cells and immune-like glial cells may dramatically alter neuronal function by the release of pro-inflammatory cytokines (Watkins, Hutchinson et al. 2007). These non-neuronal cells are implicated in the creation and maintenance of pathological pain by increasing neuronal

excitability, for instance in response to peripheral nerve injury. The effects are exerted at multiple sites along the pain pathway: in peripheral nerves, in dorsal root ganglia, and finally, in the spinal cord (Watkins, Hutchinson et al. 2007).

Activated glia do not only increase the neuronal excitability which amplifies pain. Glia are suspected to influence the pain suppressive effects of opioid drugs, contribute to opioid tolerance, and contribute to the development of opioid dependence. It also appears that glia can be activated in response to repeated administration of opioids (Watkins, Hutchinson et al. 2007). Thus, glia are intimately integrated with the functions of pre-and post-synaptic neurons, astrocytes, and microglial cells.

1.4.2 Prevalence of cancer pain

Epidemiological studies confirm that cancer pain is a substantial burden to the cancer patient. The prevalence varies according to the population being studied, and by which methods pain is assessed. Two systematic reviews enlighten this topic in more detail. Van den Beuken-van Erdingen reported a prevalence of pain of 59 % during the cancer treatment phase, increasing towards end of life to a prevalence of 64 % (van den Beuken-van Everdingen, de Rijke et al. 2007). One third of the patients reported the pain to be "moderate - severe". Teunissen reported the prevalence from patients with incurable cancer to be 71 %, being less frequent the last two weeks of life, with a prevalence of 45 % (Teunissen, Wesker et al. 2007). Cancer pain is often severe; in a study by Caraceni et al. 67 % of the cancer patients reported worst pain the last day to be 7 or more [Numeric Rating Scale (NRS) 0-10] (Caraceni and Portenoy 1999).

Systematic reviews indicate that 30- 43 % of patients with cancer pain are undertreated (Deandrea, Montanari et al. 2008, Greco, Roberto et al. 2014).

1.4.3 Classification

Classification systems are used to characterize and stratify cohorts by grouping them according to major common characteristics. This is a foundation for medicine as it is the basic idea behind diagnoses, such as for instance the "TNM Classification of Malignant Tumours"(Leslie H Sobin 2009), and for assigning an appropriate treatment. Ideally, if the variability within the classification group is confined, the classification gives important and

precise information, for instance regarding prognosis. Similarly, classification is the basis for clinical research. Classification is crucial to be able to compare the study population to real life patients: are these results applicable for my patients? A classification system should therefore ideally be a relevant and useful tool both in the clinical and the research settings (Kaasa, Apolone et al. 2011).

Cancer pain is a complex phenomenon that has both qualitative and quantitative aspects (Kaasa, Apolone et al. 2011). It can be classified according to several dimensions, as for instance intensity, variation over time, mechanism (pathophysiology), localization, aetiology, treatment response, or distress (Knudsen, Aass et al. 2009), or as specific cancer pain syndromes (Portenoy 1992, Caraceni and Portenoy 1999). Pain can also be classified according to temporal pattern (Haugen, Hjermstad et al. 2010).

IASP classifies pain in two main groups: nociceptive pain, caused by nociceptor stimulation by direct tissue injury, or neuropathic pain (IASP 1994). A verifiable lesion or a related process, for instance inflammation, often causes nociceptive pain. It can be of somatic or visceral origin. Neuropathic pain is a state of pain, which is sustained by damage or dysfunction in the nervous system, for instance tumour infiltration in a peripheral nerve or nerve damage due to chemotherapy, and not by direct nociceptor stimulation.

Despite several efforts to develop common criteria for the diagnosis and classification of cancer pain, no internationally widely accepted cancer pain classification system exists (Knudsen, Aass et al. 2009, Kaasa, Apolone et al. 2011). This is identified as one reason for undertreatment of cancer pain (Kaasa, Apolone et al. 2011).

In the upcoming, revised version of the International Classification of Diseases, ICD-11, chronic pain is included as a new category (Treede, Rief et al. 2015). This category includes chronic cancer pain as one of seven entities. The chronic cancer pain entity is subdivided into pain caused by the cancer itself (i.e. the primary tumour or metastases) and pain that is caused by cancer treatment (e.g. surgery, chemotherapy, or radiotherapy). Cancer-related pain is subdivided based on location into visceral, bony (or musculoskeletal), and somatosensory (neuropathic) pain. It is described as either continuous (background pain), or intermittent (episodic pain) if associated with physical movement or procedures (Treede, Rief et al. 2015).

1.4.4 Assessment

Pain guidelines and evidence based standards for cancer pain management recommend routine pain assessment as a standard for care (Dy, Asch et al. 2008, NCCN 2015). Assessing pain intensity has been proposed as a quality indicator (Dy, Asch et al. 2008), and as the "5th vital sign" (Lynch 2001).

Pain and other subjective symptoms should be assessed by self-reports; "patient reported outcome measures" (PROMs) (FDA 2009). The assessment tool should be validated, and preferably be applicable both in clinical practice and research (Garcia, Cella et al. 2007, Kaasa, Apolone et al. 2011).

The Edmonton Symptom Assessment System (ESAS) (Bruera, Kuehn et al. 1991), which is widely used in the clinical setting, has one pain item: "Pain intensity" in addition to eight other symptom items. Pain is rated on a numeric rating scale, NRS 0-10 (no pain – worst possible pain), with time frame "how you feel now". ESAS is the recommended standard assessment tool for use in palliative care in Norway (Nasjonalt handlingsprogram 2015). The routinely use of a screening tool can overcome barriers to pain control, such as patients who don't report pain, or health care providers who fail to assess pain (Lynch 2001). Several assessment tools for cancer pain have been developed, but few are fully validated (Hjermstad, Fainsinger et al. 2009) .Pain localization should be assessed with a body map, which can indicate the cause of the pain and demonstrate if the patient experiences more than one pain (Jaatun, Hjermstad et al. 2014).

1.5 Principles of cancer pain treatment

Pain management is an inherent and important part of comprehensive cancer care. A proper multidimentional assessment and subsequent classification of the cancer pain constitute an essential basis for its treatment. As an example, tumour directed treatment might be the most effective analgesic treatment, such as radiotherapy for painful bone metastases (Chow, Zeng et al. 2012).

Guidelines for cancer pain management (Jost, Roila et al. 2010, Caraceni, Hanks et al. 2012, Nasjonalt handlingsprogram 2015, NCCN 2015, Portenoy, Ahmed et al. 2015) are generally based on the principles WHO published in the early 80's: the WHO pain ladder (Figure 3)

(WHO 1986). It provided a tool for physicians worldwide to improve cancer pain management (Zech, Grond et al. 1995).

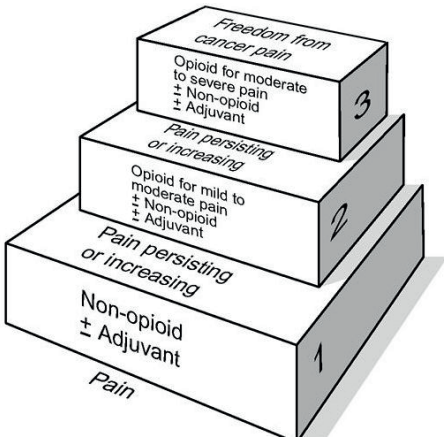

Figure 3: *WHO's Pain Relief Ladder (WHO 1986)(Used with permission)*

Studies have shown that 70-100 % of cancer pain patients may be relieved if clinicians apply the WHO ladder (Ventafridda, Tamburini et al. 1987, Jadad and Browman 1995). The WHO pain ladder denotes ”step I” as basic pain treatment with the non-opioid analgesics paracetamol and/or NSAIDs. At the second step, opioids for mild or moderate pain are added such as codeine and tramadol. At the third step, opioids for moderate to severe pain are introduced.

1.5.1 Adjuvant analgesics

According to the WHO pain ladder, it is recommended to consider adjuvant analgesics in addition to paracetamol and/or opioids. Adjuvant analgesics are additional drugs, used alongside opioid analgesics, that target commonly involved mechanisms in the generation of pain (Bennett 2011). Neuropathic pain is a frequent pain mechanism present in up to 40 % of patients (Bennett 2011). Commonly used drugs for neuropathic pain are the tricyclic antidepressants, such as amitriptyline and imipramine, and antiepileptics, such as gabapentin and pregabalin (Caraceni, Hanks et al. 2012).

Clinical guidelines and reviews also recommend other drug classes. Examples include newer antidepressants (for instance selective serotonin reuptake inhibitors), alpha2-adrenergic

agonists, topical agents and ketamine (Portenoy 2011, Bell, Eccleston et al. 2012, Swarm, Abernethy et al. 2013). However, the use of adjuvant analgesic drugs in the cancer population is partly derived from data on their use in non-malignant pain.

1.6 Cancer related fatigue and loss of appetite

1.6.1 Cancer related fatigue

Cancer related fatigue is defined as a "distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning" (Berger, Mooney et al. 2015). Cancer related fatigue is among the most frequent symptoms reported in cancer patients (van den Beuken-van Everdingen, de Rijke et al. 2009, Barsevick, Irwin et al. 2013). A systematic review reported a prevalence of 74 % in patients with incurable cancer (Teunissen, Wesker et al. 2007). It is present in all phases of the disease: at diagnosis, during treatment, in survivors, and in patients with advanced cancer disease (Hofman, Ryan et al. 2007, Miller, Ancoli-Israel et al. 2008). It is a burdensome symptom, and in one study, 58 % of cancer outpatients reported "somewhat or very much" fatigue (Stone, Richardson et al. 2000). Moreover, 14 % had received treatment or advice for the symptom, and 52 % had never reported the fatigue symptom to their doctor (Stone, Richardson et al. 2000).

Fatigue is a distressing symptom with negative impact on patients' HRQoL, physical functioning, and ability to perform activities of daily living (Hofman, Ryan et al. 2007). Fatigue was by the patients regarded as being more important than both pain and nausea/vomiting (Stone, Richardson et al. 2000).

Cancer related fatigue can be influenced by a variety of demographic, medical, psychosocial, behavioral, and biological factors (Bower 2014). Of several biological mechanisms of cancer related fatigue that have been investigated, inflammation with dysregulation of cytokines seems to have a key role (Bower 2014). Tumours and their treatment can activate the pro-inflammatory cytokine network leading to symptoms of fatigue via cytokine signalling in the central nervous system. Furthermore, neuroendocrine alterations have been proposed as an underlying mechanism; hypothalamic-pituitary-adrenal (HPA-) axis alterations, either directly or through its potent effects on inflammatory processes and regulation of cytokine

production (Irwin and Cole 2011). Alterations in the autonomic nervous system may also be relevant (Bower 2014).

1.6.2 Assessment of cancer related fatigue

Evidence based guidelines, for instance from the National Comprehensive Cancer Network (NCCN), recommend that all cancer patients are screened for fatigue at their initial visit, and later at appropriate intervals during and after cancer treatment (NCCN 2016). It is recommended to use a self report measure such as the Edmonton Symptom Assessment System (ESAS) or similar, rating the severity of fatigue the past 7 days. For patients reporting moderate or severe fatigue [i.e. screening ≥ 4 (NRS 0-10)] it is recommended to do an in-depth clinical evaluation of fatigue that includes a validated self-report instrument. Tools evaluating fatigue severity include the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scale (Berger, Mitchell et al. 2015, NCCN 2016). Other assessment tools also include other dimensions of the fatigue symptom complex.

1.6.3 Loss of appetite

Loss of appetite is defined as the loss of desire to eat (Solheim, Blum et al. 2014). Anorexia can be regarded as an overarching concept consisting of a variety of symptoms such as appetite, early satiety, taste alterations, reduced food intake and nausea /vomiting. However, in daily practice anorexia and loss of appetite are often used interchangeably (Solheim, Blum et al. 2014). Loss of appetite is a frequent symptom in advanced cancer with a prevalence of more than fifty percent (Teunissen, Wesker et al. 2007). Loss of appetite is a prognostic indicator (Quinten, Coens et al. 2009) and is associated with reduced HRQoL (Lis, Gupta et al. 2009).

The regulation of food intake, energy storage and energy expenditure is tightly regulated by complex homeostatic mechanisms, controlled by a precise interplay between the central nervous system and peripheral signals (Kim, Leyva et al. 2014). The hypothalamic melanocortin system is a major player in this regulation. Neurons expressing pro-opiomelanocortin (POMC) and melanocortin 4 receptor (MC4R) act anorexigenicly and lead

to decreased food intake and increased energy expenditure. In contrast, neuropeptide Y (NPY) and agouti-related peptide (AvRP)-expressing neurons act orexigenicly and lead to increased food intake and decreased energy expenditure, thus increasing body weight (Kim, Leyva et al. 2014). The activity of the melanocortin neurons is regulated by many peripheral signals including hormones such as leptin, ghrelin, insulin, glucocorticoids, and thyroid hormones, and the vagus nerve (Laviano, Inui et al. 2008, Kim, Leyva et al. 2014).

Data indicate that functional changes associated with cancer involve a neuroinflammatory state in hypothalamic areas caused by activated microglial cells with increased concentration of pro-inflammatory cytokines (Molfino, Gioia et al. 2015). As a result, the hypothalamic melanocortin system becomes resistant to peripheral inputs (Laviano, Inui et al. 2008), and its activity is diverted largely toward the promotion of catabolic stimuli (Laviano, Inui et al. 2008).

1.6.4 Assessment of loss of appetite

Appetite and anorexia specifically reflect the loss of desire to eat. Some authors argue that the evaluation should include other symptoms in the symptom complex of the anorexia-cachexia syndrome, such as early satiety, and food intake (Molfino, Muscaritoli et al. 2015). Different assessment tools have been proposed, including the Functional Assessment of Anorexia-Cachexia Treatment (FAACT) which rates the intensity of anorexia and cachexia and the related symptoms on a verbal rating scale (VRS), and the abridged Patient-Generated Subjective Global Assessment (aPG-SGA), assessing the symptoms on a yes or no basis together with nutritional and functional levels (Vigano, di Tomasso et al. 2014). Finally, loss of appetite can be quantitatively evaluated by a numeric rating scale (NRS) like in the Edmonton Symptom Assessment System (ESAS) and the EAPC minimum dataset (Sigurdardottir, Kaasa et al. 2014), or with HRQoL-tools like the EORTC QLQ-C30 (Aaronson, Ahmedzai et al. 1993). Loss of appetite can be measured by the EORTC QLQ-C30 in a reliable way (Kaasa, Bjordal et al. 1995).

1.7 Cancer related inflammation

In 1863, Rudolf Virchow first proposed the role of inflammation in cancer, after observing the presence of leukocytes in neoplastic tissue. Inflammation is closely linked to cancer and

is in the last decade identified as the seventh “hallmark of cancer”(Mantovani, Allavena et al. 2008).

Inflammation is an essential component of all tumours and promotes tumour development (Mantovani, Allavena et al. 2008). The established tumour contains a number of cytokines, inflammatory substances and non-malignant stromal cells, predominantly macrophages, lymphocytes, endothelial cells and fibroblasts, that influence immunosuppression, growth of cancer cells, tissue remodelling and angiogenesis (Seruga, Zhang et al. 2008, Lippitz and Harris 2016).

Cytokines are key inflammatory mediators that take part in all immune reactions. They provide homeostasis and immune control through an intricate interplay with mutually dependent positive and negative feedback mechanisms (Lippitz 2013). They work through extensive networks and many of them exhibit functions in multiple pathways (Brenner, Scherer et al. 2014). Cytokines show a large variability and are usually not detectable in healthy persons (Schubert, Hong et al. 2007). Cytokines, in particular TNF-α and IL-1, are potent biological molecules; it has been quoted that as few as four molecules of IL-1 need to bind to a cell to elicit a physiological response (Watkins and Maier 2003).

Cytokines are also part of the innate immune system, a non-specific and short-lasting first line of host defence that in addition to humoral immunity (cytokines, chemokines and complement system) also depends on cellular immunity including neutrophils, macrophages, dendritic cells, mast cells, and natural killer cells (Seruga, Zhang et al. 2008).

Most tumour cells express antigens that are recognized by the immune system and both innate and adaptive immune reactions to cancer are well known (Lippitz 2013). However, the immune response is dysfunctional as the tumour induced immune stimulation is paralleled with initially local and later general immunosuppression that protects the cancer cells. A complex tumour-host interaction leads to tumour evading the antitumour immune response (Gajewski, Schreiber et al. 2013).

Components of the innate immune response are known to have interactions potentially detrimental to the host. In colorectal cancer, for example, innate immune responses such as increased tumour or circulating granulocytes or pentraxin C-reactive protein are associated with a poor outcome independent of tumour node metastases (TNM) stage (Roxburgh and

McMillan 2016). Adaptive immune cells are displaced by innate immune cells, resulting in tissue repair and stromal changes supporting the growth of tumor and protection against adaptive immune responses (Roxburgh and McMillan 2016).

Cytokines are produced as a part of the host's immune response, but are also secreted by the tumour cells themselves. In patients with advanced stage cancer, the pattern of cytokines reflects the pro-and anti-inflammatory immune stimulation and includes macrophage migration inhibitory factor (MIF), tumour necrosis factor α (TNFα), interleukin (IL) -6, IL-8, IL-10, IL-18, and transforming growth factor β (TGFβ). Moreover, this is claimed to be a common pattern of cytokines independent of the different cancer types (Lippitz 2013). High serum concentrations of IL- 6 and IL-10 are associated with negative prognosis in multiple cancer types (Seruga, Zhang et al. 2008, Lippitz 2013, Lippitz and Harris 2016).

Specific cytokines have been utilized therapeutically. One example is high dose IL-2 which has the potential to elicit durable responses in patients with malignant melanoma and renal cell carcinoma (Amin and White 2013). An increasing understanding of the immunoregulatory processes, tumour-host interaction and mechanisms of tumour escape has led to new cancer therapies, in particular immunotherapies that target steps in the host antitumour immune response.

During the course of the disease, signs of systemic inflammation become more evident. Systemic inflammation is thought to be one of the main mechanisms behind cardinal symptoms of advanced malignant disease, such as cancer cachexia (Fearon, Arends et al. 2013).

1.7.1 Symptoms in cancer patients and inflammation

In the 80's it was noted that patients treated with recombinant Interferon–γ and other cytokines developed fever, fatigue, weight loss and night sweats (Kurzrock 2001). Symptoms were found to correlate with serum concentrations of IL-6 and could in some cases be prevented by cytokine antagonists. This led to the theory that cytokines could be involved in the biological mechanism eliciting these symptoms (Kurzrock 2001, Cleeland, Bennett et al. 2003, Lee, Dantzer et al. 2004).

Experimental data have shown that the brain recognizes cytokines as molecular signals of sickness (Dantzer 2009). Peripherally released cytokines act on the brain (Dantzer 2001) through neuroendocrine pathways that impact on central nervous system functions including neurotransmitter metabolism (serotonin, norepinephrine and dopamine), corticotropin releasing hormone (CRH) function, sleep-wake cycles, regional brain activity and ultimately behaviour (Miller, Ancoli-Israel et al. 2008). Cytokines produced in the brain are a part of the response (Dantzer 2009).

Systemic inflammation is associated with a wide plethora of symptoms and is accepted as the unifying mechanism for the entire cluster of sickness behaviours: asthenia, increased slow wave sleep, mood alterations, lethargy, depression, anorexia, fever, anhedonia, cognitive impairment, hyperalgesia and decreased social interaction (Fearon, Arends et al. 2013).

1.7.2 Inflammation and its effects on pain, fatigue, and loss of appetite

Pain is one of the four cardinal signs of inflammation "rubor et tumor cum calore et dolore" (redness and swelling with heat and pain) defined by Celcius in the first century (Scott, Khan et al. 2004, Celsus A.D. 25). As referred earlier, localized inflammation will lead to stimulation of pain receptors in the tissue (Falk and Dickenson 2014).

Pain is also a part of the more generalized sickness response. Sickness-induced hyperalgesia, which is elicited by pro-inflammatory cytokines in the periphery, can be induced or prevented by the administration or by pharmacologically blocking IL-1 or TNF-α, respectively (Watkins and Maier 2000). This is also supported by clinical data. In patients with head and neck cancer and breast cancer, pain assessed before starting antitumour treatment was associated with CRP and TNF-α, and with CRP and IL-13, respectively (Starkweather, Lyon et al. 2013, Oliveira, von Zeidler et al. 2014).

Pro-inflammatory cytokines are significant modulating factors for different types of pain. First, there is evidence that pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α are involved in the development of inflammatory or neuropathic pain (Zhang and An 2007). Second, the immune-competent glia cells (microglia and astrocytes) have a major role in pain regulation (Watkins and Maier 2003, Watkins, Hutchinson et al. 2007). Activated glia

cells enhance pain, in part by releasing several key pro-inflammatory cytokines. The activated glia cells can increase the neuronal excitability at multiple sites along the pain pathway, including the peripheral nerve, the dorsal horn and the spinal cord (Watkins, Hutchinson et al. 2007), and animal models of chronic and neuropathic pain have shown involvement of a number of inflammatory mediators (Ji, Xu et al. 2014).

Data also support that cancer pain may be modulated by inflammatory mediators. In animal data, monocyte chemoattractant protein -1 (MCP-1/CCL2) was increased in the spinal cord in a rat model of cancer-induced bone pain (Hu, Zheng et al. 2012). Furthermore, intrathecal injection of an MCP-1 neutralizing antibody attenuated, and recombinant MCP-1 induced mechanical allodynia in this cancer pain model.

Translational research has indicated associations between variability in the immune response genes coding prostaglandin-endoperoxide synthase 2 (PTGS2), TNF-α, nuclear factor κBIA (NF- κBIA), IL-6, and IL-8 and pain severity in cancer patients (Reyes-Gibby, Swartz et al. 2013). Finally, perioperative treatment with pentoxifylline, which inhibits the production of TNF-α, IL-1 and IL-6, reduced postoperative morphine consumption in patients undergoing colorectal cancer surgery (Lu, Chao et al. 2004).

For fatigue, studies in patients with advanced cancer have reported association between cancer related fatigue and serum concentrations of IL-1ra, IL-6, CRP, and neopterin (Schubert, Hong et al. 2007, de Raaf, Sleijfer et al. 2012, Kwak, Choi et al. 2012, Liu, Mills et al. 2012, Laird, McMillan et al. 2013). In lung cancer patients, gene variants for IL-8 were associated with fatigue, similar findings were observed for IL-10 in women, and IL-1ra in men (Reyes-Gibby, Wang et al. 2013).

Three small trials, one which administered TNFα antibody to patients with advanced cancer (Tookman, Jones et al. 2008), and two with co-administration of TNF-α or IL-6 - cytokine antagonists with cancer therapy (Nishimoto, Kanakura et al. 2005, Monk, Phillips et al. 2006), all showed less fatigue in the intervention groups.

Inflammation is a factor in the development of cancer related anorexia. Animal models demonstrated increased brain levels of pro-inflammatory cytokines (IL-1 and TNF-α) in cancer anorexia; and further, inhibition of these cytokines enhanced food intake (Molfino, Gioia et al. 2015).

Targeting inflammation in clinical anorexia trials includes treatment with thalidomide, a drug shown to inhibit the production of TNF-α by human macrophages. Trials, although small, have indicated improvement in anorexia and nausea (Bruera, Neumann et al. 1999), as well as less weight loss in oesophageal and pancreatic cancer (Khan, Simpson et al. 2003, Gordon, Trebble et al. 2005). Megestrol acetate, which has shown appetite stimulating properties (Mantovani, Maccio et al. 1998, Loprinzi, Kugler et al. 1999), improves food intake by reducing the expression of IL-1 (Mantovani, Maccio et al. 1998) and by increasing hypothalamic concentrations of neuropeptide Y (Molfino, Gioia et al. 2015). Furthermore, an RCT comparing eicasopentaenoic acid (EPA) supplementation and megestrol acetat showed similar improvement in appetite (Jatoi, Rowland et al. 2004). EPA has an anti-inflammatory action as the prostaglandins and leukotrienes deriving from the degradation of EPA exert less pro-inflammatory activities when compared to those deriving from omega-6 fatty acids. Finally, phase I and II studies on an experimental, monoclonal antibody IL-6 antagonist ameliorated cachexia in patients with non-small cell lung cancer (Bayliss, Smith et al. 2011).

These results support a strong relationship between pro-inflammatory cytokines and pain, cancer-related fatigue and loss of appetite.

1.8 Corticosteroids

Steroids consist of the saturated tetracyclic hydrocarbon (1,2-cyclopentanoperhydrophen-anthrene) group also called sterane. Steroids endogenously produced in vertebrates are generally classified into four families including corticosteroids (glucocorticosteroids and mineralocorticosteroids), progestagens, androgens and estrogens (Figure 4). Although mainly produced by the adrenals and gonads, they are also synthesized or metabolized in the bowel, liver, prostate and nervous system (Mensah-Nyagan, Meyer et al. 2009).

The chemical nature of steroids allows them to behave as lipophilic molecules, particularly when they are free or non-conjugated; they may therefore reach or act on several tissues in the body including the peripheral and central nervous systems (Mensah-Nyagan, Meyer et al. 2009). They exert a large array of biological effects including the control of sex behavior, reproduction, development, stress and the regulation of the activity of various

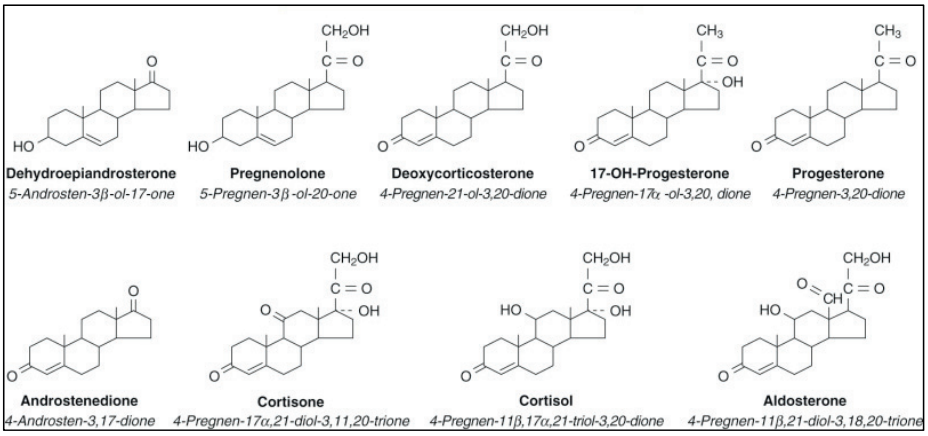

Figure 4: *The cyclopentanoperhydrophenanthrene structure of corticosteroid hormones, highlighting the structure of some endogenous steroid hormones together with their nomenclature (Paul M. Stewart 2016) (Used with permission)*

important physiological systems such as the immune, cardiovascular, respiratory and nervous systems (Mensah-Nyagan, Meyer et al. 2009).

1.8.1 Anti-inflammatory effects

The anti-inflammatory and immunosuppressive effects of corticosteroids are mediated at many levels, mainly via genomic effects. The main mechanisms include:

Firstly, cortisol binds to the glucocorticoid receptor (GR) in the cytoplasma. The GR-cortisol complex translocates to the nucleus, where it stimulates gene expression (Ramamoorthy and Cidlowski 2016). Secondly, most of the anti-inflammatory effects of glucocorticoids seem to result from “transrepression”, inhibition of effects of pro-inflammatory transcription factors, especially nuclear factor–κB (NF-κB) and activator protein-1 (AP-1). Many hundred glucocorticoid-responsive genes have been identified (Paul M. Stewart 2016). Finally, nongenomic effects include activation of signaling cascades.

In terms of inflammation, cortisol results in a decreased production of multiple inflammatory proteins, such as cytokines, including IL-1 to IL-6, TNF-α; chemokines; adhesion molecules; inflammatory enzymes and receptors; and peptides. Corticosteroids induce anti-inflammatory cytokines including IL1-ra, annexin 1 and IL-10, and lipocortin which inhibit

prostaglandin synthesis (Barnes 2006). They inhibit the expression of collagenase (Mensah-Nyagan, Meyer et al. 2009).

The immunologic effects of corticosteroids include inhibition of immunoglobuline synthesis in B and T lymphocytes and stimulation of lymphocyte apoptosis. Furthermore, the anti-inflammatory effects include inhibition of monocyte differentiation into macrophages, macrophage phagocytosis and cytotoxic activity (Paul M. Stewart 2016). Corticosteroids have anti-inflammatory effects on multiple components of cellular immunity. In contrast, they have relatively little effect on humoral immunity (Gilman 2006).

Glucocorticoids are primary stress hormones that regulate a vast array of physiologic processes and with consequences for most organ systems if produced in excess (Ramamoorthy and Cidlowski 2016).

1.8.2 Systemic corticosteroids

The corticosteroid drugs are grouped according to their anti-inflammatory potency, mineralcorticoid potency (water retaining properties), duration of action, and equivalent doses (Table 1).

Compound	Anti-iflammatory potency	Na-retaining potency	Duration of action*	Equivalent dose, mg
Cortisol (hydrocortisone)	1	1	S	20
Cortisone	0.8	0.8	S	25
Fludrocortisone	10	125	I	**
Prednisone	4	0.8	I	5
Prednisolone	4	0.8	I	5
Methylprednisolone	5	0.5	I	4
Triamcinolone	5	0	I	4
Betamethasone	25	0	L	0.75
Dexamethasone	25	0	L	0.75

Table 1: *Relative potencies and equivalent doses of representative corticosteroids*
**S, short (i.e., 8-12 hours biological half-life); I, intermediate (i.e., 12-36 hours biological half-life; L, long (i.e., 36-72 hour biological half-life) **This agent is not used for glucocorticoid effects*
Adapted from Goodman&Gilman's "The Pharmacological Basis of Therapeutics" 11th Edition, 2006, Chapter 59 (Schimmer BP, Parker KL), p 1594 (Gilman 2006)

1.8.3 Corticosteroids and pain perception

Data from animal studies have indicated that pain can be modulated by corticosteroids. The spinal cord in rats has a high density of glucocorticoid receptors found in laminae I and II of the dorsal horn (Gonzalez, Moses et al. 1990, Marlier, Csikos et al. 1995).

Locally applied corticosteroids suppress spontaneous discharge in neuromas (Devor, Govrin-Lippmann et al. 1985), and attenuate experimental neuropathic hyperalgesia and mechano-allodynia from nerve injury in rats (Johansson and Bennett 1997). Moreover, epidural (Lee, Weinstein et al. 1998), intrathecal (Takeda, Sawamura et al. 2004) and systemic corticosteroids (Kingery, Agashe et al. 2001, Beaudry, Girard et al. 2007, Makimura, Arao et al. 2011) reversed neuropathic hyperalgesia and mechanical allodynia in rats; the effect persisted one week after discontinuation (Kingery, Agashe et al. 2001). Likewise, mechanical allodynia and thermal hyperalgesia in experimental neuropathic pain were exacerbated by a glucocorticoid receptor antagonist, and reduced by an agonist (Gu, Wang et al. 2007). Besides, this improvement was associated with a reduction in the number of TNF-α positive mast cells in the endoneurium of damaged neurons (Hayashi, Xiao et al. 2008), less inflammation at nerve constriction site (Beaudry, Girard et al. 2007), reduced glial activation (Takeda, Sawamura et al. 2004), and normalization of elevated cytokines (Li, Xie et al. 2007).

Chronic dexamethasone treatment showed anti-nociceptive effect measured by tail-flick test in rats, the medication altered the expression of neuropeptides involved in nociceptive transmission at the spinal cord level (Pinto-Ribeiro, Moreira et al. 2009). Finally, dexamethasone enhanced sciatic nerve regeneration and function recovery in a rat model of sciatic nerve injury through immunosuppressive and potential neurotrophic effects (Feng and Yuan 2015).

In relation to patients with cancer pain, a pilot study showed that betamethasone intrathecally once a week in ten patients gave long lasting analgesia for seven days in half of the patients. Notably, the analgesic effect came within 10 minutes (Taguchi, Oishi et al. 2007). In another patient series, thirteen patients with intractable pain due to vertebral metastases received betamethasone intrathecally. Six patients achieved a significant decrease in pain intensity (Inada, Kushida et al. 2007); this was associated with a significant decrease in the concentrations of IL-8 and prostaglandin E_2 (Inada, Kushida et al. 2007).

Trials have shown that systemic corticosteroid therapy may improve pain control after surgery. Romundstad et al. found significant analgesic effect for up to 72 hours of a single dose of 125 mg methylprednisolone given the first day after orthopedic surgery (Romundstad, Breivik et al. 2004). Corticosteroids are recommended therapy as an adjunct for postoperative pain (Salerno and Hermann 2006).

1.8.4 Corticosteroids in oncology

Corticosteroids are beneficial in a number of clinical settings in oncology. They have a wide distribution to most tissues, and have a broad range of effects, some of which are:

1. Corticosteroids have antineoplastic effects. This is demonstrated in hematologic malignancies (Inaba and Pui 2010), probably by inducing apoptosis (programmed cell death) (Schimmer and Funder 2011). This is also shown in monotherapy in breast and prostate cancer, in the latter probably by adrenal androgen suppression (Minton, Knight et al. 1981, Tannock, Gospodarowicz et al. 1989, Keith 2008, Jongen, Paridaens et al. 2016).

2. Corticosteroids' potent anti-inflammatory effects (Rhen and Cidlowski 2005) are probably main effects in syndromes with tumour-compression against essential structures. Examples include superior vena cava syndrome, nerve compression syndrome; or spinal cord compression (Loblaw, Perry et al. 2005), in which corticosteroids can provide prompt symptom relief (Posner, Howieson et al. 1977, Greenberg, Kim et al. 1980). Reduced oedema may be a part of the effect (Holte and Kehlet 2002) as demonstrated after dental surgery (Skjelbred and Lokken 1982). Reduction of peritumour inflammatory oedema is thought to be the effect that can bring about the resolution of malignant bowel obstruction (Feuer and Broadley 2000). Furthermore, corticosteroids may have neuroprotective actions in acute neuronal injury (Hall 1993, Bracken 2012).

3. Corticosteroids are shown to restore the incompetent blood-brain barrier surrounding brain tumours, reducing the vasogenic oedema (Yamada, Ushio et al. 1983, Dietrich, Rao et al. 2011), thereby reducing symptoms caused by cerebral oedema (Ryan 2012).

4. Corticosteroid effects can be mediated through the alterations in the hypothalamic-pituitary-adrenal (HPA) axis and a blunted cortisol-response that have been demonstrated in cancer patients and survivors (Bower 2014), as for example in cancer related fatigue.

5. Corticosteroids are frequently used in combination with other drugs in anti-emetic regimens in chemotherapy treatment (Ioannidis, Hesketh et al. 2000, Basch, Prestrud et al. 2011, Perwitasari, Gelderblom et al. 2011).

1.8.5 Use of corticosteroids in palliative care

Corticosteroids are used in a large proportion of cancer patients. They are considered by palliative care physicians to be an essensial medicine for palliative care (Dickerson 1999, WHO 2015). A European survey of 3030 patients admitted to palliative care programmes showed that 39 % used corticosteroids (Klepstad, Kaasa et al. 2005), similar numbers were reported in ambulatory patients receiving supportive care in a Canadian hospital (Riechelmann, Krzyzanowska et al. 2007). A Swedish cross-sectional study showed that 50 % of cancer patients in palliative care received corticosteroids (Lundstrom and Furst 2006). Likewise, data from German and UK palliative care units report corticosteroids to be the third most used drug class (Twycross, Bergl et al. 1994, Nauck, Ostgathe et al. 2004). In a study from a British hospice, one third of the patients were taking corticosteroids. More than half of the patients did not know why they were taking the drug and few (8/28) claimed to have benefited. Only in two patients were the dose and indication for the prescription documented by the referring physician (Needham, Daley et al. 1992).

Corticosteroids' broad range of effects is reflected in the number of indications for their use. Three prospective surveys and one cross-sectional study showed that appetite loss, fatigue, poor wellbeing, nausea, and pain were the most frequent indications for corticosteroids in palliative care (Table 2).

1.8.6 Adverse effects from corticosteroids

A major concern in the clinical use of corticosteroids is the number of potentially serious adverse effects associated with their use (Table 3). In general, most adverse effects are correlated to total daily dose and duration of steroid administration (Vecht, Hovestadt et al. 1994, Fardet, Kassar et al. 2007, Dietrich, Rao et al. 2011).

In palliative care, prospective studies have found oral candidosis to be the most frequent adverse effect (Hanks, Trueman et al. 1983, Hardy, Rees et al. 2001). The patients are at risk

Indication for corticosteroids	**Hanks 1983 (*n*=159)** **(**Hanks, Trueman et al. 1983**)**	**Hardy 2001 (*n*=106)** (Hardy, Rees et al. 2001)	**Mercadante 2001 (*n*=50)** (Mercadante, Fulfaro et al. 2001)	**Lundstrøm 2006 (*n*=608)** (Lundstrom and Furst 2006)
Appetite loss		19	60	37
Fatigue	*	4**	74**	36
Poor wellbeing	36*	12		33
Nausea		12	29	27
Pain	21	19		25
Brain tumour	15	4	14	18
Dyspnea	11	6	36	9
Antitumour treatment	17			6
Spinal cord compression	4	6		4
Malignant bowel obstruction		3		2
Other	33	14	30	

Table 2: *Indications for corticosteroids in palliative care. All numbers in percentage*
**"Non-specific tonic" **"Weakness"*

for psychosocial disturbance, hyperactivity and sleeplessness, oedema, weight gain, dyspepsia, diabetes, and proximal myopathy (Hanks, Trueman et al. 1983, Hardy, Rees et al. 2001) (Table 3). In one of these studies, five percent stopped treatment with corticosteroids because of adverse effects (Hanks, Trueman et al. 1983).

High dose corticosteroid therapy, defined by the NCCN guidelines as a dose of prednisolone ≥ 20 mg /day for ≥ 4 weeks (Lindsey Robert Baden 2015) or equivalent , can result in clinically significant suppression of the immune system, and an increased risk for infections [relative risk (RR) 2.1 (CI 1.3,3.6) for infections] (Fardet, Kassar et al. 2007); this relates even more to cancer patients receiving anticancer treatment. This includes the risk for opportunistic infections such as Pneumocistis jirovecii (Kelly and Cronin 2014). Moreover, corticosteroids may blunt fever and local signs of infection, as for instance in peritonitis (ReMine and McIlrath 1980), delaying the time of diagnosis.

Adverse effect	Hanks 1983 (*n* = 218)*	Hardy 2001 (*n* =106)*	Lundstrøm 2006 (*n* = 181)**
Drug, dose	Prednisolone n=146 Dexamethasone n=109 Variable dose	Dexamethasone Variable dose	Betametasone Variable dose, but > 3.5 mg/day in 33 %
Duration of use	Median 4-8 weeks	Median 21.5 days	66 % > 4 weeks
Oral candidosis	31	34	28
Oedema	20	34	
Cushingoid appearance	18	19	43
Restlessness	2	27	
Sleeplessness	2	25	
Weight gain	4	22	
Skin changes	4	27	31
Dyspepsia	7	19	
Proximal myopathy	2	24	34
Confusion/psychosis	4	5	
Hyperglycemia	2	2	17
Infection		1	
Weight gain	4		

Table 3: *Corticosteroid toxicity in palliative care: Side effects reported in two prospective surveys and one cross-sectional study. All numbers in percentages*
**Recorded by checklist, weekly registration **Reported the five most common adverse effects*

Myopathy was reported in 2-34 % of patients using corticosteroids in palliative care (Table 3). It is observed in up to ten percent in patients with primary brain tumours using dexamethasone (Dietrich, Rao et al. 2011). Myopathy can interfere with activities of daily living (Batchelor, Taylor et al. 1997). Muscle proteolysis and blunted muscle protein synthesis are major factors in the development of corticosteroid induced muscle atrophy (Schakman, Gilson et al. 2008). Myopathy can start abruptly, associated with high corticosteroid doses and rhabdomyolysis, or insidious after prolonged use (Frieze 2010). Fluorinated glucocorticoids, i.e. dexamethasone and betamethasone, are thought to more likely cause myopathy (Dietrich, Rao et al. 2011). Myopathy is probably related to the dose of corticosteroids (Vecht, Hovestadt et al. 1994, Batchelor, Taylor et al. 1997, Vecht 1998,

Fardet, Kassar et al. 2007). Studies have suggested corticosteroid dose reduction, cessation, or switching to a nonfluorinated agent for the treatment of myopathy (Fardet, Kassar et al. 2007, Frieze 2010, Yennurajalingam and Bruera 2014). Aerobic training is beneficial in preventing and treating this complication (Frieze 2010).

The risk of peptic ulcer and gastrointestinal bleeding has been debated. A recent meta-analysis in unselected patients showed an increased risk of gastrointestinal bleeding or perforation in patients using corticosteroids. However, this finding was only significant for hospitalized patients (Narum, Westergren et al. 2014). Other reviews have showed no significant differences in incidence of peptic ulcer during corticosteroid treatment (Conn and Poynard 1994). Incidence of peptic ulcer tend to increase with dose and duration of therapy (Heimdal, Hirschberg et al. 1992, Fardet, Kassar et al. 2007, Garcia Rodriguez, Lin et al. 2011). Co-administration with non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk for peptic ulcer more than 4-fold (Piper, Ray et al. 1991). Similarly, low dose acetylsalicylic acid (ASA) added to high dose corticosteroid therapy increases the risk for upper gastrointestinal bleeding 4-fold (Garcia Rodriguez, Lin et al. 2011).

Mild neuropsychiatric and behavioral consequences of corticosteroid therapy such as insomnia and restlessness are frequent. Severe neuropsychiatric consequences are reported in 15.7 per 100 persons per year of corticosteroid treatment and include suicide, delirium, mania, depression, psychosis and panic disorder (Judd, Schettler et al. 2014, Boettger, Jenewein et al. 2015). Despite the frequent side effects reported in studies, 65 % of palliative care physicians in Sweden stated that they did not consider side effects as a major problem in patients receiving corticosteroids (Lundstrom and Furst 2006).

1.8.7 Corticosteroids as adjuvant analgesic

Guidelines (Jost, Roila et al. 2010, NCCN 2015, Portenoy, Ahmed et al. 2015), clinical papers, and textbooks on cancer pain (Fallon, Hanks et al. 2006, Knotkova and Pappagallo 2007, Lussier and Portenoy 2010, Portenoy 2011) include corticosteroids as one of the adjuvant drugs. These publications specify several indications for corticosteroids as adjuvants analgesics, given in Table 4.

Author	Indication for the use of corticosteroid for cancer pain treatment
Watanabe (Watanabe and Bruera 1994)	Bone pain Visceral pain Neuropathic pain Brain metastases Reflex sympathetic dystrophy
Lussier (Lussier, Huskey et al. 2004)	Bone pain Neuropathic pain (infiltration or compression) Headache due to intracranial pressure Arthralgia Pain due to obstruction of hollow viscus Pain due to organ capsule distention
Management of cancer pain: ESMO Clinical Practice Guidelines (Jost, Roila et al. 2010)	Nerve compression
National Comprehensive Cancer Network®: NCCN Guidelines®: Adult Cancer Pain (NCCN 2015)	Bowel obstruction Nerve pain due to nerve compression or inflammation Pain associated with inflammation Diffuse bone pain Acute management pain crisis involving neural structures or bones
UpToDate (Portenoy, Ahmed et al. 2015)	Headache Neuropathic pain Bone pain Pain associated with capsular expansion or duct obstruction Pain caused by lymphoedema Bowel obstruction Pain crisis: Dexamethasone 50-100 mg
Fallon et al. (Fallon, Hanks et al. 2006)	Raised intracranial pressure Nerve compresssion Soft tissue infiltration Hepatomegaly
Knotkova and Pappagallo (Knotkova and Pappagallo 2007)	Headache pain associated with intracranial pressure Inflammatory neuropathic pain from peripheral nerve injuries Bone pain Pain from bowel obstruciton Pain from lympoedema
Lussier and Portenoy (Lussier and Portenoy 2010)	Bone pain Neuropathic pain Headache due to increased intracranial pressure Arthralgia Obstruction of hollow viscus Pain crisis: Dexamethasone 20-100 mg
Portenoy (Portenoy 2011)	Headache Neuropathic pain Bone pain Lympoedema pain Bowel obstruction

Table 4: *Published recommendations for the use of corticosteroids in pain treatment*

Several trials have assessed the efficacy of corticosteroids for cancer pain, in general most often combined with the aim to reduce other symptoms (Table 5) (Bruera, Roca et al. 1985, Della Cuna, Pellegrini et al. 1989, Popiela, Lucchi et al. 1989, Bruera, Moyano et al. 2004, Mercadante, Berchovich et al. 2007).

These studies show conflicting evidence. In order to combine findings from the various studies, a systematic review was needed. This review is presented as Paper I in this thesis.

1.8.8 Corticosteroids for cancer related anorexia and fatigue

Appetite was the primary endpoint in one trial (Willox, Corr et al. 1984); and one of several endpoints in six trials (Table 5). A total of 900 patients with advanced disease were included. All trials reported improvement in the corticosteroid group, after one week (n=1), two weeks (n=2), or four weeks (n=1). An RCT found the appetite stimulating effects from dexamethasone similar to megestrol acetate (Loprinzi, Kugler et al. 1999) but with a higher rate of drug discontinuation in the dexamethasone group. A systematic review of the treatment of cancer-associated anorexia and weight loss reported evidence to support the use of corticosteroids in short courses as an appetite stimulant (Yavuzsen, Davis et al. 2005).

Cancer related fatigue was evaluated in seven studies (Table 5). An expert working group of the European Association for Palliative Care stated that “steroids might be effective in relieving fatigue for a short period of time, but the documentation was weak” (Radbruch, Strasser et al. 2008).

1.9 Summary

In summary, corticosteroids are often used in palliative care patients to relieve pain and other symptoms. However, the evidence base for this practice is limited. This is the background for initiating the studies included in this thesis.

Author, Year, Aim	**Population** Performance	**Method** Intervention period	**Intervention**	**Pain**	**Analgesic consumption**	**Appetite**	**Fatigue**	**Adverse events**	**Comment**
Moertel 1974 (Moertel, Schutt et al. 1974) Primary aim: evaluate CS on symptomatic status and survival in patients with advanced cancer	116 patients far-advanced gastro-intestinal cancer Expected survival <2 months 81 evaluated week 4 Performance status not reported	RCT Double blind Until death or stopped oral medication	Dexamethasone 1.5 mg four times daily, OR dexamethasone 0.75 mg four times daily OR Placebo			Improved appetite: Week 2: 57 % in CS vs 44 % in plac Week 4: 55 % in CS vs 26 % in plac $p < .05$ (Weekly self assessment)	”Improved strenght”: Week 2: 26 % in CS vs 15 % in plac Week 4: 34 % in CS vs 13 % in plac $p < .07$ (Weekly self-assessment)	Oedema 33 % in CS vs 30 % in plac	No difference in symptomatic results between dexamethasone 0.75 and 1.5 mg dosages Median survival 5.2 - 6.6 weeks No change in weight in CS vs plac
Willox 1984 (Willox, Corr et al. 1984) Examine the effectiveness of CS in stimulating appetite, increase body weight, energy intake and general wellbeing	61 patients complaining of poor appetite and weight loss 41 evaluated (18 on chemotherapy) Performance status not reported	RCT, double blind cross-over 14 days, week 3: reduced dose Evaluation week 2 and 5	Prednisolone 5 mg three times daily OR Placebo			Improvement in appetite: 33 patients (80 %) in CS period, 23 patients (56 %) in plac period (VAS) $P < .01$		No side effects were reported	Increased wellbeing in CS period ($p < .01$) Seven patients stopped taking medication. Not included in analysis No change in weight or food intake
Bruera 1985 (Bruera, Roca et al. 1985) Evaluate the effect of CS on pain, psychiatric status, appetite, nutritional status, daily activity, and performance in patients with terminally ill cancer	40 patients with advanced cancer 31 evaluated ECOG 3.5 ± 0.7	RCT, cross over, double blind, 5 days - 3 days washout - 5 days (+ 20 days open label corticosteroid)	Methyl-prednisolone 16 mg twice daily OR Placebo	Improvement in favour of CS 13.3 (CS: 36.8 ± 14, Plac 50.1 ± 15) (VAS 0-100) $p < .01$	Improvement in favour of CS 1.5 (CS 1.8 ± 1.7, Plac 3.3 ± 1.5) (No of analgesic capsules)*** $p < .05$	Improvement in favour of CS 10.6 (CS 40.1 ± 15, plac 29.5 ± 15) (VAS 0-100)* $p < .05$	Improvement in favour of CS 3.3 (CS 6.7 ± 2.4, plac 3.4 ± 2) (Score 0-10)** $p < .01$	Discontinued: CS 3, Plac 1	Pain one of multiple outcomes Low analgesic usage at baseline No of analgesic capsules: 3.6 ± 1.5*** 3 patients no pain at baseline
Twycross 1985 (Twycross and Guppy 1985) Examine the effect of corticosteroids on several symptoms	56 patients with breast or bronchogenic carcinoma, 27 evaluated	RCT, double blinded, 7 days	Prednisolone 5 mg three times daily OR Placebo	Pain (VAS 0-100) unchanged		Improvement in favour of CS 22.1 ± 3.3 (VAS 0-100) $p = .14$	”Strength” Improvement in favour of CS 8,7 ± 3.4 (VAS 0-100) Sign. not reported		Low level of pain in CS group.
Della Cuna 1989 (Della Cuna, Pellegrini et al. 1989) Effectiveness of CS in improving quality of life in patients with preterminal cancer Short-term survival	403 patients, ”advanced, preterminal carcinoma” 198 evaluated Performance status not reported	RCT, double blind 8 weeks	Methyl-prednisolone 125 mg intravenously OR Placebo	”Improved at each weekly evaluation” (numbers not given) $p < .05$ (LASA 0-100)	Not reported	”Improved at each weekly evaluation” (Numbers not given) (LASA 0-100) $p < .05$	”No difference” in the weakness, sleepiness or drowsiness-score (Numbers not given) (LASA 0-100)	38.2 % in CS vs 28.1 % in plac ($p < .05$) 11 discontinued due to side effects (10 CS, 1 plac) Higher mortality in female CS group	Pain not primary outcome Mortality: 8 weeks: 36 % Physicians judgement HRQoL ”good to excellent” 42 % in CS vs 21 % in plac ($p < .001$)
Popiela 1989 (Popiela, Lucchi et al. 1989) Survival data for women receiving CS Secondary: Quality of life with 10 symptoms)	173 female patients with advanced, terminal cancer 87 evaluated Performance status not reported	RCT Double blind, 8 weeks	Methyl-prednisolone 125 mg intravenously OR placebo	”There were no significant changes across time for pain” (Numbers not given) (LASA 0-100)	”No difference in narcotic anagesic usage at any point during study follow up” (Numbers not given)	Improvement on week 2 in favour of CS 8.2 ± 0,5, $p < .05$ (LASA 0-100)	Improved ”Feeling of weakness” in favour of CS, week 1: 9.5 ± 0.35, $p < .01$ week 2:	Medical events: 63.5 % in CS vs 53.4 % in plac Related or probably related to investig therapy: 21 % in CS vs 1 % plac,	Pain not primary outcome Mortality: 8 weeks: 34 %

							8.8 ± 0.46, $p < .05$ (LASA 0-100)	$p < .05$	
Loprinzi 1999 (Loprinzi, Kugler et al. 1999) To prospectively compare megestrolacetat, dexamethasone and fluoxymesterone for the treatment of cancer anorexia / cachexia.	492 incurable cancer with weight loss or reduced caloric intake.ECOG ≤ 2 66 % completed questionnaire at baseline and at least one follow up Primarily lung or GI cancer (not breast, prostate, ovarian or endometrial cancer) Life expectancy ≥ 3 months	RCT Open label Monthly evaluation until discontinuation or death Performance status (WHO) : 0-1: 64 % 2: 36 %	Dexamethasone (CS) 0,75 mg four times daily OR Megestrol Acetat (MAc) 800 mg orally OR Fluoxymesterone (FM) 10 mg twice daily			At one month: Appetite "better as compared to baseline": MAc: 42 %, CS 44 %, FM: 28 % (p=.001)		Discontinued: MAc < CS: 25 % vs 36 %, p= .03 Deep venous thrombosis: MAc > CS: 5 % vs 1 %, p= .06 Other adverse effects: (all MAc vs FM vs CS) Myopathy: 6 vs 6 vs 18 % p=.0006. Cushingoid: 1 vs 0 vs 6 % p= .0008 Peptic ulcers: 0 vs 0 vs 3 % p= .04 Infections: 11 vs 8 vs 16 %, n.s. Thromboembolic: 5 vs 2 vs 1 %, n.s. Insomnia: 0 vs 1 vs 4 %, p= .005	Median time on study MAc: 64, Fluoxy 54, Dex 57 days (p= .02) No significant differences in weight gain between the groups
Bruera 2004 (Bruera, Moyano et al. 2004) Evaluate the anti-emetic effect of CS. Secondary: appetite, fatigue, pain	51 patients with advanced cancer and nausea ≥3 (NRS 0-10) 43 evaluated ECOG status 2	RCT, Double blind 7 days	Dexamethasone 10 mg twice daily OR Placebo	No improvement (secondary endpoint)	Not reported	Equal improvement in both groups	Equal improvement in both groups 0.2 ± 1.0 (NRS 0-10) (CS>plac)	Discontinued CS 3, Plac 4	Pain secondary outcome Too low pain intensity at inclusion: 2.5 ± 2.9 (CS) vs 3.1 ± 3.5 (plac) (NRS 0-10) 12 in CS/ 12 in plac used opioids
Mercadante 2007 (Mercadante, Berchovich et al. 2007) To evaluate the adjuvant effect of CS added to strong opioids in advanced cancer patients	76 cancer patients with pain, on strong opioids admitted to palliative care unit 65 evaluated day 7 Performance not reported Life expectancy > 2 weeks	RCT, open label, weekly evaluation until death	Dexamethasone 8 mg orally OR control group (treatment as usual)	No difference in pain intensity between groups Baseline: CS: 7.1 (6.3-7.8) Control: 5.4 (4.7-6.1) Week 1: CS: 3.1 (2.4-3.7), Control: 3.2 (2.5-3.9) (NRS 0 – 10)	No difference in opioid consumption or opioid escalation index Baseline: CS: 275 (197-442) Control 568 (-34-1552) Week 1: CS: 467 (4.7-930) Control: 372 (225-519) mg OME		Improvement in "weakness" at week 2 in favour of CS: CS: 1.7 (1.3-2.1) Contr 2.5 (2.2-2.8) p< .01 (VRS 0-3)	No relevant adverse effects were noted.	Difference in pain intensity and analgesic consumption between groups at baseline High attrition: week 1: 65 patients, week 2: 58 patients, week 3: 31 patients, Survival 35 days (mean) (range 26-45)

Table 5: *Randomized controlled trials evaluating the effect of corticosteroids for pain, appetite, and fatigue*
Mean ± SD (not calculated SD's for Bruera -85 as this was a cross over study)
SD = Standard deviation CS = corticosteroids, plac = placebo, MAc = Megestrol Acetate, FM = Fluoxymesterone, n.s. = non significant, OME = oral morphine equivalents
** Improvement of 15 % ±15 (% of each meal) in favour of CS ** "Activity score" based on stuctured interview (score 0-10) *** No of capsules with 400 mg dipyrone and 98 mg propoxyphene*

2 Aims and Research questions

The aims of this thesis was to assess the analgesic effects of corticosteroids in patients with cancer pain; to assess the effects of corticosteroids on fatigue and anorexia; to assess the pattern of use of corticosteroids in cancer patients using opioids; and, finally, to explore if pain, anorexia and fatigue are related to systemic inflammation.

More specifically the following research questions were asked:

1. What is the evidence in the literature that corticosteroids improve analgesia in adult patients with pain caused by cancer?

2. How frequently are corticosteroids and non-opioid analgesics used in a cohort of European cancer patients using opioids?

3. What is the analgesic efficacy of corticosteroids in patients with cancer related pain using opioid analgesics?

4. Do corticosteroids improve appetite and fatigue in cancer patients using opioids?

5. Are inflammatory biomarkers associated with pain, loss of appetite and fatigue in cancer patients with advanced disease? Are the corticosteroid responses on pain, appetite, or fatigue in cancer patients associated with specific inflammatory biomarkers?

3 Patients and Methods

3.1 Study design

This thesis is based on studies with four different designs: a randomized, placebo-controlled double-blinded phase III study; an exploratory study; a cross-sectional study; and, finally, a systematic review (Table 6).

Design	Title	Paper number
Systematic literature review	Do corticosteroids provide analgesic effects in cancer patients?	Paper I
Cross-sectional study	European Pharmacogenetic Opioid Study (EPOS)	Paper II
Randomized placebo-controlled phase III trial	The "Corticosteroid for cancer pain"-trial	Paper III
Exploratory analysis	Are serum concentrations of inflammatory cytokines associated with symptoms or effect from corticosteroids?	Paper IV

Table 6: *Study designs in this thesis*

3.2 Patient cohort

3.2.1 The cross-sectional "European Pharmacogenetic Opioid Study"

EPOS included patients from 17 different cancer and palliative care centres, in 11 European countries. Study sites included surgical wards, general oncology wards, palliative care units / hospices, and outpatient clinics. Patients older than 18 years, with a verified malignant disease, and who had been using a step III opioid (WHO analgesic ladder) for moderate to severe pain for at least three days were eligible for the study. Patients unable to communicate in the language used at the study centre were excluded.

3.2.2 The randomized controlled trial ”Corticosteroids for Cancer Pain”

The trial was conducted at five palliative care units and outpatient oncology services in Norway; Telemark Hospital, Haraldsplass Deaconess Hospital, Sørlandet Hospital, St. Olav’s University Hospital, and Oslo University Hospital, from April 2008 to January 2012.

Cancer patients ≥ 18 years of age with average pain ≥ 4 the last 24 hours (NRS 0–10), with more than four weeks expected survival, and receiving an opioid for moderate or severe cancer pain, were eligible for the study. Exclusion criteria were: excruciating pain (average pain NRS ≥ 8 the last 24 hours), use of corticosteroids the last four weeks, diabetes mellitus, peptic ulcer disease, concurrent medication with non-steroidal anti-inflammatory drugs (NSAIDs), radiotherapy or systemic cancer treatment started less than four weeks prior to entering the study, or planned to start within the study period, spinal cord compression or in need of bone surgery, and, finally, severe cognitive impairment. No changes in the current scheduled opioid medication were allowed during the last 48 hours before inclusion and throughout the study period. The patients could use an additional opioid for breakthrough pain. In- and outpatients were screened for participation.

3.2.3 The exploratory analysis

The cohort (n=49) from the randomized “Corticosteroids for Cancer Pain” trial was used to explore associations between symptoms at baseline and serum concentrations of cytokines. The analyses of association between pretreatment concentrations of biomarkers and effects of corticosteroids included 38 patients at follow up: 25 patients randomized to receive methylprednisolone in the intervention period and 13 patients receiving corticosteroids on an open basis after the intervention period.

3.3 Methods

3.3.1 Systematic literature review

Procedures: A systematic literature search was performed in the databases PubMed, Embase through OvidSP, and the Cochrane Central Register of Controlled Trials 25 May 2010 and updated 6 December 2011.

The search strategy for PubMed was as follows: ("Steroids/ therapeutic use"[mh] OR "Adrenal cortex hormones/therapeutic use"[mh]) AND ("Pain"[mh] OR "Pain Measurement"[mh] or "Pain Clinics"[mh] or "Pain Threshold"[mh] OR Analgesia[mh] OR Analgesics[mesh:noexp] OR Hyperalgesia[mh]) AND ("Controlled clinical trial "[pt] OR "Randomized controlled trial"[pt] or "Multicentre study"[pt] OR Therapy/narrow[filter]) AND Neoplasms[mesh] NOT (child*[ti] OR paediatr*[ti] OR pediatr*[ti]). (Abbreviations: mh = medical subject headings, noexp = not including narrower terms (mesh), ti = title, pt = publication type, * = truncation). The search was later adapted for the other databases and was limited to humans.

The reference lists of the retrieved papers and reviews, and international conference proceedings from the previous three years were checked. Studies eligible for the review were RCTs that included adult cancer patients (>18 years) with cancer pain, compared corticosteroids with placebo or control when added to standard pain treatment, assessed outcomes on pain, analgesic consumption and adverse events, and were written in English.

The contents and quality of the included studies were assessed by two independent reviewers according to the Grading of Recommendations Assessment, Development and Evaluations (GRADE) system (Atkins, Eccles et al. 2004). A standardized data extraction form was used to assess study characteristics. Study design, study limitations (allocation concealment, blinding, losses to follow-up, adherence to intention to treat analysis, stopping early for benefit, and failure to report outcomes), participants (number of patients and clinical setting), and reporting of results (choice of outcome measures, summary and reported results) were jugded. Evidence profiles were made for the outcomes pain intensity, analgesic consumption and adverse events.

The following factors were considered to decrease the evidence profile by 1-2 grades as specified in the GRADE system: serious or very serious limitation in study quality, some or major uncertainty about directness (external validity), inconsistency of results, imprecision or sparse data, and publication bias. Conversely, factors considered to increase the evidence by 1-2 grades were: a large or very large magnitude of effect, plausible confounding which would reduce a demonstrated effect, and demonstration of a dose-response gradient. For

each research outcome, quality of evidence was finally graded in four categories: high quality (A), moderate quality (B), low quality (C), or very low quality (D).

3.3.2 Cross-sectional multicentre observational study

Assessment and registration: Health care providers registered information on patient characteristics: age, gender, ethnic group, weight, height; medical history: cancer diagnosis, time since diagnosis, site of metastases, use of anticancer therapy, concomitant diseases, and body mass index; medications last 24 h: both scheduled and used as rescues, including over the counter medication; and Karnofsky performance status (KPS).

Procedures: All documented drugs were classified by their generic names, pharmacological class, and indications in the palliative care setting. 1. Opioids, non-opioid analgesics, and corticosteroids were recorded with respect to dose and route of administration. Opioids and corticosteroid doses were converted to equipotent oral morphine or dexamethasone doses, respectively. 2. Unnecessary drugs were defined as: unnecessary drugs, potentially unnecessary drugs, duplicate drugs, and drugs with antagonist effects. Drugs were considered unnecessary in cases when no short-term benefit to patients with respect to survival, symptom control or quality of life was anticipated. 3. The cohort was reviewed for drugs and drug combinations that cause an increased risk for clinically relevant pharmacodynamic and pharmacokinetic drug-drug interactions (DDIs) and potential DDIs via cytochrome P450.

3.3.3 Randomized placebo-controlled double-blinded study

Procedure: At inclusion and after written consent, patients were randomized to receive methylprednisolone 16 mg or placebo twice daily for 7 days. Computerised randomisation was performed at the NTNU by personnel not otherwise involved in the study. Randomisation was stratified for study centre and for pain related to verified bone metastases.

Methylprednisolone or placebo was administered as identical looking unflavoured capsules prepared by the Hospital Pharmacy at the Telemark Hospital Trust. The patients' analgesic treatment was maintained unchanged throughout the study period, but patients received short acting opioids as needed. Patients were contacted daily during the intervention period

by a study nurse to ensure compliance with the protocol. Patients were evaluated during a clinical visit at day 7. Clinicians were allowed to prescribe corticosteroids on an open basis from day 7.

Assessment: A screening tool was designed especially for the trial, adding a single item ”Average Pain Intensity last 24 hours” (Numeric rating scale, NRS 0-10) to the regular ESAS (Bruera, Kuehn et al. 1991).

Patient demographics, medications, clinical characteristics, pain categories as judged by clinical evaluation, and the patient’s performance status (KPS) (Yates, Chalmer et al. 1980) were recorded at baseline by a study nurse or study physician. The patients recorded pain intensity by use of the Brief Pain Inventory (BPI) (Cleeland and Ryan 1994); HRQoL using the EORTC QLQ-C30 (Aaronson, Ahmedzai et al. 1993); and cognitive function was assessed by the Mini Mental State Examination (MMSE) (Folstein, Folstein et al. 1975). All PROMs were recorded at baseline and at day 7. Blood samples were drawn at baseline before starting study medication.

The ESAS, including the average pain item, was measured once daily from day 1 through day 7, and reported in a diary together with daily analgesic consumption. Patients were days 1 – 7 daily contacted by a study nurse by telephone to ensure compliance with the protocol. Overall satisfaction with the intervention (NRS 0 “No benefit” – 10 “Major benefit”) was assessed at day 7. The presence of adverse effects (yes/no) was assessed by the investigator at day 7 using a semi-structured interview (presence of oedema, sleeplessness, restlessness, anxiety, muscle weakness, psychological changes, dyspepsia, mouth symptoms, and other).

Patients were evaluated day 14 and 21 by telephone by the study nurse: changes in medication, analgesic consumption, adverse effects, and current corticosteroid medication were recorded. Finally, EORTC QLQ-C30, and ESAS were scored.

3.3.4 Exploratory analysis

Procedure: This was an exploratory analysis of the databank established in the “Corticosteroids for pain” trial.

At study entry and prior to any corticosteroid medication given, blood samples were drawn and kept in a biobank. The inflammatory markers and cytokines selected for this study

included high sensitivity CRP, IL-1β, IL-1ra, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12(p70), IL-18, Interferon γ (INF-γ), TGF- β1, MIF, TNF- α, MIP 1α, MCP-1 and sTNF-R1. The sera underwent two freeze/thaw cycles before analysis. High sensitivity CRP was analysed at Fürst laboratories, Oslo. The cytokine analyses were performed at the Norwegian University of Life Sciences, Ås using multiplex technology (Multiplex System, Bio-Rad Laboratories Inc., Austin, Texas).

3.4 Assessments

3.4.1 The Brief Pain Inventory (BPI) (Appendix I)

The BPI short form is a widely used tool for cancer pain assessment (Cleeland and Ryan 1994). It is a self-report assessment tool used in both research and the clinical setting to measure pain intensity as well as interference caused by pain the last 24 hours. The BPI has 15 items: four pain intensity items (NRS 0-10) ("worst", "least", "average", and "now"), seven interference items (NRS 0-10) (general activity, walking, work, mood, enjoyment of life, relations with others, and sleep), a preliminary screening question (Yes/No), percentage pain relief provided by pain treatments, and, finally, a body map. The scales' anchors are 0 "no pain/impairment" and 10 "worst imaginable pain/impairment". BPI is sensitive to changes (Lydick, Epstein et al. 1995), and is recommended as pain assessment tool by an expert working group of the EAPC (Caraceni, Cherny et al. 2002). The Norwegian translation is validated (Klepstad, Loge et al. 2002). BPI was used in Paper III.

3.4.2 The European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire C30 (EORTC QLQ-C30) (Appendix II)

The EORTC QLQ-C30 is a multidimensional assessment instrument for self-reported function, symptoms and overall quality of life. It is designed for cancer patients and consists of 30 items. Intensities of nine symptoms are reported: fatigue (three items), nausea and vomiting (two items), pain (two items), and dyspnoea, insomnia, appetite loss, constipation, and diarrhoea (one item each). Additionally, five functional domains are reported: physical functioning (five items), role functioning (two items), emotional functioning (four items), and cognitive, and social functioning (two items each). Finally, global health status is reported (two items); this is reported by two numerical rating scales (NRS 1-7) with the anchors "very

poor" and "excellent". The other items are reported on a verbal rating scale (VRS) 1-4 ("Not at all", "A little", Quite a bit", "Very much").

The symptom scores are calculated according to guidelines, scores range from 0 to 100 (Fayers, Aaronson et al. 2001). A higher score represents a higher level of symptoms ("worse") on the symptom scores, whereas high values represent good functional capacity on the functional scales. EORTC QLQ-C30 has high test/retest reliability, is validated in Norwegian translation, and has acceptable psychometric properties (Aaronson, Ahmedzai et al. 1993, Kaasa, Bjordal et al. 1995). The EORTC QLQ-C30 was used in Papers III and IV.

3.4.3 The Edmonton Symptom Assessment System (ESAS) (Appendix III)

The Norwegian version of ESAS has 10 numerical rating scales (NRS) 0-10 for patient-reported symptom scores, and was originally developed by Bruera and colleagues as a clinical tool for symptom assessment in palliative care. The first version of the original tool contained visual analog scales (VAS 0-100) for the following ten items: pain, tiredness, nausea, depression, anxiety, drowsiness, lack of appetite, wellbeing, shortness of breath, and other (Bruera, Kuehn et al. 1991). The tool was validated in the palliative care population by Chang (Chang, Hwang et al. 2000). However, a review by Richardson and Jones found frequent modifications of the ESAS (altered items, scales and time periods) (Richardson and Jones 2009). They found the tool reliable, but with limited validity. The assessment system is lately revised (Watanabe, Nekolaichuk et al. 2011)

In the corticosteroid RCT, we used the Norwegian version of ESAS with ten items. In addition to tiredness, nausea, dyspnoea, appetite, anxiety, depression, and overall wellbeing from the original version, this version held two pain items: pain at rest, and pain on movement, and dry mouth. Specifically for our trial, we added an extra pain item: "pain intensity on average for the last 24 hours", which is a pain intensity measure recommended for clinical trials (Appendix III) (Kaasa, Apolone et al. 2011) ESAS was used in Paper III.

3.4.4 Mini Mental State Examination (MMSE) (Appendix IV)

The Mini Mental State Examination (MMSE) is a widely used screening tool for cognitive functioning. It is valid, reliable and sensitive to changes in cognitive function (Folstein, Folstein et al. 1975). The score range is from 0 to 30, a high score indicates better cognitive

functioning, and a score of 24 points is used as a cut off value indicating cognitive failure (Carsten Strobel 2008, Mitchell 2009). Pereira has demonstrated the feasibility of using the MMSE in terminal cancer patients (Pereira, Hanson et al. 1997). The MMSE was used to assess cognitive function in the corticosteroid RCT (Paper III).

3.4.5 Edmonton Classification System for Cancer Pain (rECS-CP)

The Revised Edmonton Classification System for Cancer Pain (rECS-CP) was used in Paper III (Bruera, MacMillan et al. 1989, Fainsinger and Nekolaichuk 2008). It consists of five domains: pain mechanism, incidental pain, psychological distress, addictive behavior (CAGE questionnaire), and cognitive function (the MMSE). It is partially validated (Nekolaichuk, Fainsinger et al. 2005, Knudsen, Aass et al. 2009). The rECS-CP has shown to be associated with time, number of modalities, and required mean morphine equivalent daily dose to reach stable pain control (Fainsinger, Nekolaichuk et al. 2005). This classification system has been recommended for research and clinical practice (Kaasa, Apolone et al. 2011). Bone pain mechanism was explicitely reported in our trial to support the stratification factor “pain related to verified bone metastasis”.

3.4.6 Karnofsky Performance Status (KPS) (Appendix V)

Karnofsky Performance Status (KPS) (Yates, Chalmer et al. 1980) is one of the commonly used scales for rating overall functional status in oncology and palliative care, and was used in the EPOS study (Paper II) and the corticosteroid RCT (Papers III and IV). This is an observer rated 11-point scale ranging from 0 ”Death” to 100 ”Normal performance”. Performance status is included in the European Association for Palliative Care Basic Dataset, for instance measured by KPS (Sigurdardottir, Kaasa et al. 2014). The KPS scale was used in Papers II and III.

3.4.7 Adverse events

The presence of adverse effects (AEs) was assessed by the investigator on day 7 by a semi-structured interview (yes/no): presence of oedema, sleeplessness, restlessness, anxiety, muscle weakness, psychological changes, dyspepsia, mouth symptoms, and other (could be specified by the investigator).

3.5 Laboratory analyses

3.5.1 Laboratory analyses

In the ”Corticosteroids for Cancer Pain” trial, standard clinical chemistry analyses were performed at each study site according to the local procedures: erythrocyte sedimentation rate (ESR), hemoglobin, creatinine, total-calcium, albumine, alcaline phosphatase, and lactate dehydrogenase. Additionally, a blood sample was drawn at baseline. Blood was separated and kept frozen in a -80 degree centigrade freezer and transferred to Telemark Hospital until analyses.

3.5.2 Cytokine measurement

The cytokine analyses were performed at the Norwegian University of Life Sciences, Ås, using multiplex technology (Multiplex System, Bio-Rad Laboratories Inc., Austin, Texas) measuring serum cytokine concentrations in high-sensitivity assays (sensitivities <1 pg/ml). In the ELISA (enzyme-linked immunosorbent assay) technique, each well is coated with a specific capture antibody specific to the cytokine of interest, which binds the cytokine. The well is then incubated with a specific detection antibody which carries an enzyme. When a substrate is added, a colour change is observed (Figure 5).

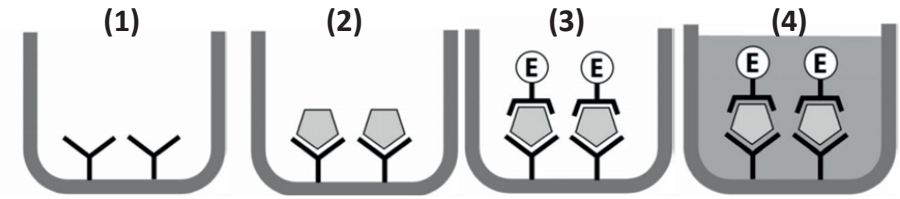

Figure 5: *Schematic illustration of the experimental principle for ELISA : Coat well with capture antibody (1), Incubate with cytokine (antigen) (2), Incubate with detection antibody that has been linked to enxyme (E) (3), and add substrate and observe color change (4) (From (Leng, McElhaney et al. 2008) (Used with permission)*

In contrast, the multiplex assays run multiple analytes in a single run in which all reactions take place among molecules and antigens that are freely mobile in solution (Figure 6).

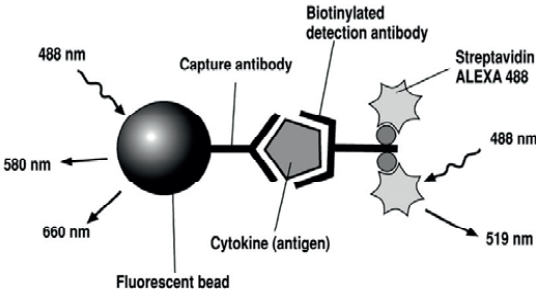

Figure 6: *Proprietary bead sets provide additional differential detection power in bead-based multiplex arrays (From (Leng, McElhaney et al. 2008) (Used with permission)*

A standard curve prepared by making serial dilutions of a standard with a known concentration. Cytokine / chemokine concentrations are calculated by interpolation from the standard curve (Figure 7).

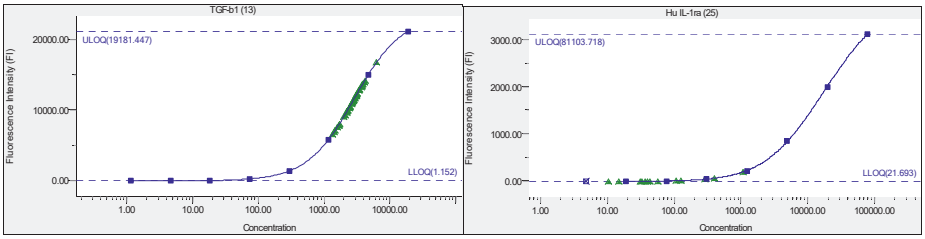

Figure 7: *TGF-β1 (left): all values (green) within the standard curve (blue), and IL-1ra (right): 11 values within the range of the standard curve (data from analyses for Paper IV).*

All samples were assayed in duplicate and the assays performed according to manufacturer's instructions. Bio Rad Human Inflammation panels 6 plex kit containing IL-2, IL-8, IL-10, IL-12(p70), INF-γ, and sTNF-r1; Bio Rad human group 1 and 2 9 plex kit containing IL-1β, IL-1ra, IL-4, IL-6, IL-18, MCP-1, MIP-1α, TNF-α, and MIF; and Bio Rad singleplex kit TGF-β1 were used.

3.6 Statistics

The statistical software IBM SPSS (Statistical Package for Social Science) for Windows (Armonk, NY: IBM Corp.) was used for all analyses in Paper I (version 15.0), Paper III (versions 15.0 and 19.0), and Paper IV (version 21.0). In Paper II, statistical analyses were performed

with the STATISTICA v.10 software package (StatSoft Inc., Tulsa OK). Statistical analyses were performed according to the intention to treat principle (Paper III).

In the systematic review (Paper I), no meta-analysis could be performed due to limited data; only a qualitative analysis could be made.

3.6.1 Sample size calculations

Sample size estimation was performed for the randomized trial (Paper III). A change in EORTC QLQ-C30 score of 10-20 is reported to be a "moderate" and >20 a "large" (or "very much") change in quality of life in cancer patients (Osoba, Rodrigues et al. 1998). Data from chronic pain trials support a clinical important difference in pain intensity of two points (NRS 0-10) or approximately 30 % (Farrar, Young et al. 2001). The trial was designed to detect a difference in average pain intensity of 1.5 (NRS 0–10) between the intervention and the placebo group measured on day 7. With a standard deviation 1.5, a two-sided t-test, a power of 0.90 and a significance level of 0.05, the estimated sample size was 22 evaluable patients in each group. Thus, the study aimed at recruiting a total of 55 patients to allow for drop outs.

As Paper IV was an exploratory analysis, no formal sample size calculation was performed.

3.6.2 Descriptive statistics

All data in the papers were reported as means, 95 % confidence intervals (CI) or standard deviations (SD), medians, ranges, interquartile ranges, or frequencies as appropriate.

3.6.3 Comparisons of groups

In the comparison between two groups, the independent student's t-test was used for continuous variables after checking for normality. Mann-Whitney U test was used in Paper II and for not normally distributed variables in Paper III. In comparisons between more than two groups, Kruskal-Wallis ANOVA and Dunn's post hoc test (if appropriate) were performed in Paper II. Statistical significance was set at $p < 0.05$.

3.6.4 Bivariate analysis

Bivariate analyses were performed in the exploratory analysis (Paper IV) to investigate possible associations between biomarkers and symptoms at baseline. As the cytokines were

not normally distributed, Spearman Rho-Rank correlation was applied for the correlation analyses.

3.6.5 Regression models

Regression analyses were used in Paper III to adjust for pain intensity, analgesic consumption and other differences between the groups at baseline and the stratification factors: pain related to verified bone metastases and study centre.

Multiple regression analyses were performed for the correlation analyses between serum concentration of biomarkers and quality of life and symptom parameters. Gender, BMI, and age were explored as possible confounding factors based on previous research (Saligan and Kim 2012); gender and BMI were included as covariates. Biomarkers were log-transformed, except for ESR and sTNF-r1 which were normally distributed.

Multiple regression analyses were also performed to explore associations between pretreatment inflammatory biomarkers and change in pain, appetite, and fatigue following corticosteroid treatment. Gender and BMI were included as covariates. Biomarkers were log-transformed, except for ESR and sTNF-r1 which were normally distributed.

3.7 Data monitoring

Data from the randomized trial (Paper III) were recorded in Case Record Forms, and later transferred to an electronic database. The trial was independently monitored by staff members from Kontor for klinisk forskning (Office for Clinical Research), Oslo University Hospital. All sites were monitored at least twice. All patients were monitored; the first patients at each site were monitored 100 %, later 20 % of the patients were monitored 100 % according to good clinical practice, GCP.

3.8 Ethics and approvals

Both trials included in the thesis, the EPOS study (Paper II) and the “Corticosteroid for Cancer Pain” trial (Papers III and IV) were conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki (WMA 2008). Written informed consent was obtained from each patient before study-related procedures were performed in both trials. Ethical approval of the protocol for the EPOS study was obtained at each centre

or in each country according to national and/or regional recommendations. The RCT trial was approved by the Regional Committee for Medical Research Ethics, REC Central, ID 4.2007.846 and the Norwegian Directorate of Health. The trial was registered in ClinicalTrial.gov on 05/08/2008, ID: NCT00676936.

3.9 Financial support

Ørnulf Paulsen received his phd-grant from the South-Eastern Norway Regional Health Authority and grants for running costs from Telemark Hospital Trust. The study sponsors had no role in planning the study, study design, collection of data, analyses or interpretation of data, writing of the report, or decision to submit the papers for publication.

4 Results and summary of papers

Patient characteristics	Paper II, EPOS	Papers III-IV
Time of inclusion	2004-2006	2008-2012
Number of participating centres	17	5
Number of included patients	*n*=2282	*n*=49
Female / male	1087/1195	24/25
Type of study	Cross-sectional	Randomized controlled
Department		
Palliative care	823 (36 %)	39
General oncology	952 (42 %)	3
General surgical / medical	78 (3 %)	4
Other	429 (19 %)	3
Setting		
Hospitalized	1850 (81.2 %)	n.r.*
Outpatients	428 (18.8 %)	n.r.*
Age (mean, range)	62.2 (18-98)	63.7 (44-83)
Survival (days) (median, range)	102 (92-111)	86 (4-933)
Performance status (KPS) (mean, range)	59 (10-100)	66 (30-90)
Main tumour diagnosis, n of patients		
Gastrointestinal	522 (23 %)	11
Lung	384 (17 %)	11
Breast	301 (13 %)	2
Prostate	264 (12 %)	6
Gynecologic	173 (8 %)	10
Other	638 (30%)	11
Metastasis, n of patients		
Bone	1017 (45 %)	15
Liver	561 (25 %)	17
Lung	505 (22 %)	7
Central nervous system	132 (6 %)	2
Other	898 (40 %)	33
Opioid dose (mg/d) OME	230.3 ± SD 456.7	218.5 ± SD 219.7
Range	10-9090	10 – 840

Table 8: *The patient cohorts included in this thesis*
*OME = Oral morphine equivalents, KPS= Karnofsky performance status, *n.r. = not recorded*

4.1 Paper I

"Do Corticosteroids Provide Analgesic Effect in Cancer Patients? A Systematic Literature Review"

Despite their frequent use in cancer patients, including cancer pain treatment, the evidence base for corticosteroids as analgesic drugs was not established. As a starting point for this thesis, a systematic literature review was performed. The aim was to evaluate the current evidence in the literature for the use of corticosteroids as adjuvant analgesics in patients with cancer pain.

A systematic literature search was performed. The search identified a total of 472 abstracts, including two abstracts from hand search. These were screened and six full text articles were assessed. Two of the six papers were later exluded; one because corticosteroids were combined with a somatostatin analogue in the intervention group (Mitsiades, Bogdanos et al. 2006) and one because of differences in the doses of opioids, differences in pain intensities, and potential differences in treatment between the study groups (low internal validity) (Mercadante, Berchovich et al. 2007).

Thus, four papers were included in the review, comprising a total of 667 patients.

Only one of the four included articles included an adequate assessment of the outcomes. This cross-over trial (Bruera, Roca et al. 1985) showed a significant reduction in pain intensity of 13 points on a 0-100 visual analogue scale, accompanied by significant lower analgesic consumption in favour of the corticosteroid group. The patients used a mean dose of 353 mg of propoxyphene (an opioid for mild or moderate pain); the opioid was used in combination with dipyrone. The second study showed no effect on pain (Bruera, Moyano et al. 2004), but this trial may have been subject to a type II-error. Pain intensity, which was a secondary outcome in the study, was low at baseline: 2.5 in the corticosteroid group compared with 3.1.in the placebo group (NRS 0-10). In the two other large studies (Della Cuna, Pellegrini et al. 1989, Popiela, Lucchi et al. 1989), outcomes for pain intensity or analgesic consumption were not reported; one of these paper still claimed a significant pain reduction, while the other found no effect.

Supported by the two studies by Bruera and coworkers, corticosteroids given in medium doses for up to seven days were well tolerated. But, more importantly, the two studies administrating high doses of corticosteroids intravenously (Methylprednisolone 125 mg) for 8 weeks indicated that corticosteroids might have serious toxicity including higher mortality (Della Cuna, Pellegrini et al. 1989, Popiela, Lucchi et al. 1989). Mortality at eight weeks was significantly higher in the corticosteroid group as compared to the placebo group, 115 (39 %) of 292 patients vs. 85 (30 %) of 284 patients, respectively (p= .017).

The evidence profiles of the outcomes pain intentisy and analgesic consumption were both graded (B), but decreased to level (D) due to small number of patients, and because the intention-to-treat approach was not applied. Adverse effects were adequately reported in two randomized trials, the evidence profile initially rated as moderate (B), but because of small number of patients (imprecision) evidence for adverse effects was finally rated as low (C). No meta-analysis could be undertaken, and only a qualitative analysis could be made.

The paper concluded by giving a weak recommendation for the use of corticosteroids for cancer pain: evidence supported that moderate doses of corticosteroids (eg, methylprednisolone 32 mg or dexamethasone 8 mg daily) may have analgesic efficacy in patients with cancer pain, and was well tolerated in this dose in treatment of short duration.

4.2 Paper II

"Polypharmacy in Patients with Advanced Cancer and Pain: A European Cross-sectional Study of 2282 Patients"

Patients with advanced cancer use multiple drugs for symptom control and for the treatment of concomitant diseases. Corticosteroids and non-opioids are frequently used, but doses and patterns of use between countries and centers are not well described. Moreover, as the patients' clinical condition detoriates, the risk of side effects due to polypharmacy and exposure to unnecessary medication and drug-drug interactions increases.

The aims were to analyze the use of medications and to identify unneccessary drugs and drug combinations with a risk for drug-drug interactions (DDIs) in a cohort of patients with advanced cancer using opioids, and to identify differences in the use of non-opioids, adjuvant analgesic drugs and corticosteroids between 17 European medical centres.

The dataset included 2282 patients, of which 91 % had metastatic disease. The patients received a mean of 7.8 drugs (range 1-20), and 28 % used 10 or more medications. The number of drugs was higher in older patients as compared to younger, in worse performance status as compared to better, and in patients recruited at oncology wards and palliative care units as compered to surgical wards and outpatient clinics.

The drugs and drug classes coadministered with opioids in more than 20 % of patients were: proton pump inhibitors, laxatives, corticosteroids, paracetamol, NSAIDS, metoclopramide, benzodiazepines, anticoagulants, antibiotics, anticonvulsants, diuretics and antidepressants.

Thirty -one percent of patients used paracetamol, and 30 % of patients used NSAIDs. The prescription pattern differed substantially between the centres. Paracetamol was used in one percent of patients in Germany and in 59 percent of patients in Sweden and Norway. In contrast, NSAIDs were used in nine percent in Norway as compared to 57 % in Germany and Switzerland. However, this was mainly due to the use of metamizole, which was used in 42 % of the patients, and exclusively in the two latter countries. Diclofenac was the second most utilized NSAID, used by 9 % of patients.

Forty-nine percent of the patients received corticosteroids; dexamethasone was the drug of choice in 55 % of the cases. Corticosteroids were most commonly used in Italy, Sweden and

Iceland by more than 60 % of the patients, with a median dose of 3-5.5 mg (dexamethasone equivalent doses (DED) per day). In contrast, Germany, Switzerland and United Kingdom used corticosteroids in 34-43 percent of cases and in a significantly higher dose of 6 - 8 mg (median DED per day). Corticosteroids and NSAIDs were prescribed together in 14 % of cases, increasing the risk for gastrointestinal complications.

Antiepileptics were used in one out of five patients. Amitriptyline was used in five percent of patients.

About 45 % of patients received drugs classified as unnecessary (18.5 %) or potentially unnecessary (33 %). The most frequent unnecessary drugs were lipid-lowering drugs (6.2 %) and vitamins (11.6 %); potentially unnecessary drugs included anticancer drugs (5.3 %), cardiovascular drugs (13.7 %), and gastroprotective agents (28.9 %).

Exposures to drug-drug interactions (DDIs) were frequent and held potential for increased risk of sedation in almost half of the patients. Other risks from DDIs included gastric ulcerations, bleedings, and neuropsychiatric and cardiac complications. Almost sixty percent of patients used drugs for symptom control that were substrates for cytochrome P450 isoenzyme CYP3A4, such as fentanyl, oxycodone, methadone, levomethadone, or buprenorphine. Many were at risk for pharmacokinetic DDIs, as more than ten percent of patients received an isoenzyme CYP3A4 inducer or inhibitor.

The paper draws the conclusion that patients with advanced cancer treated with step III opioid analgesics also use a high number of concomitant drugs. Corticosteroids were prescribed to every second patient, and non-opioid analgesics were used in 54 percent of the cases. Different patterns regarding drugs of choice and doses were found between the centres. Many patients received unnecessary drugs and were at risk of DDIs. This demonstrates the need for drug therapy in advanced cancer patients to be continuously evaluated.

4.3 Paper III

"Efficacy of Methylprednisolone on Pain, Fatigue and Appetite Loss in Patients with Advanced Cancer Using Opioids: A Randomized, Placebo-Controlled, Double-Blind Trial"

Despite limited evidence, corticosteroids are extensively used and are recommended in clinical guidelines for analgesic purposes in cancer patients. Due to a substantial risk of side effects, especially after prolonged use, it is important to establish their role in cancer pain treatment.

The aim of this trial was to compare the analgesic efficacy of corticosteroids to placebo in patients with cancer pain using opioids, and to evaluate the effects from corticosteroids in relation to analgesic consumption, fatigue, appetite, and patient satisfaction.

A total of 592 patients with cancer and average pain intensity ≥ 4 the last 24 hours (NRS 0-10) were identified and screened for eligibility. An identified exclusion criterion was the most common reason for non-eligibility; the main reasons for exclusion were patients receiving corticosteroids (31 %) or systemic anticancer treatment (23 %).

Fifty patients were randomized from April 2008 to January 2012, 26 were allocated to the corticosteroid group, and 24 to the placebo group. Forty-seven of the included patients had metastatic disease. The mean Karnofsky performance status was 66 (95 % confidence interval, CI: 60-72). Opioid consumption in the cohort was 218.5 ± SD 219.7 mg; 269.9 mg in the corticosteroid group and 160.3 mg in the placebo group (not significant, n.s.) (mean oral morphine equivalents/day).

Three patients were withdrawn from the study (withdrawn consent *n*=1, serious adverse event *n*=2); twenty-five patients in the corticosteroid group and twenty-two in the placebo group were analysed.

At evaluation day 7 there were no differences in average pain intensity between the groups. The mean difference between the groups was -0.08 (NRS 0-10) (CI: -0.97 to 1.13), *p*= .88. Likewise, there was no significant difference in pain intensity between the groups when reported as change from baseline: - 0.48 (CI: -1.43 to 0.47), *p*= .50; when specified: -1.16 (CI: -1.96 to -0.35) in the corticosteroid group compared to -0.68 (CI: -1.28 to -0.08) in the placebo group (Table 3, Paper III).

Moreover, daily registrations of pain intensity at rest during the intervention period (area under the curve) showed no difference between the study groups. There was no difference in opioid consumption between the groups.

At day 7 there were significant improvements in fatigue and appetite in the corticosteroid group compared to the placebo group (EORTC QLQ-C30: 0-100). Reported as change from baseline, fatigue improved 17 points (CI: -27 to -6) in the corticosteroid group versus a deterioration of 3 points (CI: -5 to 11) in the placebo group, *p*= .003. Appetite improved 24 points (CI: -38 to -11) in the corticosteroid group versus a deterioration of 2 points (CI: -8 to 11) in the placebo group, *p*= .003.

Overall satisfaction with treatment was significantly higher in the corticosteroid group compared to placebo; 5.4 (CI: 4.1 to 6.7) versus 2.0 (CI: 0.7 to 3.3), *p*= .001 (NRS 0-10).

There were no differences between number of adverse effects in the corticosteroid group compared to the placebo group; average number 1.08 (CI: 0.52 to 1.64) compared to 1.55 (CI: 0.85 to 2.24), respectively (*p*= .28). Three serious adverse events (SAEs) were reported during the treatment period, none of these were suspected to be caused by the study medication.

The paper concluded that the trial found no evidence of an analgesic effect of methylprednisolone 32 mg daily in cancer patients receiving opioids. Patients receiving corticosteroids reported a clinically significant improvement in fatigue and appetite, as well as significantly higher level of treatment satisfaction. The medication was well tolerated.

4.4 Paper IV

"The Relationship between Pro-Inflammatory Cytokines and Fatigue, Loss of Appetite and Pain in Patients with Advanced Cancer"

Data have shown that quality of life and symptom variables are associated with the systemic inflammatory response in patients with advanced cancer.

The aims of this study were to examine the relationship between individual inflammatory biomarkers and fatigue, loss of appetite and pain, and to explore whether biomarkers at baseline were associated with changes in these symptoms following treatment with corticosteroids.

This was an exploratory analysis of the biobank established in the "Corticosteroids for pain"-trial (Paper III). Data were available on 49 patients at baseline, and 38 patients at follow-up. Median survival was 86 days (interquartile range (IQR) 39-197).

The plasma levels of interleukin (IL)-1β, IL-2, IL-4, IL-8, IL-10, IL-12(p70), interferon-γ, MIP-1α, and TNF-α were below level of detection. The biomarkers sTNF-r1, IL-6, IL-18, MIF, MCP-1, TGF-β1, IL-1ra, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were elevated.

Moderate correlations were observed between appetite and IL-6, and CRP, and fatigue and IL-1ra (rs: 0.380-0.413, $p < .01$). Pain was not significantly associated with any biomarkers. Physical function and role function were strongly correlated to serum concentrations of CRP, IL-6 and sTNF-r1, ESR, and IL-18 (rs: 0.51-0.89, $p < .001$) and moderately correlated to ESR, IL-18 and MIF; cognitive function was moderately correlated to TGF-β1 (rs: 0.425, $p < .01$).

There was no significant association between pretreatment biomarkers and change in pain, loss of appetite, or fatigue following corticosteroid treatment.

The analyses showed a number of strong correlations between the individual biomarkers.

The paper concluded that inflammatory markers were correlated to appetite and fatigue. No association between baseline biomarkers and efficacy of corticosteroid therapy was found.

5. Discussion

5.1 Discussion of Main Findings

The primary aim of this thesis was to assess the analgesic effects of corticosteroids in patients with cancer related pain (Papers I and III). Secondarily, we explored the effects of corticosteroids in the treatment of anorexia and cancer related fatigue in the same patient cohort (Paper III). Furthermore, we investigated the general use of corticosteroids in a European patient population (Paper II). Finally, baseline biomarkers of systemic inflammation were analyzed to assess associations with pain, appetite, and fatigue, and to explore their associations with the effects of corticosteroids on these symptoms (Paper IV).

The thesis confirms that corticosteroids are frequently used in palliative care. It was the third most utilized drug, and was prescribed to every second patient in the EPOS cohort of European cancer patients using opioids (Paper II).

The randomized, controlled ”Corticosteroids for Cancer Pain” trial (Paper III) found no evidence of an analgesic effect of methylprednisolone 32 mg/day for seven days in patients with cancer pain treated with opioids. The results were consistent across all endpoints for pain, including analgesic consumption.

The findings in the empirical study (Paper III) are in contrast to the systematic literature review (Paper I). The review resulted in a weak recommendation for the use of a moderate dose of corticosteroids as an adjuvant analgesic in patients with cancer pain. The recommendation was based on one small crossover trial (Bruera, Roca et al. 1985), and the evidence was graded as very low. After the systematic review was published, a placebo controlled RCT was published which evaluated the effect of dexamethasone 4 mg twice daily for cancer related fatigue in patients with advanced cancer (Yennurajalingam, Frisbee-Hume et al. 2013). This study reported a temporarily improved pain control after one week in the corticosteroid group. Major limitations in this study were related to the assessment of multiple endpoints, and to the use of opioids, which was not reported.

In the RCT in this thesis (Paper III), corticosteroids were used as an general adjuvant analgesic, or ”add-on” to the basic pain management, irrespective of whether the patients had any specific clinical indications for the use of corticosteroids or not. As of today, several

clinical guidelines recommend the use of corticosteroids in patients with neuropathic pain or cancer induced bone pain (Table 4). The anti-inflammatory and anti-oedema effects of corticosteroids could theoretically support these drugs to be useful in these pain categories. Interestingly, in addition to seven patients with visceral pain, the study by Bruera et al. included patients with bone pain (n=16) or pain due to nerve compression (n=5). Furthermore, the patients received less intense opioid therapy, i.e. opioids for moderate pain (WHO- step II opioids) or no opioids. These study characteristics may contribute to the observed analgesic response from corticosteroids (Bruera, Roca et al. 1985). One may expect that the effect size would have been larger in the RCT in this thesis (Paper III) in favour of the use of corticosteroids in subgroups of patients, for instance with nerve compression and/or cancer induced bone pain. We did not observe any clinically significant effects from corticosteroids in these subgroups. However, the RCT was not designed and sampled for subgroup analyses, and larger studies are needed to conclude on efficacy in specific subgroups of patients with cancer pain.

Because of the contradictory results in the trials concerning corticosteroids and pain, the level of evidence should still be considered as low. Correspondingly, it may still be argued for a weak support for the use of methylprednisolone or dexamethasone in specific subgroups of patients. However, the lack of evidence argues against recommending a general use of corticosteroids in the treatment of cancer pain.

It should be emphasized that corticosteroids are still considered important in the clinical management of specific pain syndromes such as spinal cord compression (Loblaw, Perry et al. 2005) and brain metastases (Dietrich, Rao et al. 2011). Likewise, the antitumour effects of corticosteroids may provide analgesia, for instance in patients with hematological malignancies (Inaba and Pui 2010) and prostate cancer (Tannock, Gospodarowicz et al. 1989, Venkitaraman, Lorente et al. 2015).

Another important clinical indication for the use of corticosteroids is cancer related anorexia. The RCT (Paper III) demonstrated a significant improvement in appetite, measured as a secondary endpoint. This finding corresponds with the results from ten other randomized trials that evaluated the effect of corticosteroids on anorexia in patients with advanced cancer (Table 6, Paper III) (Yennurajalingam, Frisbee-Hume et al. 2013). Although the trials

represent differences in duration of intervention periods, patient selection, corticosteroid drugs, and doses, consistent results across the trials support the use of corticosteroids for anorexia in patients with advanced cancer. This recommendation is also supported by systematic reviews (Yavuzsen, Davis et al. 2005, Miller, McNutt et al. 2014). However, there are no published data regarding the effects of corticosteroids on nutritional status or weight gain.

Until recently, the evidence for the use of corticosteroids for cancer related fatigue was weak. However, the RCT by Yennurajalingam et al., which assessed the efficacy of dexamethasone 8 mg for 14 days for cancer related fatigue, observed a clinically significant improvement in fatigue of 5.9 points as measured by FACIT-F (0-52) in favour of dexamethasone (Yennurajalingam, Frisbee-Hume et al. 2013). Likewise, our RCT (Paper III) found a similar, clinically significant improvement in the corticosteroid group. These trials provide data to support the use of corticosteroids for 1-2 weeks for cancer related fatigue. This is also consistent with recently updated guidelines for cancer related fatigue (NCCN 2016).

Frequently asked questions in clinical practice are: which corticosteroid drug should be chosen; which dose should be preferred; and for how long should corticosteroids be prescribed? In the eleven published RCTs on pain, cancer related fatigue and appetite (Table 6, Paper III) (Yennurajalingam, Frisbee-Hume et al. 2013), three different corticosteroid drugs were studied: dexamethasone (n=5), methylprednisolone (n=4), and prednisolone (n=2). Dexamethasone was the preferred corticosteroid and was used in more than 50 percent of corticosteroid users in our cohort of European cancer patients (Paper II). However, there are no studies comparing the clinical efficacy of the different corticosteroid drugs.

Different doses of corticosteroids were applied in the RCTs. Three studies assessed the efficacy of dexamethasone equivalent doses of 6-8 mg on the endpoints pain (n=3) and fatigue (n=2). In contrast, doses equivalent to dexamethasone 3-8 mg were studied for cancer related anorexia in seven RCTs, six of these showed improved appetite. Moertel's study indicated that there was no difference between dexamethasone 3 mg versus 6 mg as compared to placebo for appetite and well-being (Moertel, Schutt et al. 1974). Except for

this study, no published trial has compared different doses of corticosteroids for appetite, pain or cancer related fatigue.

Regarding duration of corticosteroid therapy for symptom control, few trials have assessed their efficacy for more than two weeks. Two trials assessed the efficacy on appetite after 4 weeks; both showed improvement on 3-6 mg dexamethasone/day (Moertel, Schutt et al. 1974, Loprinzi, Kugler et al. 1999). Loprinzi's trial demonstrated that dexamethasone 3 mg daily at evaluation at four weeks had significantly more drug discontinuations and adverse effects such as myopathy, cushingoid changes, peptic ulcers, and insomnia compared to megestrol acetate. The other trial did not record adverse effects prospectively. Two early RCTs investigated the use of high dose methylprednisolone, 125 mg, for eight weeks for quality of life. One paper reported a significant effect in appetite in week 2; the other claimed a significant improvement in appetite and pain in all eight weeks in favour of the corticosteroid group (Della Cuna, Pellegrini et al. 1989, Popiela, Lucchi et al. 1989). However, the lack of detailed results in these two studies restricts the judgement of the treatment effects. Importantly, both trials reported significantly more adverse effects in the corticosteroid arm compared to placebo. The papers also indicate that the use of corticosteroids in this manner may increase mortality (Paper I) (Della Cuna, Pellegrini et al. 1989, Popiela, Lucchi et al. 1989).

Moreover, adverse effects from corticosteroids, such as for instance muscle atrophy and myopathy, can impair patients' functional status (Batchelor, Taylor et al. 1997, Braun, Zhu et al. 2011, Dietrich, Rao et al. 2011). In the trial by Vecht et al., higher doses of corticosteroids (8-16 mg/day as compared to 4 mg/day) administered for four weeks were associated with more side effects, reduced Karnofsky Performance Status and a reduced net benefit of the corticosteroid treatment in patients with brain metastases (Vecht 1998). To conclude, there are still insufficient data to recommend corticosteroid therapy for more than 1-2 weeks for appetite or fatigue.

Lundström found that starting corticosteroid treatment had an existential impact, giving patients a perception of a normalized life, strengthened autonomy, health and hope (Lundstrom, Furst et al. 2009). This may be reflected in the major difference in favour of corticosteroids in the "Patient satisfaction with treatment" item in the present RCT (Paper

III). The substantial positive response patients with advanced disease experience from starting corticosteroids can imply a risk of overenthusiastic initiation of these drugs (Gannon and McNamara 2002).

Thus, the lack of documentation of long-term symptom control in addition to corticosteroids' significant long-term adverse effects, do favour their use for short-time periods and in patients with limited life expectancy. It also calls for continuous evaluation of patients on corticosteroids in terms of efficacy and toxicity of treatment.

5.1.1 What is the evidence in the literature that corticosteroids improve analgesia in adult patients with pain caused by cancer?

The review confirmed that there is a paucity of high quality studies addressing the efficacy of corticosteroids as analgesics in patients with cancer pain. Despite identifying six randomized trials, important issues were raised concerning their validity, one of which was the reporting of outcomes. All but one trial were excluded in the analyses. Accordingly, only a weak recommendation could be made that a moderate dose of corticosteroids may contribute to analgesia in patients with cancer pain.

The lack of or insufficient reporting of data is identified as a major problem in reviews (Caraceni, Brunelli et al. 2005, Bell, Wisloff et al. 2006) and was also observed in our review. This makes it difficult to perform valid meta-analyses. The CONSORT statement (Schulz, Altman et al. 2010) provides a template to improve the quality of reporting of data.

The strength of the recommendation in paper I was judged as weak. In the EAPC evidence based recommendations, twenty-two topics were discussed. Only nine of the 29 recommendations were rated as "strong"; the rest were graded as "weak" (Caraceni, Hanks et al. 2012). Likewise, 22 out of 25 Cochrane reviews in palliative care reported only weak evidence due to too few and small primary studies that were clinically heterogeneous, and of poor quality and external validity (Wee, Hadley et al. 2008).

Systematic literature reviews and meta-analyses are of substantial value for clinicians to efficiently integrate existing information and provide data for rational decision-making and evidence-based practice (Mulrow 1994). They are important both in providing strong recommendations where these exist, and in highlighting the areas with weaknesses in the

evidence base (Wee, Hadley et al. 2008). The weak evidence for use of corticosteroids for cancer pain identified in the systematic review (Paper I) questions their frequent use for this indication (Table 2). It also exemplifies the importance of developing evidence-based clinical guidelines to direct clinical practice.

5.1.2 How frequently are corticosteroids and non-opioid analgesics used in a cohort of European cancer patients using opioids?

The cross-sectional study stated that more than a half of this cohort of European cancer patients using step III opioids also used non-opioid analgesics (Paper II). This is comparable to a European survey performed some years earlier (Klepstad, Kaasa et al. 2005). Some interesting similarities were found when countries included in both studies were compared: 1. Paracetamol and NSAIDs were used by 23-31 % of the patients in both studies. 2. Large contrasts were demonstrated; paracetamol was used by 35-60 % of the patients in Norway, Sweden, and UK, in contrast to negligible use in palliative care units in Germany. NSAIDs were used by 9-13 % of patients in Norway at the lower extreme (Figure 8). 3. Metamizol was exclusively used in Germany (Table 3, paper II).

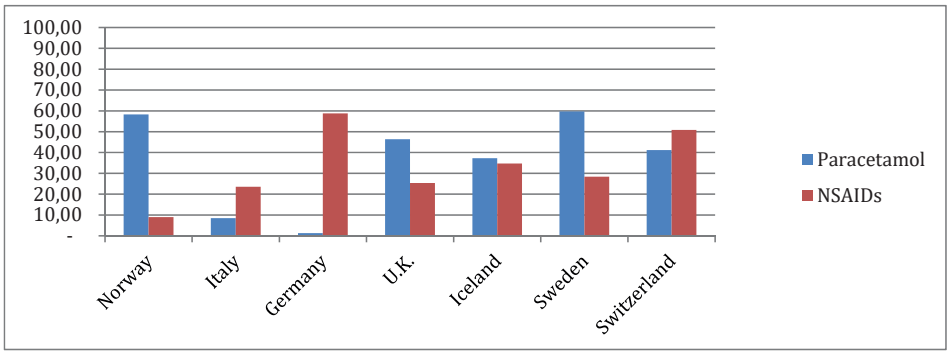

Figure 8: *Use of paracetamol (blue bars) and NSAIDs (red bars), percent of patients. Data from Paper II*

In the case of corticosteroids, these drugs were used by 49 % of the patients in the study (Paper II), which is similar to observations from other studies (Nauck, Ostgathe et al. 2004, Klepstad, Kaasa et al. 2005, Lundstrom and Furst 2006). Furthermore, the data showed widely differing prescription practices for the use of corticosteroids with Italy and Sweden

(72 % of patients) and the UK and Germany (34 % of patients) representing the extremes. This was similar to the pattern described in a study from 2000 (Klepstad, Kaasa et al. 2005). Moreover, the median corticosteroid doses seemed to be inversely correlated with the prevalence of corticosteroid use; 7-8 mg/day in the UK, Germany and Switzerland as compared to 3.8-5.5 mg/day in Sweden and Italy (Figure 9). The drugs of choice differed between the countries, as for instance demonstrated by the predominant use of methylprednisolone in Norway relative to betamethasone in Sweden.

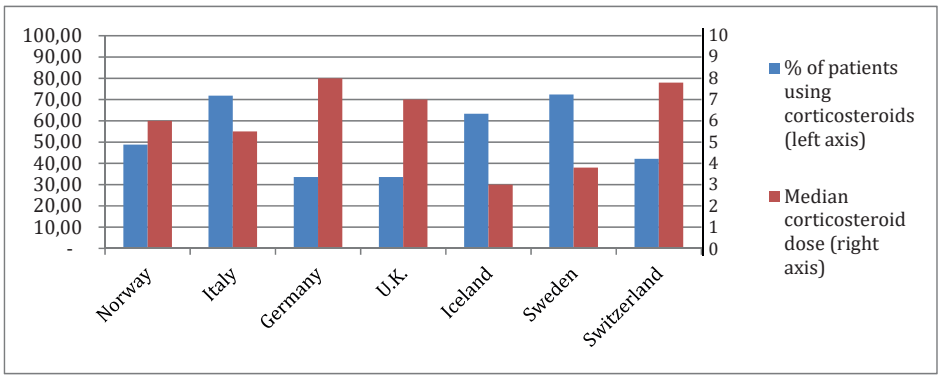

Figure 9: *Use of corticosteroids (percent of patients, blue bars) and corticosteroid dose (median dexamethasone equivalent dose (mg), red bars). Data from Paper II*

Overall, the data show dissimilarities in prescription practices regarding non-opioid analgesics between countries, also within regions with expected similar practices such as the Scandinavian countries. Compared to the survey from the year 2000, the observations in Paper II suggest that prescription patterns seem to be stable. Although methodological issues may influence this finding, for instance differences in patient cohorts between the centres, other studies have also shown differences in cancer pain management between European countries (Breivik, Cherny et al. 2009). One reason may be the scarce scientific documentation for the use of non-opioid drugs, as exemplified in the EAPC recommendations from 2012 (Caraceni, Hanks et al. 2012). This makes clinical practice vulnerable to cultural differences, as well as local consensus and practice (Exton 2009). Other reasons may be differences in the services provided, focus on pain control versus curative disease management, and differences in education for health care professionals, in

national strategies for pain control, and reimbursement mechanisms. Nevertheless, the varied prescription practices are a persuasive argument for the need for high quality research in palliative care, as well as for the need to implement evidence-based guidelines for symptom management, such as the EAPC recommendations (Caraceni, Hanks et al. 2012) or NCCN guidelines (NCCN 2015).

Paper II revealed that the patients used a high number of drugs. One third used 10 drugs or more, and this resulted in frequent potential drug-drug interactions. Polypharmacy is in itself a burden to patients with respect to the number of medications taken per day, but also with regard to an increased exposure to individual drugs' adverse effects. A cross-sectional study in outpatients receiving anticancer therapy showed that the number of potential drug-drug interactions was associated with the total number of drugs the patient was prescribed (Riechelmann, Tannock et al. 2007). Moreover, the same study indicated that drugs used to treat comorbid conditions were associated with more potential drug interactions than supportive care medications.

The fact that 45 % of the population in the survey (Paper II) were prescribed unnecessary or potentially unnecessary drugs, emphasizes the need to develop deprescribing strategies for patients with life-limiting illnesses (Todd, Husband et al. 2016). High quality research such as the RCT by Kutner et al.'s assessing discontinuation of statins, is important (Kutner, Blatchford et al. 2015) . Additionally, our trial observed that 14 % of the patients were using NSAIDs and corticosteroids concurrently, a combination which substantially increases the risk for peptic ulcer (Piper, Ray et al. 1991). This is a disturbing example of drug therapy implying a high risk of serious negative impact on the patients.

5.1.3 What is the analgesic efficacy of corticosteroids in patients with cancer related pain using opioid analgesics?

The "Corticosteroids for Cancer Pain" trial found no evidence of an analgesic effect of methylprednisolone 32 mg daily for seven days. All end points for pain intensity (average pain intensity day 7, and pain intensity measured daily by ESAS), and analgesic consumption showed no difference between the corticosteroid and the placebo groups in terms of improved analgesia.

About 60 % of patients enrolled in palliative care services use opioids at the time of admission (Hjermstad, Aass et al. 2016). Moreover, in 2009 82 % of Norwegian cancer patients in their last year of life received opioids (Brelin, Fredheim et al. 2016). Therefore, to ensure the external validity of the study, an important inclusion criterion in the RCT (Paper III) was that patients should be receiving pain management with opioids. The mean oral opioid equivalent dose in our trial was similar to the doses found in the EPOS cohort (Paper II).

The efficacy of corticosteroids for the management of cancer-related pain in adults was recently addressed in a Cochrane review (Haywood, Good et al. 2015). Fifteen studies were identified. Six trials were included in the meta-analysis of pain intensity at one week, showing a mean reduction of 0.84 (CI -1.38 to - 0.3) (NRS 0-10) (p=.002) in favour of corticosteroid treatment (Figure 10). Evidence was rated ”low quality” due to the small number of participants in each arm in the included studies.

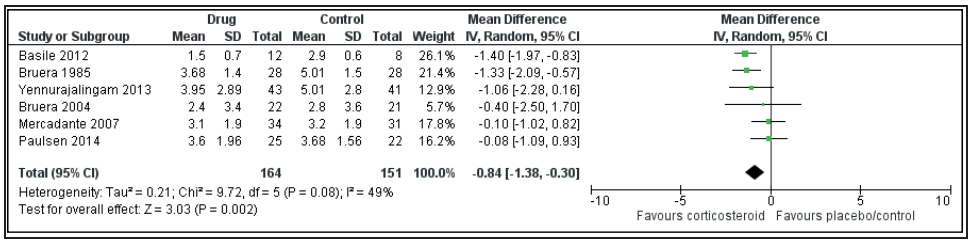

Figure 10: *Forest plot of pain at 1 week in the Cochrane review (Haywood, Good et al. 2015)(Used with permission)*

The metaanalysis included the RCTs by Bruera et al. from 1985 and the RCT in this thesis (Paper III). Four other trials were included. Yennurajalingam et al. assessed the efficacy of dexamethasone 4 mg twice daily for cancer related fatigue in patients with advanced disease (Yennurajalingam, Frisbee-Hume et al. 2013). In this study, the secondary endpoint pain improved transiently at day 7 by 1.64 points (NRS 0-10) in the corticosteroid as compared to the placebo group (p = .014). There was no effect at day 14. Important limitations include

many endpoints; pain intensity was one of 22 symptom scales reported and analgesic consumption or pain classification was not reported in the paper.

The international consensus on palliative radiotherapy endpoints includes stable or reduced analgesic intake as a factor for the categories “complete response” or “partial response” (Chow, Hoskin et al. 2012). The importance of reporting analgesic consumption also when assessing the effect of adjuvant analgesic drugs was illustrated by one of the trials in the meta-analysis. This open-label RCT compared dexamethasone with treatment as usual (Mercadante, Berchovich et al. 2007). A substantial difference was observed in mean pain intensity and mean opioid consumption between the treatment groups at baseline. Further, mean pain intensity improved in both treatment arms during the intervention period. However, opioid consumption increased in the corticosteroid group and decreased in the control group during the intervention period, which makes evaluation of the effects of the intervention drug on pain intensity impossible. This was the reason to exclude this trial in our systematic review. To include this particular study in the Forest plot and meta-analysis only by reporting the marginal difference of 0.1 points between the study groups at week 1 is misleading.

The meta-analysis also included a study that randomized patients to vertebroplasty plus dexamethasone (dose not reported) versus vertebroplasty alone (Basile, Masala et al. 2012). At day 7 the pain intensity score on a visual analoge scale (VAS 0-10) was on the average 5 in the corticosteroid group versus 6.5 in the control group. Firstly, 16 of the 20 included patients had multiple myeloma or lymphoma; haematological diseases in which corticosteroids have an antitumour effect. Secondly, vertebroplasty is an interventional procedure where cement is injected into a localized symptomatic neoplasm or pathological fracture of the vertebral body. Moreover, corticosteroids have been shown to reduce postoperative pain including orthopedic surgery (Romundstad, Breivik et al. 2004, Jakobsson 2010). Thirdly, opioid consumption was not reported in the vertebroplasty trial. These factors question the internal validity of the trial, and the external validity in the general cancer pain management setting.

Finally, the 2004 RCT by Bruera et al., which primarily evaluated dexamethasone for nausea, was included in the meta-analysis (Bruera, Moyano et al. 2004). In this study, however, the

mean pain intensity at baseline was too low to be able to assess analgesic efficacy, and the study was therefore excluded in the systematic review in this thesis (Paper I). In conclusion, it can be questioned how much the trials included in the meta-analysis, apart from Bruera et al. from 1985 and the present RCT (Paper III), add to the evaluation of the research question.

A clinical practice using very high dexamethasone doses in patients with very severe pain poorly responsive to opioids has been described (Lussier and Portenoy 2010). The loading dose is described to be 50-100 mg dexametasone, followed by the divided daily doses tapered over several weeks. A similar regimen has been considered in several reports in the acute management of metastatic spinal cord compression (Greenberg, Kim et al. 1980, Hanks, Trueman et al. 1983, Sorensen, Helweg-Larsen et al. 1994, Rousseau 2001). This high dose regimen was abandoned at a Norwegian centre due to a high number of adverse effects (Heimdal, Hirschberg et al. 1992). Additionally, an RCT, although small, comparing the loading dose of dexamethasone 100 vs 10 mg in 37 patients with spinal cord compression found no difference in pain intensity between the groups (Vecht, Haaxma-Reiche et al. 1989). Due to the possible risk of serious side effects, the described practice using very high doses of corticosteroids should not be recommended until empirically tested.

Two published patient series have described the administration of 1-3 mg betamethasone intrathecally once weekly in patients with vertebral metastases or cancer pain in the lower half of the body (Inada, Kushida et al. 2007, Taguchi, Oishi et al. 2007). The authors reported improvement in pain in half of the patients. This indicates that higher doses of corticosteroids or other routes of administration may have an analgesic effect in cancer pain.

5.1.4 Do corticosteroids improve appetite and fatigue in cancer patients using opioids?

The RCT found statistically significant effects on appetite and fatigue endpoints (Paper III). The differences of 25.5 points (EORTC QLQ –C30, 0-100) for appetite and 20 points for fatigue between the groups in favour of corticosteroids should be regarded as clinically significant (Osoba, Rodrigues et al. 1998).

In addition to Yennurajalingam's RCT (Yennurajalingam, Frisbee-Hume et al. 2013) discussed earlier, another RCT assessed methylprednisolone 16 mg twice daily for fatigue. This trial

recruited under half (n=34) of the planned number of patients according to sample size estimation (n=40 in each arm) despite a multicentre organization with 22 sites (Eguchi, Honda et al. 2015), and showed no effect.

Appetite and cancer related fatigue were secondary endpoints in the RCT (Paper III). Analysis of multiple endpoints in clinical trials provides in general data with larger risks of bias and larger statistical uncertainties compared to the primary endpoint, which has a precalculated sample size and a formal statistical inference. This also applies for this patient cohort, which was selected and stratified on the basis of the primary aim of the trial. By including patients on the basis of pain intensity, we could not ensure that patients had symptom intensities of fatigue and anorexia needed to demonstrate an eventual improvement due to corticosteroid treatment.

5.1.5 Are inflammatory biomarkers associated with pain, loss of appetite and fatigue in cancer patients with advanced disease?

The exploratory analysis (Paper IV) showed that appetite was moderately correlated with IL-6 and CRP, and that fatigue was moderately correlated with IL-1ra in this cohort of cancer patients with advanced disease and cancer pain. There was no correlation between pain and pro-inflammatory markers.

Cancer is associated with upregulation of the innate immune/inflammatory response (Roxburgh and McMillan 2014). Systemic effects of pro-inflammatory cytokines are associated with symptoms in patients with cancer (Seruga, Zhang et al. 2008). Patients in the RCT in this thesis, who had different primary cancer diagnoses, showed signs of systemic inflammation with increased serum concentrations of CRP, ESR, sTNF-r1, IL-1ra, IL-6, IL-18, MCP-1, MIF, and TGF-β. This is similar to a pattern of cytokines previously described in patients with advanced cancer (Lippitz 2013).

An interesting observation in Paper IV was the relation between biomarkers and physical and role function. Reduced physical function and impaired role function were both strongly correlated to increased serum concentrations of CRP, IL-6 and sTNF-r1 (Paper IV). Further, this also corresponds with the effects from corticosteroids in the RCT. In secondary analyses from the “Corticosteroids for pain” trial (Paper III), a significant improvement in role function

of 17.4 points in the corticosteroid arm compared to placebo was observed [corticosteroid 11.3 (CI: 0.0 to 22.7) vs placebo -6.1 (CI: -15.8 to 6.5)] (*p*= .026) (data not published). Similar observations were made in Yennurajalingam et al. and Bruera et al.'s RCTs on corticosteroids: both noted improvement in physical well-being and activity scores (Bruera, Roca et al. 1985, Yennurajalingam, Frisbee-Hume et al. 2013). Role function is closely related to the physical function item (Kaasa, Bjordal et al. 1995) and probably reflects the same construct.

These findings also correspond to data from a large cross-sectional study where appetite, fatigue and role function were the only EORTC QLQ-C30 items independently associated with systemic inflammation (Laird, Fallon et al. 2016). All together, these observations support that appetite, fatigue, and role function are associated with systemic inflammation in patients with advanced cancer. Moreover, in context with the observed improvements in appetite, fatigue and role function from anti-inflammatory treatment with corticosteroids, these data indicate that systemic inflammation may be a causal factor underlying these symptoms and HRQoL-variables.

Other data have shown that ameliorating systemic inflammation can improve anorexia and fatigue. Oral supplement with Eicosapentaenoic acid (EPA), an omega-3 fatty acid, improved appetite in an RCT, although not better than megestrol-acetate (Jatoi, Rowland et al. 2004). Eicosapentaenoic acid has been shown to reduce inflammation and may have a sustained positive effect in incrementing lean body mass (Pappalardo, Almeida et al. 2015).

Specific pro-inflammatory cytokines may be involved in symptom improvement. A decrease in IL-6, IL-1 or TNF-α-level may for instance be involved in the anti-anorectic mechanism of progestins and ghrelin (Yamashita, Hideshima et al. 1996, Mantovani, Maccio et al. 1998, Akamizu and Kangawa 2010). Inhibition of specific pro-inflammatory cytokines has shown some efficacy for appetite and fatigue. Although not reporting improved appetite, reports on preliminary trials of monoclonal anti-IL-6 antibody therapy have shown improved fatigue and reduced weight loss in patients with Castleman´s disease and lung cancer (Bayliss, Smith et al. 2011, Kurzrock, Voorhees et al. 2013). A small trial with the novel broad-spectrum immune modulator drug OHR118, which targets both TNF-α and IL-6, indicated improvement in appetite and stabilization of body weight (Chasen, Hirschman et al. 2011). In

contrast, the TNF-inhibitor etanercept did not impove appetite or weight gain in another trial; both trials assessed patients with advanced cancer (Jatoi, Dakhil et al. 2007).

One trial that administered a TNF-α antibody to patients with advanced cancer (Tookman, Jones et al. 2008) and two trials that co-administrated a TNF-α or IL-6 - cytokine antagonists with cancer therapy (Nishimoto, Kanakura et al. 2005, Monk, Phillips et al. 2006) all showed less fatigue in the intervention groups. Finally, recombinant IL-1ra has alleviated fatigue in rheumatoid arthritis and Sjogren's syndrome (Omdal and Gunnarsson 2005, Norheim, Harboe et al. 2012).

These findings represent in general small phase I or phase II trials; however, they do support the observations in our trial that main pro-inflammatory cytokines IL-1, IL-6, and TNF-α are related to cancer related fatigue and loss of appetite. There are an increasing number of specific inhibitors available. One example is recombinant IL-1ra (anakinra). A study is underway assessing recombinant IL-1ra for chronic fatigue syndrome (Roerink, Knoop et al. 2015). Trials testing specific inhibitors for symptom control or symptom prevention are now warranted. These will also give us important insight in the pathophysiology of inflammation and symptom genesis.

In addition to corticosteroids, other drugs that can ameliorate inflammation include non-steroidal anti-inflammatory drugs (NSAIDs), statins, methotrexate, IL-6 blockade and JAK/STAT blockade (Roxburgh and McMillan 2016). Many cellular responses to circulating IL-6 are regulated by the Janus Activated Kinase / Signal Transducer and Activator of Transcription (JAK/STAT) signal transduction pathway. The recent report of significantly improved overall survival and clinical benefit in patients receiving chemotherapy with capacitabine plus JAK1/JAK2 inhibitor ruxolitinib compared to capacitabine alone is interesting in this regard. Only patients with signs of systemic inflammation, i.e. CRP above study population median, showed this improvement. Whether this could be a result of a direct effect on the tumour or potentially a result from a modified host response to the tumour, is not clear (Hurwitz, Uppal et al. 2015).

Are the corticosteroid responses on pain, appetite, or fatigue associated with specific inflammatory biomarkers?

There were no significant associations between biomarkers at baseline and improvement in anorexia, fatigue or pain after corticosteroid therapy (Paper IV).

The ”Corticosteroids for pain” RCT in this thesis did not find evidence of an analgesic effect of corticosteroids on cancer pain. Nevertheless, there may be subgroups with better analgesic response to corticosteroids. As described in Paper IV, there are arguments that serum MCP-1 may be a biomarker of improvement in pain intensity after corticosteroid treatment. However, the association was not significant when allowing for multiple comparisons. MCP-1 is a candidate biomarker for analgesic effect from anti-inflammatory treatment, which should be explored in a larger trial.

Two reports from an observational study examinated predictive factors for response to treatment with corticosteroids on cancer related fatigue or anorexia (Matsuo, Morita et al. 2016, Matsuo, Morita et al. 2016). They found the factors high baseline symptom intensity, Palliative Performance Scale > 40, and absence of drowsiness to be associated with increased response to corticosteroids (Odds ratio, OR= 2.2 – 6.6). The Palliative Performance Scale (PPS) (0–100) is a modification of KPS that include the items ambulation, activity, evidence of disease, self-care, intake, and level of consciousness (Anderson, Downing et al. 1996). PPS=40 indicates that the patient is mainly in bed, mainly needing self-care assistance. Performance status was not associated with response to corticosteroids for appetite, fatigue or pain in the present RCT (data not shown).

5.2 Methodological considerations

5.2.1 Study design

Systematic reviews (Paper I) and meta-analyses limit bias and provide reliable and accurate conclusions if performed adequately (Greenhalgh 1997). However, bias can also be encountered in systematic reviews. A tool is developed to facilitate the assessment of quality and risk of bias in systematic reviews, for instance for authors of guidelines (Whiting, Savovic et al. 2016). Study identification is one example of source of bias. The search methods may fail to identify relevant publications, as do the hand search method. The restriction to only include English language RCTs in our review can make the scope of the review narrower. Observational studies can for instance provide evidence for more rare serious adverse events (Guyatt, Oxman et al. 2011). Finally, we did not prepare a protocol for our systematic review; this would have been useful.

Some important methodological issues were identified in the systematic literature review (Paper I). Examples include studies that assessed many outcomes and, more importantly, outcomes that were not reported in the publication. Two publications did for instance not report pain intensity at all (Della Cuna, Pellegrini et al. 1989, Popiela, Lucchi et al. 1989). Only two of the six identified papers reported analgesic consumption (Bruera, Roca et al. 1985, Mercadante, Berchovich et al. 2007). We did not request supplementary data from the authors, which might have increased available data.

Cross-sectional studies provide information concerning descriptive data. Examples include prevalence data, for instance assessing the use of certain drugs in a cohort of patients (Paper II). These studies are easy to perform and can include large samples. Many outcomes, risk factors and associations can be assessed in a cross-sectional study. These studies are not subject to loss to follow-up, which may be a problem in longitudinal studies. However, causal inferences are difficult to make from a cross-sectional study. The one time-point design gives no indication of the sequence of events, for instance whether the exposure occurred before the outcome (Levin 2006).

A number of centres participated in the EPOS study, but in many cases only one centre per country. This means that the differences observed may be diffences in prescription patterns

between centres rather than between countries. Furthermore, the centres that actively participate in such research projects may not be representative for the rest of the centres in their country.

The randomized, placebo-controlled, double blinded trial design (Paper III) is the gold standard for intervention trials, with the ability to make causal inferences and provide the stongest empirical evidence for a treatment's efficacy (Levin 2007). Further, biases like allocation bias and confounding variables are minimized (Altman and Bland 1999). Hence, the treatment and control groups are equal in all respects apart from the intervention itself, so that any difference in outcome can be attributed to the intervention (Grande and Todd 2000). Strict inclusion criteria might on the other hand select a cohort that is not representative for the patient population.

The RCT design has some practical and ethical challenges in the palliative care population. Patients' limited survival, reduced performance status, high burden of symptoms and risk of postponing active treatment if allocated to control group are examples of issues of concern. Trials in palliative care are susceptible to attrition (Yennurajalingam, Frisbee-Hume et al. 2013) and missing data, especially the final weeks of life (Jordhoy, Kaasa et al. 1999). However, together with the RCT in this thesis (Paper III), two recent publications excemplify, firstly, that it is possible to undertake RCTs in this patient group. Secondly, despite being adequately powered, they demonstrate neutral findings that fail to support, and thereby question, the use of widespread clinical practice in cancer pain management in palliative care (Hardy, Quinn et al. 2012, Fallon, Hoskin et al. 2016). Indeed, the rigorous RCT-design with control or placebo arm is a key element, as one trial demonstrated a placebo response rate of 27 %.

The exploratory analysis (Paper IV) was a secondary analysis of the prospective parent trial. Performing multiple analyses in a dataset carries the risk of false positive results, i.e. getting significant results purely by chance. This inherent risk of bias makes these trials suitable for hypothesis-generation, i.e. generating hypotheses for causation or associations that have to be confirmed in other prospective, more rigidly designed trials. Given the limited sample (n=49 at baseline and n=38 at follow-up), there is also a risk of false negatives, i.e. differences or effects that could have been detected if the sample was larger.

The fact that Papers II and IV are post-hoc analyses implies some limitations. Some examples include: the indications for the prescriptions of corticosteroids were not recorded in the database, which is a disadvantage as corticosteroids hold a number of indications in oncology and palliative care (Paper II). Similarly, the judgement of unnecessary drugs would have been easier if it was performed prospectively at inclusion (Paper II). Finally, the cytokine analysis in Paper IV was planned after the trial was finalized. Unfortunately, we did not obtain a second blood sample after the intervention period, which would have given important information about changes in cytokine concentrations following corticosteroid treatment. Pre-planned cytokine analyses would also imply a specific time of venipuncture (morning) and a more rigid procedure for handling of blood samples (de Jager, Bourcier et al. 2009).

5.2.2 Patient-related outcome measures

Patient-related outcomes measures (PROMs) are defined as "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else" (FDA 2009).

When chosing assessment tools for research, it is important to use widely recognized instruments with sufficient psychometric properties to ensure comparability across studies and across patient populations (Kaasa, Apolone et al. 2011). The term validity describes the appropriateness or usefulness of the tool and that the tool really measures what it intends to measure (Pickering 2002, Jensen 2003). Reliability is a term used to describe whether a score is free from measurement errors, and that the tool gives the same results when used repeatedly (Pickering 2002, Jensen 2003). Some methodological issues to consider when choosing an assessment tool for research are the ability to detect clinically relevant differences between patients and over time (Osoba, Zee et al. 1994), if the tool is formally validated in the appropriate population (Kaasa, Bjordal et al. 1995), and whether reference data from the general population are available (Hjermstad, Fayers et al. 1998).

Valid and reliable assessment of pain is essential in clinical trials assessing the efficacy of analgesic interventions (Jensen 03, Kaasa 08). There is no consensus on how to assess pain in patients with cancer. A large number of pain assessment tools are identified in palliative care

(Holen, Hjermstad et al. 2006) and this diversity inhibits comparability across studies (Kaasa and Loge 2003, Kirkova, Davis et al. 2006, Hjermstad, Gibbins et al. 2008).

In the systematic review (Paper I), the included trials did not report whether the assessment tools used were validated. In the randomized trial (Paper III), the BPI (Klepstad, Loge et al. 2002) and EORTC tools (Kaasa, Bjordal et al. 1995) are formally tested in patients with advanced cancer. The "overall satisfaction with treatment" item was generated for this study and was not validated. It read "How do you judge your overall benefit from the study medication" (NRS 0-10) with anchors "no benefit" – "very large benefit". General measures for treatment satisfaction are developed for patients with chronic diseases, such as the Treatment Satisfaction Questionnaire for Medication (TSQM)-tool (Atkinson, Sinha et al. 2004). However, apart from a few exceptions (Taylor 2013), this tool has not been applied in symptom intervention trials in cancer patients.

Self-reporting is preferably performed in the same setting throughout a study, for instance either at home or at the outpatient clinic, and by the same self-administration mode, for example assessments scored by the patients by themselves or under supervision by study personnel. In the RCT in this thesis, the assessment tools patients filled in at home showed more missing data than those scored at the outpatient clinic overseen by a study nurse. Assessments supervised by study personnel may on the other hand create social desirability bias, i.e. the tendency of the respondent to answer questions in a manner that will be viewed favorably by others.

Average pain intensity last 24 hours is recommended as the standard for the classification systems for cancer pain (Kaasa, Apolone et al. 2011). The average pain item in the Brief Pain Inventory (short form) (BPI) was the primary outcome in the randomized trial (Paper III). The tool has a recall period of 24 hours.

5.2.3 Missing data

In the randomized trial (Paper III), there were no missing data for the main outcome average pain intensity (BPI) and hence no procedure for missing data was needed. In the daily ESAS assessment (diary), five values for the "pain at rest" item were missing. These missing data

were imputed using the “last observation carried forward” technique. Except for these, missing data were classified as “missing”, and values not included in the analyses.

5.2.4 Recruitment

Recruitment in palliative care trials can be challenging (Rinck, van den Bos et al. 1997, Stone, Gwilliam et al. 2013). A recent paper points out five major barriers for recruitment: difficulties in locating eligible patients, the severity of illness, family and health care provider protectiveness (i.e. gatekeeping), seeking patients in different clinical settings, and lack of resources (Hanson, Bull et al. 2014).

The present RCT was deliberately set up with strict inclusion and exclusion criteria to secure a proper evaluation of the study drug. As an example, patients had to be without corticosteroids for at least 4 weeks prior to inclusion. If the trial had been performed in a more pragmatic way, an uncertainty would have been left in that the possible effect of the study drug could had been flawed by patients already using a low dose of corticosteroids.

The rigid inclusion and exclusion criteria made recruitment challenging. The recruitment period lasted for almost four years and the number of screened patients was substantial (n=592). Patients already receiving corticosteroids and patients receiving cancer treatment accounted for two thirds of patients meeting exclusion criteria. We did not perform prescreening, which could for instance exclude patients on chemotherapy or using corticosteroids. This would have given a substantially lower number of patients screened. However, we chose to report all patients initially screened, which we think is the most proper way to report the screening procedure.

Moreover, the way authors report “numbers of screened” does not seem to be uniform. This is exemplified by two RCTs where 62-90 % of assessed patients were randomized. Number of patients “not eligible” due to the use of corticosteroids was not reported. Considering the frequent use of these drugs, this is a surprising observation (Yennurajalingam, Frisbee-Hume et al. 2013, Eguchi, Honda et al. 2015). Such a practice could reduce the transparency of the reporting.

Only 13 of the screened patients declined to participate in our RCT. This willingness for palliative care patients to participate in trials was also reported in an Australian study

(Eastman, Le et al. 2015). This is in contrast to data from the UK, where only half of the assessed patients consented to participate in a study. Moreover, less than one tenth of patients admitted to the relevant units were recruited to this particular, carefully planned, non-interventional study with rather simple assessments (Stone, Gwilliam et al. 2013). This exemplifies that high number of screened patients apply to many palliative care trials. This can also cause slow recruitment. In an RCT investigating pregabalin for bone pain in conjunction with radiotherapy (Fallon, Hoskin et al. 2016), one in eight of screened patients consented, and the study was stopped early due to slow recruitment. Another RCT investigating corticosteroids for fatigue in palliative care cancer patients aimed at 40 patients in each group, but was preterminated due to slow accrual despite a multicentre set up with 22 sites (Eguchi, Honda et al. 2015).

The randomized trial was organized as a multicentre study. The numbers of included patients at the five centres were substantially different, with four, four, six, and eleven included patients at the other centres, compared to 25 at our own main site in Skien. This was not associated with the size of the hospital or clinic. This can, however, be a potential source of bias. Due to complex procedures in an intervention trial, quality of the research is vulnerable at sites with few included participants. Despite rigorous training, follow up and monitoring of study sites, this was also observed in our study. For instance, one of the sites had copied one of the questionnaires themselves, only copying the first of the two pages of the assessment tool; another site had no documentation of time and details of blood sampling. Except from this, no importent flaws were identified, and the analysis did not show any centre effects.

5.2.5 Patients

As compared to the prevalence in the general population, the patient cohort in the RCT (Paper III) had fewer patients with breast cancer, and higher number of patients with gynaecologic and lung cancers. Baseline characteristics were in general equally distributed between the intervention group and the control group. However, differences were observed between the groups for pain category (soft tissue pain and neuropathic pain), use of anticonvulsant adjuvant analgesics, opioid level at baseline (n.s.), pain intensity, and EORTC variables appetite, and fatigue (n.s.). However, regression analyses adjusting for these

differences in baseline characteristics did not change the results. Small sample size and stratification might have accounted for the observed differences (See 5.2.8).

Patients used a high average dose of opioids [median 135 mg/day, mean 230 mg/day (95 % CI 165-296)]. Together with the fact that only one patient in the RCT used methadone, this was quoted to be dissimilar to the opioid consumption in the American population, which was claimed to be 60 mg morphine (Cleary 2014). However, our data correspond to the European data, as demonstrated in the EPOS study (Paper II) in which the mean opioid dose was 230.0 ± 456.7 (SD) mg/d oral morphine equivalents (Table 8).

Some aspects should be mentioned regarding the external validity of the data. We did not include patients with pain intensity ≥ 8, i.e. we did not include patients in a pain crisis. Given the intervention period of one week, one would expect a high number of patient withdrawals in this subgroup. Besides, to our knowledge, the ethics committees in Norway would probably not have allowed us to include these patients due to concerns of patients being undertreated for severe pain for seven days.

5.2.6 Power considerations

The sample size of the RCT (Paper III) was based on sample size estimation with a clinical difference of interest (pain intensity) of 1.5 (NRS 0-10), giving a trial size of 44 participants, 22 per arm. The trial included and evaluated the required number of patients.

The trial did not show any analgesic effect of corticosteroids. From a theoretical point of view, one could suspect the non-significant result to be caused by a small sample effect, i.e. the study being underpowered (type II-error). As measured by change from baseline, the difference between the groups was - 0.48 (95 % CI: -1.43 – 0.47) in favour of the corticosteroid group (p= .50). After corrections for differences in opioid consumption at baseline, this difference was: -0.33 (-1.33 – 0.67) in favour of corticosteroids. The clinical difference of interest is above the upper bound of both 95 % confidence intervals, which confirms that a clinically useful effect is unlikely. Moreover, the results were consistent for all the pain outcomes, i.e. pain at rest (ESAS, NRS 0-10) measured day 1-7 (area under the curve), analgesic consumption, and when reported on a responder/non-responder-basis (data not shown).

Nevertheless, the sample size is small, which is reflected by the wide 95 % confidence limits. A small sample is by the size itself is more susceptible to selection bias, i.e. systematic differences between the study sample and those who are excluded or do not participate, making the study sample unrepresentative for the population. The Cochrane review on corticosteroids for the management of cancer-related pain rated RCTs with less than 50 participants as having "high risk of bias", 50-200 participants "unclear risk of bias", and more than 200 participants per arm as "low risk of bias" (Haywood, Good et al. 2015). Finally, the sample size in the trial in this thesis was also too small for subgroup analysis.

5.2.7 Effect size - judging of point estimates

The statistical significance in a trial informs about the probability that observed results, for instance differences between two groups, are due to chance. However, it will not reveal the size of the effect. Furthermore, statistical significance is linked to sample size. Given a large enough sample, statistical significance between groups may occur with very small differences that are clinically meaningless (McGlothlin and Lewis 2014).

When assessing subjective measures, PROMs, it is therefore important to judge whether the observed change is meaningful to the patients. The smallest benefit of value to patients is termed the minimal clinically important difference (MCID) (McGlothlin and Lewis 2014). MCID can be derived by anchor-based methods, i.e. asking the patient if they felt "about the same", "a little bit better", or "quite a bit better" after receiving treatment. These responses are then related to the numeric measurement scale used in the study. This method was applied for the EORTC QLQ-C30 (0-100), which determined that the scores could be interpreted as a "little change" for mean change in scores of about 5-10, "moderate change" for 10-20 and "very much change" for scores greater than 20 (Osoba, Rodrigues et al. 1998). If the instrument used does not have an intrinsic meaning to clinicians, or MCID is not determined, observed difference could be reported as effect size, i.e. a standardized difference between the groups (Cohen's *d)*. This is calculated by dividing the actual difference between the groups by either of the groups' standard deviation, SD, i.e. the variability of the actual outcome. Cohen (Cohen 1992) classified effect sizes as *small* (d = 0.2), *medium* (d = 0.5), and *large* ($d \geq 0.8$) (Table 9). This is also supported by a systematic review that observed that the threshold of discrimination for changes in health related

quality of life for chronic diseases appears to be approximately half a SD (Norman, Sloan et al. 2003).

As an example, the trial assessing dexamethasone for fatigue in patients with advanced cancer reported reduced fatigue in favour of the corticosteroid group of 5.9 points (SD 9.59) (p= .008) on the FACIT-F subscale (0-52) (Yennurajalingam, Frisbee-Hume et al. 2013). The calculated effect size is 0.62. As the calculated effect size is a standardized measure, it can be used to quantitatively compare results from different studies using different outcome scales as for instance in meta-analyses (Sullivan and Feinn 2012).

Finally, when judging correlations, the Pearson's r correlation and explained variability (r^2) are recommended. The first measures the degree of linear relationship between two quantitative variables, and the latter indicates which percentage of the variability in the outcome measure that can be explained by the other (Sullivan and Feinn 2012).

Effect sizes are statistical estimates. The suggested effect sizes are not a guarantee that effect sizes larger than "small" (Table 9) have practically significance. Effect sizes are in general resistant to sample size influences (Ferguson 2009).

Index	**Effect size**	**Comment**
Cohen's *d*	Small 0.2 Medium 0.5 Large 0.8 Very large 1.3	
Odds ratio	Small 1.5 medium 2 Large 3	
Relative Risk / Risk ratio (RR)	Small 2 Medium 3 Large 4	
Pearson's correlation	Small ± 0.2 Medium ± 0.5 Large ± 0.8	Range -1 to 1
R^2 coefficient for determination	Small 0.04 Medium 0.25 Large 0.64	Range 0-1 Proportion of variance in one variable explained by the other

Table 9: *Common Effect Size Indices (Adapted from (Sullivan and Feinn 2012)*

5.2.8 Randomization and blinding

Stratification is important to avoid bias from apparent major differences in the study groups. In the randomization procedure, patients were stratified on the basis of study centre and the presence of bone metastases, which could be suspected to have higher response rates to corticosteroids. Stratification together with the limited number of patients may have caused the differences in baseline characteristics observed between the study groups (see 5.2.5).

As a curiosity, the patients and physicians were asked at evaluation day 7 whether they thought the patient had received active medication during the study period or not (yes / no / I don't know). The physicians could significantly predict if patients had received corticosteroids (p= .003). In contrast, the patients could not predict which drug they received (Table 10, data not reported). A similar observation was made in another double blinded placebo-controlled trial with corticosteroids (Twycross and Guppy 1985).

	Patients			**Physicians**		
"Did receive active medication?"	Yes	No / Don't know	Sign	Yes	No / Don't know	Sign
Corticosteroid	6	18	p = .92	14	11	p = .003
Placebo	5	16		3	19	

Table 10: *Patients' and physicians' prediction of study medication. Data from Paper III (not published) (Chi-square test)*

5.2.9 Intervention

Methylprednisolone was chosen as interventional drug in the RCT (Paper III). Methyl-prednisolone is the most frequently used corticosteroid in cancer management in Norway (Paper II), and methylprednisolone has shown analgesic effects in an earlier trial in patients with advanced cancer (Bruera, Roca et al. 1985). The characteristics of the corticosteroids differ, including their pharmacokinetic properties and anti-inflammatory potency (Gilman 2006). As dexamethasone is a widely used corticosteroid in cancer and palliative care internationally, and the most used corticosteroid in the EPOS cohort, this could have been an alternative choice of interventional drug.

The dose of the interventional drug was chosen to be as high as deemed tolerable in this situation. Methylprednisolone 16 mg twice daily is approximately half the dose of

corticosteroids given in emergency situations such as malignant spinal cord compression (Schmidt, Klimo et al. 2005), and the same dose used in the study showing effect in cancer pain (Bruera, Roca et al. 1985). The drug was deliberately dosed twice daily to ensure credibility of the trial, especially as this reflects normal US practice (personal communication, Professor Eduardo Bruera).

As our RCT recruited patients with advanced malignant disease, we chose a short intervention period of seven days. The intervention period was observed sufficient in an earlier study with same drug and dose: all patients that responded did so within the first five days of the trial (Bruera, Roca et al. 1985). The significant effect on appetite, fatigue, and patient satisfaction in the "Corticosteroids for pain" trial supports that the duration of the intervention period could be regarded as sufficient. Other data also support that the effects of corticosteroids appear within 2-3 days (Greenberg, Kim et al. 1980, Mercadante, Fulfaro et al. 2001, Lundstrom, Furst et al. 2009, Matsuo, Morita et al. 2016). Daily records indicate that the corticosteroid response came within 2-4 days in our trial (Figure 11, data not published). Both groups achieved an increase of 20 % in analgesic consumption during the intervention period.

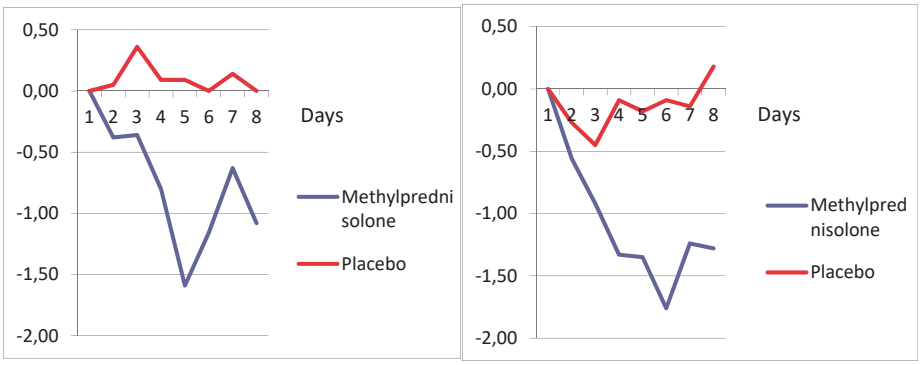

Figure 11: *Difference (mean) in fatigue (left figure) and loss of appetite (right figure); symptom intensity reported as change from baseline (left axis, ESAS NRS 0-10). Data from Paper III (not published)*

A short intervention period was favourable in two other aspects. Firstly, to optimize recruitment, as palliative care patients prefer a short intervention period when they consider to participate in trials (Middlemiss, Lloyd-Williams et al. 2015). Secondly, it helped to ensure a low attrition rate.

Attrition is a problem in randomized trials (Hewitt, Kumaravel et al. 2010). This may bias the estimates of the treatment effect, reduce the statistical power, and restrict the generalizability of the results. Attrition is also a problem in palliative care research. A review of 18 palliative care clinical trials at an American centre showed attrition rates of 26 % for the primary endpoint and 44 % for end of the study (Hui, Glitza et al. 2013), both were significantly associated with study duration. Morbidity is a major cause of attrition; in the present RCT one patient discontinued the study drug due to disease progression (Paper III). Mortality is a another concern; one patient died during the intervention period, another five died within 28 days of enrollment in the present RCT (data not published), similar to data from Australia (Eastman, Le et al. 2015). Other palliative care trials have reported attrition rates of 13-36 % (Oldervoll, Loge et al. 2011, Yennurajalingam, Frisbee-Hume et al. 2013, Chow, Meyer et al. 2015, Fallon, Hoskin et al. 2016). Compared to this, low attrition was an important strength of our "Corticosteroids for Cancer Pain" trial.

5.2.10 Recording of adverse events

Adverse events were recorded at day 7 by the investigator on a "yes" or "no" basis: presence of oral symptoms, restlessness, psychic change, anxiety, oedema, muscle weakness, sleeplessness, dyspepsia, or other. Firstly, this was not a validated way to record adverse effects. Secondly, the same data should also have been recorded at baseline. Setting up the study today, we would have used a standardized form, like the National Cancer Institute Common Toxicity Criteria, which also grades adverse effects according to seriousness (Institute 2010).

Observer reporting is important, as clinicians capture corticosteroid toxicities which may not be obvious to the patients (Agar, Koh et al. 2016). In addition to these observer-reported adverse effects, self-report measures can be applied. The symptom assessments performed in the trial will also reflect side effects, for instance the sleep and anxiety items in the ESAS questionnaire. Also, assessment scales like the Dexamethasone Symptom Questionnaire (DSQ) have been developed for this purpose (Vardy, Chiew et al. 2006). The DSQ captures adverse events of dexamethasone on a four-point Likert scale (1=not at all, 4 = very much), including nine items: insomnia, gastro-oesorphagaeal reflux, agitation, increased appetite,

weight gain, acne, hiccups, oral candida, and depression, and has been used with success in intervention trials in palliative care patients (Chow, Meyer et al. 2015).

Finally, serious adverse events (SAEs) were reported according to good clinical practice and international guidelines.

5.2.11 Laboratory analyses

Exploratory cytokine analyses were performed in Paper IV. The cytokine analyses were planned after the trial was finalized and, unfortunately, a second blood sample after the intervention period was not obtained. This would have given important information about changes in cytokine serum concentrations following corticosteroid treatment.

Robust data have shown an association between a number of diseases and serum concentrations of cytokines. In addition to inflammatory diseases like reumathoid arthritis where they also are correlated to disease activity (Kass, Lea et al. 2010), examples include associations with depression (Howren, Lamkin et al. 2009) and advanced cancer (Lippitz 2013). Data indicate that serum cytokine biomarker panels can discriminate between malignant and benign disease, for instance in pancreatic cancer (Shaw, Lane et al. 2014).

The serum cytokine concentration analyses may have some limitations. Many of the cytokines show diurnal variation, particularly those influenced by cortisol, for instance interferon-γ, TNF-α, IL-1, and IL-12 (Zhou, Fragala et al. 2010). It is therefore recommended to standardize time of sampling, ideally to the morning to attenuate the influence of circadian patterns (Zhou, Fragala et al. 2010). In our study, no recommendation for time for blood sampling was given, but 27 out of 38 samples were collected between 12 noon and 4 p.m.

The sera underwent two freeze-thaw cycles. It is generally recommended to avoid freeze-thaw cycles, as they can alter cytokine concentrations (Flower, Ahuja et al. 2000, de Jager, Bourcier et al. 2009).

Various cytokines have different stabilities during storage. Although most cytokines are stable for 2-3 years at -80˚C, IL-1β, IL-6, and IL-10 are degraded up to 50 % (de Jager, Bourcier et al. 2009). Other data have shown increased variability for CRP and IL-6 in contrast to stable sTNF-receptor concentrations during long-time storage for over 13 years

(Hardikar, Song et al. 2014). Blood samples were stored for 3-7 years in a -80˚C freezer until analysis. The serum concentrations of cytokines in our trial (Paper IV) were not associated with time since blood sample collection (data not published).

Finally, the ELISA method assesses one cytokine at a time, allowing for all conditions to be optimalized. The multiplex technology assesses many cytokines at the same time in the same well, thus trade offs in the conditions for each of the analytes have to be made. Concentrations of some of the cytokines that were below "lower limit of quantification" could probably have been within the standard curve if their individual conditions had been optimalized, for instance regarding dilution of the samples.

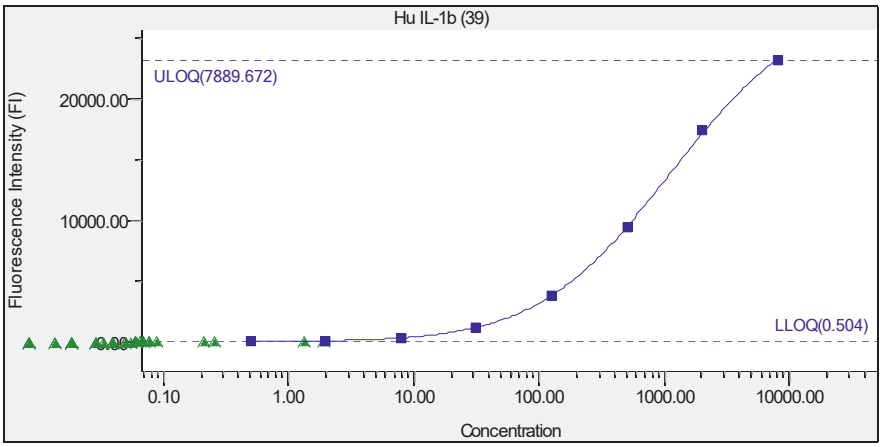

Figure 12: *Concentrations of IL-1β (green) and the standard curve (blue). Data from Paper IV.*

5.2.12 Ethical considerations in palliative care research

Ethical concerns have been raised about the appropriateness of research in the palliative care patient group. Arguments have been cited, e.g. that the goals of research conflict with the goals of care; research is a burden on vulnerable patients and families/caregivers; there is no need for further research in this topic (no need to further investigate which intervention is better); and research in the palliative care setting is too difficult (LeBlanc, Wheeler et al. 2010). These attitudes are reflected in the issue of "gate-keeping", i.e. health personnel actively or passively hindering the patients in participating in research trials (Eguchi, Honda et al. 2015). One reason for gatekeeping is the staff's fear that the research

would cause patient distress (Stone, Gwilliam et al. 2013). Studies suggest that strategies to overcome gatekeeping include study design; studies should be relevant, quick and easy to do and not too demanding on patients (Jordhoy, Kaasa et al. 1999, Stone, Gwilliam et al. 2013).

From the patients' perspectives, studies have indicated that feeling unwell, having multiple symptoms, and having advanced disease stage are some of the concerns that can make patients refuse participation in a research study (Stone, Gwilliam et al. 2013). Despite these concerns, there is evidence that palliative care patients are interested in participating in clinical research even when faced with a poor prognosis (Eastman, Le et al. 2015, Middlemiss, Lloyd-Williams et al. 2015).

The Belmont Report defined three core principles for ethical conduct of clinical research: respect, beneficence and justice (Ryan 1979). Allthough the palliative care patient group is especially vulnerable, these ethical principles are equally important in all kinds of research (Casarett, Knebel et al. 2003). Five ethical aspects of palliative care research have been emphasized (Casarett 2015):

1. Benefits to patients included: In a qualitative trial, patients main motivation for participation in research was the possibility to gain improvement from the study drug (Figure 13) (Middlemiss, Lloyd-Williams et al. 2015). This is in agreement with our own experiences in the RCT (Paper III) where patients regularly described a hope to gain better pain control as a motivation for participation. Further, the report also described that the patients had a general positive experience with the research trial, giving them potentially improved overall wellbeing despite being in a control group. The close attention from competent health personnel is probably one reason for this (Middlemiss, Lloyd-Williams et al. 2015).

2. Benefits to future patients: Altruism, i.e. the hope to gain benefit for future patients, was commonly expressed by patients included in research trials (Figure 13) (Middlemiss, Lloyd-Williams et al. 2015). The patients in our RCT also frequently expressed this attitude.

This commits and challenges us as researchers to perform high-quality research that ensures validity and value for future patients. Unfortunately, poor methodological quality and lacking validity have been identified in palliative care research (Rinck, van den Bos et al. 1997, Joly, Vardy et al. 2007). Issues like not reporting outcomes, missing sample size calculations, and biased study groups were identified in the systematic review in this thesis (Paper I). It is

unethical to expose seriously ill patients to trials that are unlikely to produce reliable results due to lack of power or sensitivity. A systematic review of controlled trials in cancer pain showed that the majority of trials were underpowered (Bell, Wisloff et al. 2006).

A rigorous trial design with strict inclusion and exclusion criteria may on the other hand make recruitment difficult. It is unethical to recruit to a study that later has to be stopped due to underrecruitment, and therefore is at risk of not reaching sufficient power to make a significant conclusion. The RCT (Paper III) was at such risk, but reached the needed number of patients by extending the recruitment period.

3. Minimizing patients' risks and burdens: To minimize interventions and assessments and to keep the intervention period short are important issues to minimize patients´ risks and burdens (Jordhoy, Kaasa et al. 1999, Mularski, Rosenfeld et al. 2007). This is also expressed by the patients themselves, who tend to avoid studies with too excessive trial demands, with perceived possible side effects, or with a lengthy trial period (Figure 13) (Middlemiss, Lloyd-Williams et al. 2015). Some of these factors were a concern in two of the trials identified in Paper I, due to the extended intervention periods of 8 weeks, and to patients receiving intravenously administered corticosteroids that might prevent them from being discharged from the hospital (Della Cuna, Pellegrini et al. 1989, Popiela, Lucchi et al. 1989).

In the RCT in this thesis (Paper III), patients in a pain crisis [pain ≥ 8 (NRS 0-10)] were excluded to minimize risk and burden.

Using a control arm has been debated as this puts some of the patients under study at risk of postponing efficient symptom control. Furthermore, research indicates that patients are less willing to participate in studies involving randomization for fear of drawing the dummy arm (Stone, Gwilliam et al. 2013).

Nevertheless, randomization and blinding are very important parts of a rigorously performed intervention study. If one of the aspects is missing, the risk of exaggeration of treatment effect can be as much as 17-40 % (Schulz, Chalmers et al. 1995, Carroll, Tramer et al. 1996). This is especially important in pain studies, as pain is a subjective symptom. Furthermore, the experience of pain arises from both physiological and psychological factors. Patients' expectations of pain have been shown to alter analgesia and the effect of opioids (Wager, Rilling et al. 2004, Bingel, Wanigasekera et al. 2011). Accordingly, a placebo control design is

recommended in pain trials (Bell, Wisloff et al. 2006). A control group is also needed because the symptoms in palliative care patients will be progressing in prospective studies (Bruera, Roca et al. 1985).

4. Ensure decision making capacity: Cognitive impairment is frequent in the palliative care population (Pereira, Hanson et al. 1997). Likewise, severe symptoms may also interfere with the decision-making capacity (Kristjanson Hanson 1994). In the RCT in this thesis (Paper III), decision-making capacity was an explicit inclusion criterion, and cognitive function was assessed at baseline and at evaluation day 7.

5. Protecting voluntariness: An important ethical principle is that patients enter a trial voluntarily. An honest discussion about the benefits and burdens of participation in the study should be conveyed and understood by the patient (American Academy of Hospice and Palliative Medicine 2014). Researchers need to be sensitive to the patient's situation, and some patients are afraid that participation will alter their relationship with their physician (Stone, Gwilliam et al. 2013). This is especially important when the research consultant also is responsible for patient care, like the situation was at most centres in the present RCT (Paper III).

Informed consent in this population may be a process rather than a one-time discussion (American Academy of Hospice and Palliative Medicine 2014). Data indicate that patients feel they need more time to consider participation (Ling, Rees et al. 2000). It is also of crucial

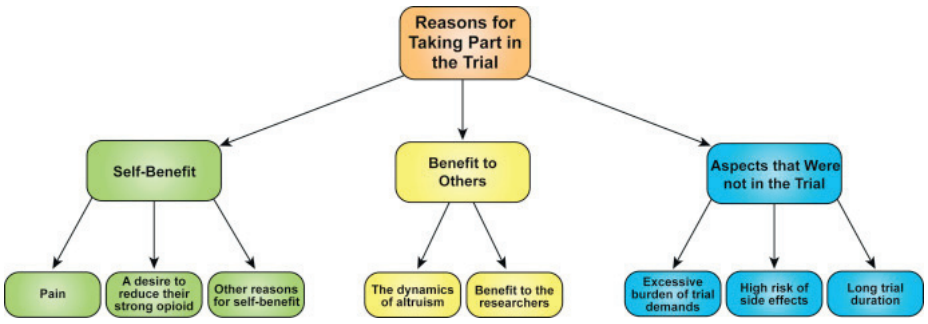

Figure 13: *Reason for trial participation. This figure illustrates the wide range of reasons why participants wanted to take part in a clinical trial. Participants might have several of the reasons outlined. The reasons were grouped into self-benefit, benefits to others, and aspects that were not in the trial (Middlemiss, Lloyd-Williams et al. 2015). (Used with permission)*

importance that patients feel confident that they will receive the same good quality care if not participating in the research trial.

To perform high quality research in the palliative care population is challenging. However, there is a need for rigorously performed trials to increase the evidence base of palliative medicine (Bell, Wisloff et al. 2006, Twycross 2009, Fallon, Hoskin et al. 2016). We have an ethical responsibility towards our profession and our patients to conduct high quality research that informs therapeutic decisions. Only when our clinical decisions are based on solid research evidence, we can be sure that we are providing our patients beneficient and just care that optimizes quality of life, even at the end of life.

The need of high quality research has been recognized by the palliative care associations, and the start of the Position Statement of the American Academy of Hospice and Palliative Medicine on research in palliative care patients reads: “Patients who receive palliative care should be considered for participation in clinical studies, regardless of where they are in the disease trajectory” (American Academy of Hospice and Palliative Medicine 2014).

6 Conclusions

1. What is the evidence in the literature that corticosteroids improve analgesia in adult patients with pain caused by cancer?

    - A moderate dose of corticosteroids may contribute to analgesia and seemed to be well tolerated. Due to the lack of high quality studies, the level of evidence was graded ”low”.

2. How frequently are corticosteroids and non-opioid analgesics used in a cohort of European cancer patients using opioids?

    - Corticosteroids and non-opioid analgesics were frequently used in advanced cancer patients using opioids. Across the centres, there were large differences in prescription patterns, drugs of choice, and doses for corticosteroids, non-opioid analgesics and co-analgesic drugs.

    - Patients in this European cohort with cancer treated with WHO step III opioids used a high number of drugs. Many patients received unnecessary medications and were at risk for serious drug-drug-interactions. These findings demonstrate that drug therapy needs to be frequently evaluated in this patient group.

3. What is the analgesic efficacy of corticosteroids in patients with cancer related pain using opioid analgesics?

    - Methylprednisolone 32 mg daily did not improve pain or decrease analgesic consumption as compared to placebo in cancer patients using opioids. Corticosteroids were well tolerated when used for seven days.

4. Do corticosteroids improve appetite and fatigue in cancer patients using opioids?

- Methylprednisolone 32 mg daily was significantly better than placebo in improving appetite and fatigue in patients with metastatic cancer disease.

5. Are inflammatory biomarkers associated with pain, loss of appetite and fatigue in cancer patients with advanced disease?

   - Loss of appetite and fatigue were correlated to the inflammatory biomarkers CRP and IL-6, and IL-1ra, respectively, in this cohort of cancer patients with metastatic disease.

   Are the corticosteroid responses on pain, appetite or fatigue in cancer patients associated with specific inflammatory biomarkers?

   - There was no significant association between serum concentrations of inflammatory biomarkers and response to corticosteroids on pain, appetite and fatigue in this cohort of cancer pain patients using opioids.

7 Further perspectives

7.1 Corticosteroids for symptom control

Corticosteroids for cancer pain: The level of evidence for methylprednisolone 32 mg daily as adjuvant analgesics for patients with cancer-related pain is still low due to conflicting data and small trials. There are still unanswered questions: do corticosteroids have analgesic effects in specific subgroups of cancer pain, such as bone pain and neuropathic pain? These questions should be studied in a prospective, randomized trial. The frequent use of corticosteroids in cancer patients may challenge the recruitment to such a study (Paper III). This necessitates an international multicentre RCT design. The European Palliative Care Research Centre (PRC) has taken such an initiative. Due to the risk of attrition (Yennurajalingam, Frisbee-Hume et al. 2013), the intervention period should be kept at one week.

Corticosteroids for cancer related fatigue: Corticosteroids (methylprednisolone 32 mg or dexamethasone 8 mg) have shown a clinically significant effect in cancer related fatigue when prescribed for 7-14 days (Paper III) (Yennurajalingam, Frisbee-Hume et al. 2013). Further studies should investigate whether a lower starting dose of corticosteroid would be equally effective in relieving fatigue, for instance comparing dexamethasone 4 mg versus 8 mg. This should also include once daily administration of corticosteroids, which is not empirically studied.

Corticosteroids' effects and adverse effects in long-term treatment: One major issue concerning the use of corticosteroids is their efficacy in symptom control and adverse effects in long-term use. Adverse effects include myopathy, dyspepsia, infections, diabetes, and psychiatric and behavioral effects. Appetite and fatigue are possible endpoints in such a trial. However, as described in this thesis, attrition will be a problem if a long-term intervention period is applied (Della Cuna, Pellegrini et al. 1989, Popiela, Lucchi et al. 1989). Therefore, a rigidly conducted observational trial is probably the best design for a long-term follow up study in these patients (Geborek, Crnkic et al. 2002). Alternatively, clinical patient registries with unselected patient cohorts can also be used for this purpose. A third option is a randomized open trial comparing long-term treatment with short courses of corticosteroids. The trial should be based upon clinical guidelines.

7.2 Anti-inflammatory medication in symptom control

The effects of corticosteroids on systemic inflammation: Corticosteroids' effects on inflammatory biomarkers have not been established in cancer patients. It is of interest to assess the influence of corticosteroid treatment on serum concentrations of major inflammatory biomarkers such as IL-1β, IL-1ra, IL-6, IL-8, IL-10, IL-18, TNF-α, TGF-β1, MIF, MCP, and sTNF-r1 at baseline and during the first one-two weeks after starting corticosteroid treatment. This could be assessed using an observational longitudinal design in unselected cancer patients starting corticosteroids. HRQoL, fatigue and appetite should be assessed with validated measures at the same time points. As cytokines have a diurnal rhythm, blood sampling should be standardized. Preferably, blood samples should be collected in the morning; alternatively, the follow up samples could be collected at the same time of day as the baseline sample (Bower, Ganz et al. 2009).

Predictors of corticosteroid effects: MCP-1 was suggested as a potential biomarker of treatment effect of corticosteroids on cancer pain (Paper IV). This should be assessed in future studies. Prospective register data can be used for this purpose. The ongoing Palliative Radiotherapy and Inflammation Study (PRAIS) (Klepstad), which includes patients undergoing radiation therapy for bone metastases, assesses biomarkers at baseline and after treatment. The primary aim is to identify clinical and biomarker predictors of pain reduction in response to palliative radiotherapy for cancer induced bone pain. Explorative research questions include predictors of cachexia and depression, and to identify inflammatory biomarkers' association with cancer pain, cachexia and depression.

Other anti-inflammatory drugs: This thesis indicates that not only systemic inflammation in general, but also specific biomarkers like IL-1, IL-6, and TNF-α may drive symptom generation. This may have therapeutic implications. As for today, recombinant IL-1ra (anakinra) is a viable therapeutic option and intervention trials on IL-1ra administration for chronic fatigue syndrome are underway (Roerink, Knoop et al. 2015). Trials targeting inflammation through specific or broad approaches that have quality of life variables as primary end points are now warranted.

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Appendix

Appendix I	The Brief Pain Inventory (BPI)
Appendix II	The European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire C30 (EORTC QLQ-C30)
Appendix III	The Edmonton Symptom Assessment System (ESAS) Screening tool for the RCT (eleven items)
Appendix IV	Mini Mental State Examination (MMSE)
Appendix V	Karnofsky Performance Status (KPS)

The protocol for the randomized controlled trial «Corticosteroids for cancer pain» can be found at:
http://www.ntnu.edu/documents/12821430/0/Corticosteroids+for+cancer+pain_Protocol/17e9dedb-c408-4ebc-9bb0-116b3e90d7d3

Appendix I: The Brief Pain Inventory

11900

Kortikosteroiders effekt på smerte hos kreftpasienter Pasnr: ☐☐☐

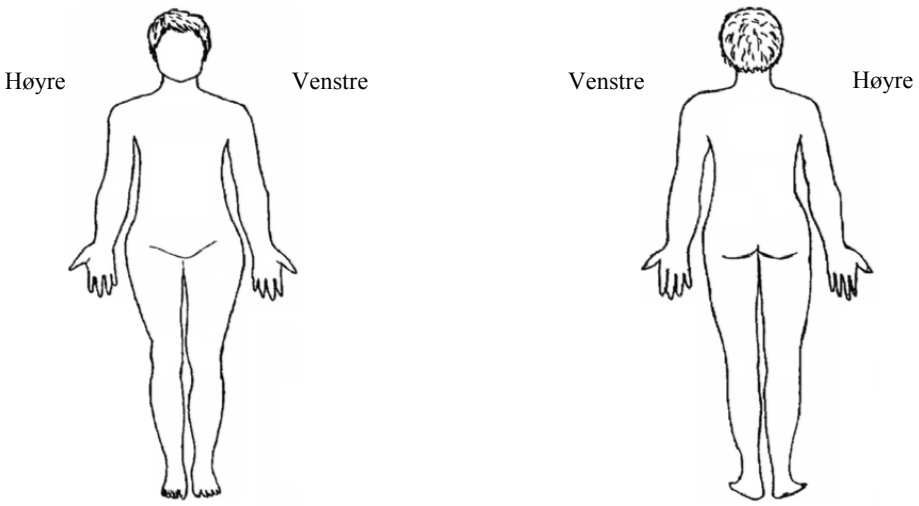
☐ Dag 0 ☐ Dag 7 Dato: ☐☐.☐☐.☐☐☐☐

Brief Pain Inventory

1. Gjennom livet har de fleste av oss hatt smerter (som lett hodepine, forstuelser eller tannpine). Har du i dag smerter av et annet slag enn slike dagligdagse smerter.

   ☐ Ja ☐ Nei

2. Vil du skravere de områdene på kroppen hvor du har smerter. Marker med et kryss der du har mest vondt.



3. Vennligst sett ring rundt det tallet som best beskriver de sterkeste smertene du har hatt i løpet av de siste 24 timer.

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter Verst tenkelige smerter

4. Vennligst sett ring rundt det tallet som best beskriver de svakeste smertene du har hatt i løpet av de siste 24 timer.

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter Verst tenkelige smerter

5. Vennligst sett ring rundt det tallet som best angir hvor sterke smerter du har i gjennomsnitt.

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter Verst tenkelige smerter

6. Vennligst sett ring rundt det tallet som best angir hvor sterke smerter du har akkurat nå.

0 1 2 3 4 5 6 7 8 9 10

Ingen smerter Verst tenkelige smerter

Vennligst snu arket

11900

7. Hvilken behandling eller medisiner får du for å lindre smertene dine?

8. I hvor stor grad har behandling eller medisiner lindret smertene dine de siste 24 timene?
Vennligst sett en ring rundt det prosenttallet som viser hvor stor smertelindring du har fått.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

Ingen lindring **Fullstendig lindring**

Sett en ring rundt det tallet som for de siste 24 timene best beskriver hvor mye smertene har virket inn på:

9. Daglig aktivitet

0 1 2 3 4 5 6 7 8 9 10

Ikke påvirket Fullstendig påvirket

10. Humør

0 1 2 3 4 5 6 7 8 9 10

Ikke påvirket Fullstendig påvirket

11. Evne til å gå

0 1 2 3 4 5 6 7 8 9 10

Ikke påvirket Fullstendig påvirket

12. Vanlig arbeid (gjelder både arbeid utenfor hjemmet og husarbeid)

0 1 2 3 4 5 6 7 8 9 10

Ikke påvirket Fullstendig påvirket

13. Forhold til andre mennesker

0 1 2 3 4 5 6 7 8 9 10

Ikke påvirket Fullstendig påvirket

14. Søvn

0 1 2 3 4 5 6 7 8 9 10

Ikke påvirket Fullstendig påvirket

15. Livsglede

0 1 2 3 4 5 6 7 8 9 10

Ikke påvirket Fullstendig påvirket

Tusen takk for hjelpen!

Appendix II: The European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire C30 (EORTC QLQ-C30)

Kortikosteroiders effekt på smerte hos kreftpasienter Pasnr: ☐☐☐

☐ Dag 0 ☐ Dag 7 ☐ Dag 14 ☐ Dag 21 Dato: ☐☐.☐☐.☐☐☐☐

EORTC QLQ-C30

(Versjon 3.0)

Vi er interessert i forhold vedrørende deg og din helse. Vær så vennlig å besvare hvert spørsmål ved å sette et kryss x i den boksen som best beskriver din tilstand. Det er ingen «riktige» eller «gale» svar. Alle opplysningene vil bli behandlet konfidensielt.

	Ikke i det hele tatt	Litt	En del	Svært mye
1. Har du vanskeligheter med å utføre anstrengende aktiviteter, slik som å bære en tung handlekurv eller en koffert?	☐	☐	☐	☐
2. Har du vanskeligheter med å gå en lang tur?	☐	☐	☐	☐
3. Har du vanskeligheter med å gå en kort tur utendørs?	☐	☐	☐	☐
4. Er du nødt til å ligge til sengs eller sitte i en stol i løpet av dagen?	☐	☐	☐	☐
5. Trenger du hjelp til å spise, kle på deg, vaske deg eller gå på toalettet?	☐	☐	☐	☐

I løpet av den siste uka:	Ikke i det hele tatt	Litt	En del	Svært mye
6. Har du hatt redusert evne til å arbeide eller utføre andre daglige aktiviteter?	☐	☐	☐	☐
7. Har du hatt redusert evne til å utføre dine hobbyer eller andre fritidsaktiviteter?	☐	☐	☐	☐
8. Har du vært tung i pusten?	☐	☐	☐	☐
9. Har du hatt smerter?	☐	☐	☐	☐
10. Har du hatt behov for å hvile?	☐	☐	☐	☐
11. Har du hatt søvnproblemer?	☐	☐	☐	☐
12. Har du følt deg slapp?	☐	☐	☐	☐
13. Har du hatt dårlig matlyst?	☐	☐	☐	☐
14. Har du vært kvalm?	☐	☐	☐	☐

Bla om til neste side

I løpet av den siste uka:	**Ikke i det hele tatt**	**Litt**	**En del**	**Svært mye**
15. Har du kastet opp?	☐	☐	☐	☐
16. Har du hatt treg mage?	☐	☐	☐	☐
17. Har du hatt løs mage?	☐	☐	☐	☐
18. Har du følt deg trett?	☐	☐	☐	☐
19. Har smerter påvirket dine daglige aktiviteter?	☐	☐	☐	☐
20. Har du hatt problemer med å konsentrere deg, f.eks. med å lese en avis eller se på TV?	☐	☐	☐	☐
21. Har du følt deg anspent?	☐	☐	☐	☐
22. Har du vært engstelig?	☐	☐	☐	☐
23. Har du følt deg irritabel?	☐	☐	☐	☐
24. Har du følt deg deprimert?	☐	☐	☐	☐
25. Har du hatt problemer med å huske ting?	☐	☐	☐	☐
26. Har din fysiske tilstand eller medisinske behandling påvirket ditt familieliv?	☐	☐	☐	☐
27. Har din fysiske tilstand eller medisinske behandling påvirket dine sosiale aktiviteter?	☐	☐	☐	☐
28. Har din fysiske tilstand eller medisinske behandling gitt deg økonomiske problemer?	☐	☐	☐	☐

Som svar på de neste spørsmålene, sett et kryss i den boksen fra 1 til 7 som best beskriver din tilstand.

29. Hvordan har din helse vært i løpet av den siste uka?

☐ **1** ☐ **2** ☐ **3** ☐ **4** ☐ **5** ☐ **6** ☐ **7**

Svært dårlig Helt utmerket

30. Hvordan har livskvaliteten din vært i løpet av den siste uka?

☐ **1** ☐ **2** ☐ **3** ☐ **4** ☐ **5** ☐ **6** ☐ **7**

Svært dårlig Helt utmerket

Appendix III: The Edmonton Symptom Assessment System (ESAS) Screening tool for the RCT (eleven items)

Sykehuset Telemark	Pasientidentifikasjon

ESAS **(Edmonton Symptom Assesment System)**	**Utfylt av:……**	**Dato:** **Kl:**

Smerte – i ro	**Ingen**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Verst tenkelig**
Smerte - ved bevegelse	**Ingen**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Verst tenkelig**
Slapphet	**Ingen**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Verst tenkelig**
Kvalme	**Ingen**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Verst tenkelig**
Tungpust	**Ingen**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Verst tenkelig**
Munntørrhet	**Ingen**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Verst tenkelig**
Matlyst	**God**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Svært dårlig**
Angst / Uro	**Ingen**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Verst tenkelig**
Trist / deprimert	**Ingen**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Verst tenkelig**

Alt tatt i betraktning, hvordan har du det i dag?

Bra	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Verst tenkelig**

Gi dette skjema til behandlende lege / sykepleier.
Resultatene overføres til kurve for grafisk ESAS (dette skjema kastes etter bruk)

Appendix IV: Mini Mental State Examination (MMSE)

57274

Kortikosteroiders effekt på smerte hos kreftpasienter Pasnr: ☐☐☐

☐ Dag 0 ☐ Dag 7 Dato: ☐☐.☐☐.☐☐☐☐

Minimental status - MMS		**Skår**	**Maks. skår**
1. ORIENTERING	Hvilket år er det?	☐	1
	Hvilken måned er det?	☐	1
	Hvilken årstid er det?	☐	1
	Hvilken dato er det i dag?	☐	1
	Hvilken dag er det idag?	☐	1
	I hvilket land er vi nå?	☐	1
	I hvilken landsdel er vi nå?	☐	1
	I hvilken by er vi nå?	☐	1
	I hvilket sykehus er vi nå? (Hva er din hjemmeadresse?	☐	1
	I hvilken avdeling er vi nå? (Hvilket postnummer har du?)	☐	1
2. LÆRING Noter antall forsøk ☐	Si 3 ord. Bruk 1 sekund til å uttale hvert ord. OST - SYKKEL - BOK. Be pasienten gjenta alle 3 ordene. Gjenta ordene, inntil pasienten har lært dem, og kan huske dem	☐	3
3. ABSTRAKT TENKNING	Stav ordet SVERD baklengs. Ett poeng for hver riktig bokstav sagt i den rette rekkefølge. Alternativt: Start med tallet 100. Trekk fra 7, rekk fra 7 igjen, og fortsett subtraksjonen i alt 5 ganger.	☐	5
4. KORTTID HUKOMMELSE	Kan du si meg de ordene du skulle huske for litt siden? (OST - SYKKEL - BOK)	☐	3
5. HØYERE KORTIKALE FUNKSJONER	Vis fram en blyant. Hva er dette?	☐	1
	Vis fram en klokke. Hva er dette?	☐	1
	Gjenta følgende setning: "Aldri annet enn om og men."	☐	1
	Ta et stykke papir med din høyre hånd. Brett det over på midten og legg det på gulvet.	☐	3
	Les og utfør: "Lukk øynene dine."	☐	1
	Skriv en setning.	☐	1
	Kopier denne tegningen.	☐	1
TOTAL SKÅR		☐☐	30

LUKK ØYNENE

57274

MIMI MENTAL STATUS EKSIMINASJON

Før testen gjennomføres, prøv å få pasienten til å sitte med ansiktet vendt mot deg. Vurder pasientens hørsel og syn. Dersom pasienten benytter hørsels els- og synshjelpemidler, skal disse brukes under testen.

Appendix V: Karnofsky Performance Status (KPS)

KARNOFSKY INDEX

Kriterier for aktivitesstatus ved skjelettmetastatisk kreftsykdom

Utfører normal aktivitet, trenger ikke spesielt stell	100%	Normal. Ingen plager eller subjektive tegn på sykdom.
	90%	Klarer normal aktivitet, sykdommen gir lite symptomer.
	80%	Klarer med nød normal aktivitet. Sykdommen gir en del symptomer.
Ute av stand til å arbeide. Klarer seg hjemme, greier personlig stell. Trenger varierende grad av hjelp.	70%	Klarer seg selv, ute av stand til normal aktivitet aller aktivt arbeid.
	60%	Trenger noe hjelp, men klarer stort sett å tilfredstille egne behov.
	50%	Trenger betydelig hjelp og stadig medisinsk omsorg.
Ute av stand til å greie seg selv. Avhengig av pleie. Sykdommen i progresjon.	40%	Ufør, trenger spesiell hjelp og omsorg.
	30%	Helt ufør, hospitalisering nødvendig, men fare for død er ikke overhengende.
	20%	Svært syk, hospitalisering og understøttende behandling nødvendig.
	10%	Moribund, dødsprosessen er i rask fremmarsj.
	0%	Død

Paper I

Review Article

Do Corticosteroids Provide Analgesic Effects in Cancer Patients? A Systematic Literature Review

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Abstract

Context. Corticosteroids are frequently used in cancer patients for their analgesic properties. The evidence for analgesic effects of corticosteroids in palliative care has not been established.

Objectives. To assess the evidence for the use of corticosteroids in cancer pain management.

Methods. A systematic literature search was performed. The articles were evaluated according to the Grading of Recommendations Assessment, Development and Evaluations system by two independent reviewers.

Results. The search provided 514 references, four of which were included. Another two trials were identified from reference lists. Two of these six studies were excluded from the qualitative review. One crossover study showed a significant reduction in pain intensity of 13 (visual analogue 0–100 scale) accompanied by significant lower analgesic consumption in favor of the steroid group. In another study, the addition of steroids did not have any effect on pain. In two studies, outcomes of pain intensity or analgesic consumption were not adequately reported. However, one of these studies showed significant pain reduction, whereas the other found no effect. Corticosteroids given in medium doses were well tolerated in studies for up to seven days. However, the studies indicated that corticosteroids may have serious toxicity and even higher mortality when administered in high doses over eight weeks.

Conclusion. Corticosteroids may have a moderate analgesic effect in cancer patients. The paucity of relevant studies was striking; consequently, the evidence was graded as "very low." More studies addressing the analgesic efficacy in cancer

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patients are required. J Pain Symptom Manage 2013;46:96–105.

Key Words
Corticosteroids, cancer, pain, palliative care

Introduction

Pain is one of the most frequent symptoms in patients with advanced cancer. Many patients suffer from insufficient pain control. In a Norwegian survey of hospitalized cancer patients, 20% reported cancer-related pain with a mean intensity of ≥5 in the last 24 hours (measured on a numeric rating scale [NRS] 0–10).[1] Cancer pain may be controlled by tumor-directed treatments such as radio- and/or chemotherapy, analgesics, or a combination of these treatment strategies. According to the World Health Organization pain ladder[2] and the European Association for Palliative Care cancer pain guidelines,[3] nonopioids and opioids are the basic analgesics. However, in addition, it is recommended to always consider adjuvant analgesics.

The multimodal approach is justified by the complex neurophysiology of cancer pain involving inflammatory, neuropathic, ischemic, and compression mechanisms. In the individual patient, cancer pain results from a combination of mechanisms, often occurring at multiple sites, and these change over time.[4] Moreover, nociception is modulated at all levels of the nervous system, such as the peripheral nerves, dorsal horn, and cerebral loci.

It is now widely accepted that inflammation is a significant pain modulating factor. First, proinflammatory cytokines are thought to be involved in the development of inflammatory and neuropathic pain.[5] Corticosteroids may act as anti-inflammatory agents through the inhibition of the expression of collagenase and proinflammatory cytokines or by stimulating the synthesis of lipocortin, which in turn blocks the production of eicosanoids.[6] Second, the immunocompetent glial cells have a major role in pain regulation.[7] Activated glial cells enhance pain, in part by releasing several key proinflammatory cytokines.

Animal studies have shown that corticosteroids can modulate pain perception. The spinal cord in rats was shown to be responsive to corticosteroids,[8] and a high density of glucocorticoid receptor was found in Laminae I and II of the dorsal horn.[9] Locally applied corticosteroids suppressed spontaneous discharge in neuromas[10] and attenuated established hyperalgesia and mechano-allodynia from nerve injury.[11] Moreover, epidural[12] and systemic corticosteroids[13] reversed neuropathic hyperalgesia in rats, and the effects persisted one week after discontinuation.[13] Finally, chronic dexamethasone treatment was found to exhibit a pronounced antinociceptive effect measured by the tail-flick test in rats, and the medication altered the expression of neuropeptides involved in nociceptive transmission at the spinal cord level.[14]

Clinical trials have shown that systemic corticosteroid therapy may improve pain control. Romundstad et al.[15] found a significant analgesic effect for up to 72 hours of a single dose of 125 mg methylprednisolone given the first day after orthopedic surgery. Clinical guidelines recommend the use of corticosteroids as adjuvant analgesics for cancer pain.[16–18] However, these guidelines are based on expert recommendations rather than evidence. The aim of this systematic literature review was to assess the evidence for the use of corticosteroids as adjuvant analgesics as formulated in the research question: What is the published evidence that corticosteroids improve analgesia in adult patients with pain caused by cancer?

Methods

Studies eligible for the present literature review were English-language randomized controlled trials that included adult cancer patients (>18 years) with cancer pain, compared corticosteroids when added to standard pain treatment, and assessed outcomes on pain, analgesic consumption, and adverse events.

A systematic literature search was performed on May 25, 2010 and updated on December 6, 2011 in the following databases: PubMed, Embase through OvidSP (from 1980), and the Cochrane Central Register of Controlled Trials through the Wiley Interscience Cochrane Library.

A search strategy including free text and medical subject headings was made for PubMed and later adapted for the other databases (Fig. 1). In addition, the metaregister of Current Controlled Trials (active registers) was searched. The reference lists of the retrieved articles, as well as major international conference proceedings and reviews concerning pain and palliative care for the last three years, were checked.

The contents and quality of the included studies were assessed by two independent reviewers (Ø. P. and N. A.) according to the Grading of Recommendations Assessment, Development and Evaluations system.[19] A standardized data extraction form was used to assess the following study characteristics: study design, study limitations (allocation concealment, blinding, losses to follow-up, adherence to intention-to-treat analysis, stopping early for benefit, and failure to report outcomes), participants (number of patients and clinical setting), and reporting of results (choice of outcome measures, summary, and judgment of the reported results). Evidence profiles were made for the outcomes of pain intensity, analgesic consumption, and adverse events. The following factors were considered to decrease the evidence profile by one to two grades as specified in the Grading of Recommendations Assessment, Development and Evaluations system: serious or very serious limitations in study quality, some or major uncertainty about directness (external validity), inconsistency of results, imprecision or sparse data, and publication bias. Conversely, factors considered to increase the evidence by one to two grades were the following: a large or very large magnitude of effect, plausible confounding that would reduce a demonstrated effect, and demonstration of a dose-response gradient. For each research outcome, quality of evidence was finally graded in four categories: high quality (A), moderate quality (B), low quality (C), or very low quality (D).

Results

Fig. 2 shows the selection process for the studies finally included in the review. The search provided 514 references. Additionally, two randomized trials were identified from reference lists,[20,21] and 472 references remained after duplicates were removed. By evaluating the abstracts, 466 references could be excluded, most of these addressing corticosteroids used in chemotherapy treatment. Six full-text articles were retrieved for evaluation.[20–25] One article was excluded because corticosteroids were combined with a somatostatin analogue in the intervention group.[25] Of the remaining five articles, one open parallel group study[24] showed substantial and statistically significant differences in mean dose of opioids and mean pain intensity between intervention and control group at baseline. Furthermore, it was a concern whether the study groups were equally treated, and, therefore, the study was excluded because of low internal validity (Table 1). Only one study met all the inclusion criteria by reporting

("Steroids/therapeutic use"[mh] OR "Adrenal cortex hormones/therapeutic use"[mh]) AND ("Pain"[mh] OR "Pain Measurement"[mh] or "Pain Clinics"[mh] or "Pain Threshold"[mh] OR Analgesia[mh] OR Analgesics[mh:noexp] OR Hyperalgesia[mh]) AND ("Controlled clinical trial "[pt] OR "Randomized controlled trial"[pt] or "Multicenter study"[pt] OR Therapy/narrow[filter]) AND Neoplasms[mh] NOT (child*[ti] OR paediatr*[ti] OR pediatr*[ti]) Limited to humans.

Fig. 1. Search strategy (mh = medical subject headings; noexp = not including narrower terms; ti = title; pt = publication type; * = truncation).

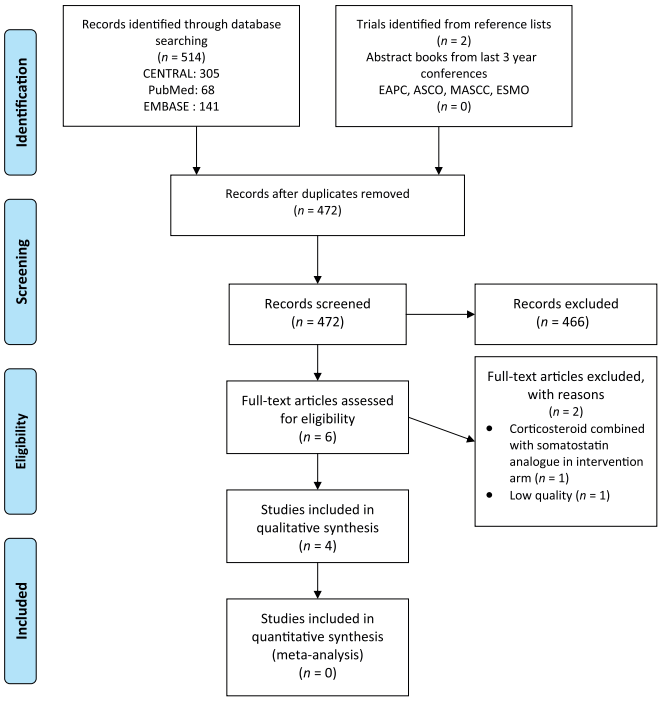

Fig. 2. Selection of relevant articles, presented as a flow diagram in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Adapted from: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(6):e1000097. http://dx.doi.org/10.1371/journal.pmed1000097. For more information, visit www.prisma-statement.org. EAPC = European Association for Palliative Care.

outcomes of pain intensity, analgesic consumption, and adverse events.[22] However, considering the few identified trials, the trials by Bruera et al.,[23] Della Cuna et al.,[20] and Popiela et al.[21] also were evaluated as they provide relevant information that should be communicated. Thus, four studies were included in this review.

The four trials comprised 667 (40–403) cancer patients,[20–23] and the most frequent primary tumors were gastrointestinal, breast, lung, and genitourinary cancers. Characteristics of each study are summarized in Table 2. The studies had in common that they aimed at palliation and not cure. All studies were randomized and blinded. Three of the studies

Table 1
"Risk of Bias" Assessment According to the Cochrane Collaboration

Item	Study Design	Allocation Concealment	Blinded	Large Losses to Follow-Up	Intention to Treat	Stopping Early for Benefit	Failure to Report Outcomes
Bruera et al.[22]	Crossover	Unclear	Yes	No	No	No	No
Bruera et al.[23]	Parallel group	Unclear	Yes	No	No	No	No
Della Cuna et al.[20]	Parallel group	Yes	Yes	No	Yes	No	Yes
Popiela et al.[21]	Parallel group	Yes	Yes	No	Yes	No	Yes
Mercadante et al.[24]	Parallel group	Unclear	No	No	No	No	No
Mitsiades et al.[25]	Parallel group	Unclear	No	Unclear	No	Yes	No

Table 2
Important Characteristics of the Included Studies

Study	Aim of Study/Outcome Measures	Study Arms/ Duration	Participants Included/Completed	Pain Intensity	Analgesic Consumption	Adverse Events	Conclusion and Comments
Bruera et al.[22]	Evaluate the effect of methylprednisolone on pain and five other symptoms in terminally ill cancer patients Primary outcome: pain intensity, analgesic consumption, psychiatric status, appetite, nutritional status, and activity	Methylprednisolone 16 mg twice daily or placebo Duration: Five days in each period Three-day washout period	40 included 31 completed (78%) Three died Day zero to 13 (one placebo)	Mean ± SD (VAS 0–100): Baseline: 57.7 ± 15 Evaluation Placebo: 50.1 ± 15 Methylprednisolone: 36.8 ± 14 $P < 0.01$	No. of capsules[a] Baseline: 3.6 ± 1.5 Evaluation Placebo: 3.3 ± 1.5 Methylprednisolone: 1.8 ± 1.7 $P < 0.05$	AEs: Two patients cushingoid faces Two patients enhancement of anxiety Discontinued: Three methylprednisolone period One placebo period	Significant effect on pain and analgesic consumption
Bruera et al.[23]	Assess the effect of dexamethasone as adjuvant antiemetic in patients with nausea due to cancer Assess effects in pain, fatigue, and appetite loss Primary outcome: intensity of nausea Secondary outcome: pain intensity, fatigue, and appetite loss	Dexamethasone 10 mg twice daily or placebo Duration: Seven days	51 included 43 completed (80%)	Mean ± SD (NRS 0–10): Baseline Placebo: 3.1 ± 3.5 Dexamethasone: 2.5 ± 2.9 Day 8 Placebo: 2.8 ± 3.6 Dexamethasone: 2.4 ± 3.4	Not reported	AEs: Five ankle edema (two dex, three placebo) Three insomnia (one dex, two placebo) Three restlessness (one dex, two placebo) Three other (two dex, one placebo) Discontinued: Three dexamethasone, four placebo	Too low level of pain at baseline No effect on pain or analgesic consumption
Della Cuna et al.[20]	Evaluate the effectiveness of methylprednisolone for improving quality of life in patients with preterminal cancer Evaluate effects on short-term survival Primary outcome: quality of life, and pain intensity, appetite, well-being, nausea, sleepiness, weakness, drowsiness, anxiety, mood, and vomiting	Methylprednisolone 125 mg i.v. once daily or placebo Duration: Eight weeks	403 included 198 completed (49%) 142 (35%) patients died (59 placebo)	Not reported Citing from article: "Methylprednisolone was significantly more effective than placebo in improving pain (measured by LASA) at each weekly follow-up evaluation ($P < 0.05$)."	Not reported	AEs: 38.2% methylprednisolone group 28.1% placebo group ($P < 0.05$) 10 vomiting (three MP, seven placebo) Nine hypocalcaemia (six MP, three placebo) Eight anemia (one MP, seven placebo) Eight hyperglycemia (eight MP, zero	Outcomes on pain not reported; "significant effect on pain from Week 1"

	Secondary outcome: short-term survival					placebo) Discontinued: One placebo 10 methylprednisolone: three stomach pain, two gastrointestinal bleeding, two hypotension, one hypoalbuminemia, one hyperglycemia	
Popiela et al.[21]	Obtain additional data relative to total mortality rate and time to death Evaluate improvement in quality of life Primary outcome: mortality Secondary outcome: quality of life (total sum of pain intensity, appetite, sense of well-being, nausea, sleep, weakness, drowsiness, anxiety, mood, and vomiting)	Methylprednisolone 125 mg i.v. once daily or placebo Duration: Eight weeks	173 included (female patients only) 87 completed (50%) 59 (34%) died (26 placebo)	Not reported Citing from article: "There were no significant changes across time for pain."	Not reported	AEs: 54 (64%) medical events in methylprednisolone group, 47 (53%) in placebo group Gastrointestinal (11% MP vs. 2% placebo, $P < 0.05$) Cardiovascular (8% MP vs. 1% placebo, $P < 0.05$) Discontinued: 16 methylprednisolone, 12 placebo (reasons not given)	Outcomes on pain not reported; "no effects on pain"

VAS = visual analogue scale; AE = adverse events; NRS = numeric rating scale; dex = dexamethasone; i.v. = intravenous; LASA = Linear Analogue Self-Assessment Scale; MP = methylprednisolone.
[a]Capsules of 98 mg propoxyphene and 400 mg dipyrone.

included patients with low physical performance status (mean Eastern Cooperative Oncology Group status 3.5)[22] or a rather short life expectancy (about three months).[20,21]

Bruera et al.[22] assessed the effect of corticosteroids on pain and five other outcomes in a crossover design. Participants either received methylprednisolone 16 mg or placebo twice daily for five days, separated by a three-day washout period. Forty patients were included, 31 completed the trial. Twenty-eight participants were evaluable for pain. Pain intensity, assessed by a visual analogue scale 0−100, was lower in the steroid group compared with the placebo group: mean ± SD 36.8 ± 14 vs. 50.1 ± 15; $P < 0.01$. Likewise, analgesic consumption was lower in the steroid group: 1.8 capsules of propoxyphene and dipyrone a day compared with 3.3 capsules a day in the placebo group at evaluation ($P < 0.05$) (Table 2). Adverse events were mild; two patients reported cushingoid faces and two reported enhancement of anxiety.

In another study, Bruera et al.[23] examined the effectiveness of oral corticosteroids as adjuvant antiemetics in 51 cancer patients with chronic nausea, using a parallel group design. Pain was a secondary outcome. Patients received dexamethasone 10 mg twice daily or placebo for seven days. Pain intensity at baseline was 2.5 in the steroid group vs. 3.1 in the placebo group (NRS 0−10) and at Evaluation Day 7 was 2.4 vs. 2.8 in the two groups, respectively (not significant). Analgesic consumption was recorded but not reported. Adverse events were recorded in a predefined manner using daily self-reported toxicity assessments. Mild adverse events were reported in 24% of the steroid group and 31% of the placebo group (Table 2).

Della Cuna et al.[20] evaluated the effectiveness of corticosteroids for improving health-related quality of life (HRQOL) in 403 cancer patients in a parallel group design. Primary outcome was HRQOL. The intervention was 125 mg methylprednisolone given intravenously once daily during a period of eight weeks; controls received placebo injections. Only 198 patients (49%) completed the study, and 142 patients died during the study period. Pain intensity level and analgesic consumption were not adequately reported; it was only stated that "methylprednisolone was significantly more effective than placebo in improving pain at each weekly follow-up evaluation." Adverse events (definitions not recorded) were significantly more frequent in the steroid group compared with the placebo group, 38% vs. 28%, respectively ($P < 0.05$). A mortality of 40% and 30% in the steroid and placebo groups, respectively, was reported. In a subset of female patients, the difference in mortality was statistically significant, with 12% higher mortality in the steroid group.

On this basis, Popiela et al.[21] replicated the previously mentioned study with only female patients. The primary outcome was mortality, and HRQOL was a secondary outcome. One hundred seventy-three participants were included. Eighty-seven (50%) patients completed the study, 58 died during the follow-up. Neither pain intensity nor analgesic consumption was reported, but the authors stated "there were no significant changes across time for pain." Adverse events were reported as "medical events" (definitions not provided) and were significantly more frequent in the steroid group compared with the placebo group regarding gastrointestinal (11% vs. 2%) and cardiovascular events (8% vs. 1%). Mortality was 38% in the steroid group vs. 30% in the placebo group (not significant) (Table 2). Analyzing the studies of Della Cuna et al. and Popiela et al. together, mortality was significantly higher in the steroid group compared with the placebo group, 115 (39%) of 292 patients vs. 85 (30%) of 284 patients, respectively ($P = 0.017$) (Pearson Chi-square test), calculated as odds ratio = 0.66 (95% CI 0.47−0.93) (calculated by the authors). A pharmaceutical company sponsored both the studies.[20,21]

Summarizing the results, although only one study could be used to evaluate the outcomes of pain intensity and analgesic consumption,[22] the evidence profile for these outcomes were initially both graded as moderate (B). As the number of patients was small (imprecision) and the intention-to-treat approach was not used, grading was reduced to very low evidence (D). Adverse effects were properly reported in two randomized trials;[22,23] the evidence profile for adverse effects was initially rated as moderate (B). Because of the small number of patients (imprecision), evidence was finally rated as low (C).

Discussion

The major finding of this review is that the evidence for the efficacy of corticosteroids for pain control in cancer patients receiving palliative care is weak. The main reason is the paucity of relevant, well-conducted studies. Accordingly, only a qualitative analysis could be made.

Only Bruera et al.[22] reported and assessed the outcome variables pain intensity and analgesic consumption adequately; both were in favor of steroids. The reported difference in pain intensity of about 13 (visual analogue scale 0–100) is considered to be a modest improvement on a group level.[26] However, the study has limitations. It was a small study with only 28 participants evaluable for pain; pain was not a primary outcome, and adverse events were not properly assessed. Additionally, the crossover design with three-day washout period is questionable. Corticosteroids act on a cellular level and the biological half-life is expected to be 12–36 hours.[27] The biological effects, therefore, may be present for more than three days for the patients receiving steroids in the first period, and thus carried over to the placebo period.

In the study by Bruera et al.[23] from 2004, the effect of corticosteroids on nausea and vomiting was evaluated. No difference in pain intensity was seen as the participants had a very low pain intensity level at baseline, mean scores 3.1 and 2.5 (NRS 0–10) in the steroid and placebo groups, respectively. As pain was fairly well controlled, it is not likely that the pain scores would improve significantly, implying a high risk of a Type II error for this outcome. However, this was the only study recording adverse events in a predefined manner, showing a low frequency of adverse events.

Despite inadequate reporting of pain intensity and analgesic consumption, the trial by Della Cuna et al.[20] gives some support to the main finding of this review, as pain was claimed to improve significantly in the steroid group, although Popiela et al. found no difference in pain intensity between the groups.[21] The major problem with these studies in the context of both pain and adverse events was that they not only gave very high dose methylprednisolone but also administered the medication intravenously. This is not considered appropriate by today's standards, reducing their external validity significantly. Adverse events were not uniformly reported, but both studies demonstrated a significantly higher frequency of adverse events in the steroid group. Additionally, they provided some evidence that using corticosteroids in this manner may increase mortality.

The studies by Della Cuna et al.[20] and Popiela et al.[21] raise some ethical concerns. They included a large number of patients without reporting any sample size estimation, thus risking inclusion of too few patients to draw valid conclusions, or more likely to expose too many subjects to the inherent risk of the intervention. Additionally, they used very high doses of corticosteroids for as long as eight weeks, increasing the risk of serious adverse effects in this fragile patient group. However, the studies were initiated in 1978 and 1984, before the toxicity of high doses of corticosteroids in cancer patients were well known.

Corticosteroids are used as adjuvant analgesics, and one may not expect that their efficacy compares with the "primary analgesics." In a recent published systematic review, Bennett[28] reported that the addition of anticonvulsants or antidepressants was likely to result in a modest improvement in pain intensity and pain relief when added to opioids for cancer pain. However, they were unlikely to provide a greater reduction than one point on a 0–10 NRS, which is somewhat less than reported by Bruera et al.[22]

The available data suggest that moderate doses of corticosteroids equivalent to methylprednisolone 32 mg or dexamethasone 8 mg daily are well tolerated for up to seven days but that high doses equivalent to methylprednisolone 125 mg daily administered over eight weeks have a significantly adverse impact and may even increase mortality. In patients with spinal cord compression, a randomized controlled trial[29] and a case control study[30] reported serious adverse events more frequently in patients receiving dexamethasone 100 mg daily compared with those using 16 mg daily (11%–14% vs. none). This is in accordance with the general view that toxicity resulting from corticosteroids increases with the dose and the duration of therapy.[17,18] However, data indicate that pain relief from

corticosteroids appears within five to seven days.[20,22]

Conclusion and Future Directions

Given the present knowledge, a weak recommendation for the use of corticosteroids in cancer patients with pain is found. The evidence supports that a moderate dose of corticosteroids, such as methylprednisolone 32 mg, may contribute to analgesia and seems to be well tolerated. If there is no effect on pain within one week, the corticosteroid medication should be discontinued.

The analgesic properties of corticosteroids should be confirmed in a randomized trial.

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Paper II

Original Article

Polypharmacy in Patients With Advanced Cancer and Pain: A European Cross-Sectional Study of 2282 Patients

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Abstract

Context. Patients with advanced cancer need multiple drugs to control symptoms and to treat cancer and concomitant diseases. At the same time, the goal of treatment changes as life expectancy becomes limited. This results in a risk for polypharmacy, maintained use of unneeded drugs, and drug-drug interactions (DDIs).

Objectives. The aim of the study was to analyze the use of medications and to identify unneeded drugs, and drugs and drug combinations with a risk for DDIs in a cohort of advanced cancer pain patients, defined by a need for a World Health Organization analgesic ladder Step III opioid.

Methods. All drugs taken within a study day by cancer patients receiving opioids for moderate or severe pain (Step III opioids) were analyzed. Nonopioids and adjuvants were analyzed for their use across countries. Unneeded medications and drugs and drug combinations with a risk for pharmacodynamic and pharmacokinetic DDIs were identified on the basis of published literature and electronic resources.

Results. In total, 2282 patients from 17 centers in 11 European countries were included. They received a mean of 7.8 drugs (range 1–20). Over one-quarter used 10 or more medications. The drugs and drug classes most frequently coadministered with opioids were proton pump inhibitors, laxatives, corticosteroids, paracetamol (acetaminophen), nonsteroidal anti-inflammatory drugs, metoclopramide, benzodiazepines, anticoagulants, antibiotics, anticonvulsants, diuretics, and antidepressants. The use of nonopioids and essential adjuvants varied across countries. Approximately 45% of patients

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received unnecessary or potentially unnecessary drugs, and about 7% were given duplicate or antagonizing agents. Exposures to DDIs were frequent and increased the risk of sedation, gastric ulcerations, bleedings, and neuropsychiatric and cardiac complications. Many patients were exposed to pharmacokinetic DDIs involving cytochrome P450, including about 58% who used a Step III opioid CYP3A4 (izoenzyme of cytochrome P450) substrate, and more than 10% who were given major CYP3A4 inhibitors or inducers.

Conclusion. Patients with cancer treated with a World Health Organization Step III opioid use a high number of drugs. Nonopioid analgesics and corticosteroids are frequently used, but different patterns of use between countries were found. Many patients receive unneeded drugs and are at risk of serious DDIs. These findings demonstrate that drug therapy in these patients needs to be evaluated continuously. J Pain Symptom Manage 2014;48:1145–1159.

Key Words

Pharmacotherapy, polypharmacy, cancer pain, palliative care, opioids, nonopioids, coanalgesics, adjuvants, unneeded drugs, unnecessary drugs, drug-drug interactions

Introduction

Patients with advanced cancer need multiple drugs from several pharmacologic classes to control symptoms of progressing severe disease. In addition, many patients receive anticancer treatment and use medications for the management of concurrent diseases.[1–5] Because of the complexity of their illnesses, patients with advanced cancer are often treated by physicians from more than one medical specialty, including oncologists and palliative care physicians. Consequently, cancer patients with advanced disease are at high risk for complications caused by drug-induced adverse effects and drug-drug interactions (DDIs). This may represent a major limitation for adequate patient management, including pain control using opioids.[6]

Polypharmacy and DDIs have been studied in several patient populations, including elderly patients, patients with dementia, and cancer patients from general cancer care.[7–16] However, findings in such populations are only partly relevant to patients with advanced cancer who can be hypothesized to be more at risk for drug-induced complications. Previous studies of polypharmacy in supportive and palliative care include patients from one or very few centers and include a limited number of patients.[3,17–21]

Therefore, in this multicenter study, we analyze the use of medications in a large cohort of advanced cancer patients with pain, defined by a need for a World Health Organization (WHO) analgesic ladder Step III opioid.[22] This study reports the use of opioids, nonopioids, adjuvants, and other drugs and identifies unneeded medications and drugs and drug combinations with a risk of causing clinically relevant pharmacodynamic and pharmacokinetic DDIs.

Methods

Study Centers and Inclusion Criteria

The European Pharmacogenetic Opioid Study (EPOS) was performed at 17 cancer and palliative care centers, including surgical wards, general oncology wards, palliative care units/hospices, and outpatient clinics in 11 European countries from 2004 to 2008.[23]

Patients older than 18 years with a malignant disease who were using an opioid on Step III of the WHO analgesic ladder for moderate-to-severe pain for a period of no less than three days were eligible for the study.[23] Patients unable to communicate in the language used at the study center were excluded.

Data Collection

The patients' demographics, including gender, age, and body mass index, cancer diagnosis, sites of metastases, and concomitant diseases were recorded. Performance status was evaluated using the Karnofsky Performance

Status (KPS) Scale. Data on all drugs taken by the patients in the last 24 hours, both scheduled and used as rescues, including over-the-counter medications, vitamins, and herbs, were collected. Detailed information on the methods of the EPOS has been previously published.[23]

Analysis of Pharmacotherapy

All drugs were classified by generic name, pharmacologic class, and indications in the palliative care setting. Opioids, nonopioid analgesics, and corticosteroids also were recorded with respect to dose and route of administration. Opioid doses were converted to equipotent oral morphine doses.[23] Doses of corticosteroids were converted to equipotent oral dexamethasone doses.[24] The total number of drugs taken by the patients was analyzed with respect to gender, age category (18–45, 46–60, 61–75, 76–90, >90), KPS score (>50 and ≤50), and location of treatment. Drugs essential for analgesia (paracetamol [acetaminophen], nonsteroidal anti-inflammatory drugs [NSAIDs], corticosteroids, gabapentin, pregabalin, and amitriptyline) and antiemetics and laxatives were analyzed for their use across seven countries where >100 patients had been recruited.

Unneeded drugs were defined as unnecessary drugs, potentially unnecessary drugs, duplicate drugs, and drugs with antagonizing effect. Drugs were considered unnecessary in cases when the treatment was evaluated not to have beneficial effect on symptom control, patient quality of life, or survival.[25,26] Because assessment of the futility of an intervention in palliative care settings cannot be exact without ongoing monitoring of treatment benefits and knowledge of patient and family desires, we chose a conservative categorization limiting "unnecessary drugs" to lipid-lowering drugs, hormone replacement therapy, vitamins, and some minerals (except potassium, calcium, magnesium, and ferrum). We additionally defined "potentially unnecessary drugs" as medications, the futility of which cannot be definitely determined retrospectively but was very probable in a patient with low performance status (KPS score ≤ 50) and an expected short survival time. These medications included anticancer treatment, megestrol acetate, cardiovascular drugs, gastroprotective agents, and allopurinol. Cardiovascular drugs included in the assessment were antihypertensive medications (excluding diuretics), antiarrythmics, cardiac glycosides, and drugs used to protect against myocardial ischemia. Duplicate drug referred to the simultaneous use of a drug in two formulations or two drugs of the same class and similar action.[25] Concomitant use of two or three opioids was not considered duplicate as it is accepted to use different opioids for scheduled doses and when given as needed. Also, some physicians prescribe a combination of two scheduled opioids. Additionally, simultaneous use of metamizole and another NSAID was not considered duplicate because of the distinct mechanism of action and profile of adverse effects of the former. Drugs with antagonizing effect referred to drugs with opposite actions.

On the basis of a search of the literature and electronic resources,[6,20,21,27–48] the EPOS patient cohort was reviewed for drugs and drug combinations that cause an increased risk for clinically relevant pharmacodynamic and pharmacokinetic DDIs. As existing DDI identification systems and databases may overestimate the risk of pharmacokinetic DDIs via cytochrome P450 (CYP450) by extrapolating experimental studies, we included only DDIs that are supported by studies in humans.[20,29,40] Drugs with a potential inhibitory or stimulatory effect on the activity of major CYP450 isoenzymes and P-glycoprotein were determined on the basis of information from the U.S. Food and Drug Administration Web site (http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm) and other electronic resources and a literature search.[6,27–30,33–44] Only potent (strong, moderate, and major) CYP450 inhibitors and inducers were included in the DDI analysis. Weak inhibitors and inducers were not considered relevant for analysis because they are unlikely to cause clinically significant DDIs. Of those drugs that may prolong the QT interval, only those with a risk of Torsades de pointes[31] were analyzed, excluding drugs categorized to have only a potential risk.

Statistical Analyses

Descriptive data are presented as mean ± SD or as number (%). Statistical

analyses were performed with the STATISTICA v.10 software package (StatSoft Inc., Tulsa, OK). The distribution of data was analyzed with the Shapiro-Wilk test. Comparisons between two groups were performed with Mann-Whitney tests. In comparisons between more than two groups, Kruskal-Wallis analysis of variance and Dunn's post hoc test (if appropriate) were performed. Statistical significance was set at $P < 0.05$.

Ethics

The study was performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from each patient.

Results

Patients and General Characteristics of Pharmacotherapy

In total, 2294 patients with cancer pain treated according to the WHO pain ladder Step III from 17 centers located in 11 European countries were recruited into the study (Norway, $n = 565$; Italy, $n = 462$; Germany, $n = 452$; U.K., $n = 295$; Iceland, $n = 150$; Sweden, $n = 135$; Switzerland, $n = 115$; Lithuania, $n = 54$; Denmark, $n = 31$; Finland, $n = 30$; Greece, $n = 5$). Twelve patients were excluded because of lack of comprehensive data or withdrawal from the study. The characteristics of the 2282 included patients are given in Table 1.

Patients used one to 20 different medications, with a mean number of 7.8 (Table 1); 1923 patients (84.4%) received five or more drugs, and 649 patients (28.4%) received 10 or more medications. The number of drugs varied between age categories, performance categories, and location of treatment but not with gender (Table 1). The most frequently used opioid was oral morphine, followed by transdermal fentanyl and oral oxycodone (Table 2). One hundred sixty-three patients were given two opioids and eight patients used three opioids concomitantly. The drug and drug classes most frequently coadministered with opioids were proton pump inhibitors, laxatives, corticosteroids, paracetamol, NSAIDs, dopamine-receptor antagonists, benzodiazepines, anticoagulants, antibiotics,

Table 1
Patients' Characteristics and Number of Drugs Taken According to Gender, Age, KPS, and Location of Treatment

Patients' Characteristics	Total Patients ($n = 2282$)
Male/female	1195/1087
Age (yrs)	62.3 ± 12.3 (18–96)
KPS	59.2 ± 17.2 (10–100)
BMI	23.6 ± 4.6 (9.2–46.9)
Cancer diagnoses	2282
Gastrointestinal	522 (22.9)
Urologic	433 (19.0)
Lung	384 (16.8)
Breast	301 (13.2)
Female reproductive organs	173 (7.6)
Hematological	131 (5.7)
Head and neck	125 (5.5)
Unknown origin	64 (2.8)
Others	251 (11.0)
Metastases	2074 (90.9)
Bone	1017 (44.6)
Liver	561 (24.6)
Lung	505 (22.1)
Central nervous system	132 (5.8)
Other	898 (39.6)
Concomitant diseases	1384 (60.6)
Cardiovascular	809 (35.5)
Endocrine	330 (14.5)
Lung	202 (8.9)
Gastrointestinal	188 (8.2)
Musculoskeletal	178 (7.8)
Opioid dose (mg/d)[a]	230.3 ± 456.7 (10–9090)
No. of drugs taken	7.8 ± 3.2 (1–20)
Male ($n = 1195$)	7.8 ± 3.1 (1–20)
Female ($n = 1087$)	7.7 ± 3.2 (1–20)
No. of drugs taken according to age category[b]	
18–45 ($n = 195$)	7.4 ± 3.0 (1–15)
46–60 ($n = 766$)	7.3 ± 3.1 (1–18)
61–75 ($n = 986$)	8.1 ± 3.2 (1–19)
76–90 ($n = 328$)	8.5 ± 3.2 (1–20)
>90 ($n = 7$)	6.8 ± 2.9 (3–12)
No. of drugs taken according to KPS[c]	
>50 ($n = 1376$)	7.2 ± 3.0 (1–19)
≤50 ($n = 906$)	8.8 ± 3.2 (1–20)
No. of drugs taken according to treatment setting[d]	
General oncology wards ($n = 952$)	8.1 ± 3.0 (1–20)
Palliative care units/hospices ($n = 823$)	8.4 ± 3.2 (1–20)
Outpatient clinics ($n = 429$)	6.3 ± 3.1 (1–19)
Surgical wards ($n = 78$)	6.4 ± 2.6 (1–15)

KPS = Karnofsky Performance Status Scale; BMI = body mass index.
The data in the right column are given as n (%) or as mean ± SD (range).
[a]Oral morphine equivalent dose.
[b]Patients 61–75 and 76–90 yrs used more drugs than those aged 18–45 and 46–60 yrs ($P < 0.05$).
[c]Patients with KPS score ≤ 50 used more drugs than those who were scored >50 ($P < 0.05$).
[d]Patients in general oncology wards and palliative care units/hospices used more drugs than patients on surgical wards ($P < 0.05$) and from outpatient clinics ($P < 0.5$).

Table 2
Drugs and Drug Classes

Drugs and Drug Classes	Total Patients ($n = 2282$)
Anticancer treatment	343 (15.0)
Hormonal agents 153	
Opioids Step III of WHO analgesic ladder	2282 (100)
Morphine 960, fentanyl 734, oxycodone 476, hydromorphone 114, methadone 64, buprenorphine 51, levomethadone 34	
Opioids Step II of WHO analgesic ladder	91 (4.0)
Tramadol 52, codeine 39	
Paracetamol	712 (31.2)
Nonsteroidal anti-inflammatory drugs	683 (29.9)
Corticosteroids	1121 (49.1)
Immunosuppressant drugs	15 (0.7)
Megestrol acetate	37 (1.6)
Benzodiazepines	549 (24.1)
Oxazepam 132, lorazepam 119, diazepam 96, alprazolam 49, clonazepam 44, midazolam 16	
Nonbenzodiazepine hypnotic agents	348 (15.2)
Zopiclone 287, zolpidem 61	
Antidepressant drugs	451 (19.8)
Amitriptyline 122, citalopram 98, mirtazapine 60, escitalopram 39, sertraline 32, paroxetine 25, venlafaxine 24, fluoxetine 13	
Psychostimulants	36 (1.6)
Methylphenidate 23	
Anticonvulsants	485 (21.3)
Gabapentin 229, pregabalin 173, carbamazepine 28, phenytoin 11, oxcarbazepine 10	
Muscle relaxants	14 (0.6)
Antipsychotics	229 (10.0)
Haloperidol 146, levomepromazine 39, chlorpromazine 13	
Dopamine receptor antagonists	677 (29.7)
Metoclopramide 640, domperidone 37	
5-HT3 receptor antagonists	143 (6.3)
Ondansetron 95, granisetron 26, tropisetron 22	
Antihistamines	52 (2.3)
Cyclizine 37, dimenhydrinate 11	
Spasmolytics	68 (3.0)
Hyoscine 49	
Proton pump inhibitors	1425 (62.4)
Lansoprazole 418, esomeprazole 402, pantoprazole 323, omeprazole 259	
H2-receptor antagonists	60 (2.6)
Ranitidine 47, cimetidine 13	
Laxatives	1186 (52.0)
Antifungal agents	222 (9.7)
Nystatin 116, fluconazole 101	
Antibiotics	488 (21.4)
Penicillins 128, cephalosporins 106, ciprofloxacin 66, metronidazole 38, clarithromycin 13, and erythromycin 1	
Antiviral drugs	43 (1.9)
Acyclovir 30	
Anticoagulants	526 (23.0)
Low–molecular weight heparin 444, warfarin 63	
Antiplatelet agents	238 (10.4)
Acetylsalicylic acid 210	
Antifibrinolytics	23 (1.0)
Tranexamic acid 21	
Lipid-lowering drugs	142 (6.2)
Statins 140	
Inhibitors of the renin-angiotensin system	320 (14.0)
Calcium channel blockers	152 (6.7)
Beta-blockers	375 (16.4)
Amiodarone	17 (0.7)
Diuretics	458 (20.1)
Loop diuretics 356, potassium-sparing diuretics 87, thiazides 71	
Allopurinol	104 (4.6)
Antidiabetic agents	152 (6.7)
Oral hypoglycemic agents 89, insulin 70	
Thyroxin	145 (6.4)
Hormone replacement therapy	20 (0.9)
Vitamins	264 (11.6)
Herbs	79 (3.5)

WHO = World Health Organization.
The data in the right column are given as n (%) or as mean ± SD (range). For each drug class, only the drugs used by >10 patients are specified.

anticonvulsants, diuretics, and antidepressants (Tables 2 and 3).

Use of Medications

Nonopioid Analgesics. Nonopioid analgesics were used by 54.2% of patients. The use of nonopioids varied substantially across countries, ranging from 30.6% in Italy to almost 70% in Sweden and Switzerland. Paracetamol and NSAIDs were both prescribed to approximately 30% of patients. In Switzerland and Germany, NSAIDs were used most frequently (50%–60%), mainly because of the use of metamizole, which was only prescribed in these two countries. More than one nonopioid was prescribed to 184 patients, primarily an NSAID and paracetamol. Twenty patients used metamizole and paracetamol concomitantly, and 30 patients used metamizole and another NSAID. Five patients used paracetamol, metamizol, and another NSAID concomitantly. Details of the distribution in the use of nonopioid analgesics in countries with >100 participants are given in Table 3. The distribution of doses varied between countries (data not shown).

Adjuvants and Other Agents Used for Symptom Control. Systemic corticosteroids were given to 49.1% of patients, ranging from 33.6% of the patients in Germany and the U.K. to >70%

Table 3
Use of Nonopioid Analgesics and Adjuvants (*n* [%] and doses)

Drugs and Drug Classes	Total ($n = 2282$)	Norway ($n = 557$)	Italy ($n = 461$)	Germany ($n = 452$)	U.K. ($n = 295$)	Iceland ($n = 150$)	Sweden ($n = 134$)	Switzerland ($n = 114$)
Nonopioid analgesics	1236 (54.2)	370 (61.1)	141 (30.6)	270 (59.7)	167 (56.7)	93 (62.0)	93 (69.4)	89 (69.3)
Paracetamol	712 (31.2)	325 (58.3)	39 (8.5)	6 (1.3)	137 (46.4)	56 (37.3)	80 (59.7)	47 (41.2)
NSAIDs	683 (29.9)	50 (9.0)	109 (23.6)	266 (58.8)	75 (25.4)	52 (34.7)	38 (28.4)	58 (50.9)
Metamizole[a]	240 (35.1)	0 (0)	0 (0)	199 (74.8)	0 (0)	0 (0)	0 (0)	41 (70.7)
Diclofenac[a]	197 (28.8)	25 (51.0)	6 (5.5)	23 (8.6)	51 (68.0)	28 (53.8)	28 (73.3)	14 (24.1)
Ibuprofen[a]	98 (14.3)	8 (16.3)	3 (2.8)	50 (18.8)	14 (18.7)	11 (21.2)	3 (7.9)	7 (12.1)
Ketoprofen[a]	51 (10.9)	2 (4.1)	47 (43.1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Corticosteroids	1121 (49.1)	272 (48.8)	331 (71.8)	152 (33.6)	99 (33.6)	95 (63.3)	97 (72.4)	48 (42.1)
Dexamethasone[a]	619 (55.2)	76 (27.9)	245 (74.0)	130 (85.5)	85 (85.0)	42 (44.2)	0 (0)	27 (56.3)
Prednisolone[a]	186 (16.6)	63 (23.2)	7 (2.1)	16 (10.5)	13 (13.0)	52 (54.7)	7 (7.2)	18 (37.5)
Methylprednisolone[a]	181 (16.1)	131 (48.2)	47 (14.2)	1 (0.7)	1 (1.0)	0 (0)	0 (0)	1 (2.1)
Betametasone[a]	108 (9.6)	0 (0)	20 (6.0)	0 (0)	0 (0)	1 (1.1)	87 (89.7)	0 (0)
Corticosteroid dose[b]	6 (0.04–40)	6 (0.8–20)	5.5 (0.5–64)	8 (0.5–24)	7 (0.04–21)	3 (0.5–16)	3.8 (0.8–15)	7.8 (0.4–40)
Gabapentin	229 (10.0)	32 (5.7)	69 (15.0)	25 (5.5)	19 (6.4)	16 (10.7)	21 (15.7)	4 (3.5)
Pregabalin	173 (7.6)	34 (6.1)	33 (7.2)	73 (16.1)	4 (1.4)	16 (10.7)	4 (3.0)	4 (3.5)
Amitriptyline	122 (5.3)	21 (3.8)	2 (0.4)	43 (9.5)	12 (4.1)	14 (9.3)	9 (6.7)	5 (4.4)
Antiemetics	968 (42.4)	236 (42.4)	196 (42.5)	185 (40.9)	138 (46.8)	69 (46.0)	62 (46.3)	63 (55.3)
Laxatives	1186 (52.0)	387 (69.5)	181 (39.3)	213 (47.1)	172 (58.3)	86 (57.3)	35 (26.1)	89 (78.1)

NSAIDs = nonsteroidal anti-inflammatory drugs.
[a]% of NSAIDs or corticosteroids.
[b]Dose median and range.

in Italy and Sweden. Dexamethasone was used in >80% of cases in Germany and the U.K., whereas in Norway and Iceland, the most used corticosteroids were methylprednisolone and prednisolone, respectively. Betamethasone was almost exclusively used in Sweden. Oral dexamethasone equivalent doses showed a difference between countries, with median values ranging from 3 to 3.8 mg/d in Iceland and Sweden to 7.8–8 mg/d in Switzerland and Germany (Table 3). Fourteen percent of patients used both NSAIDs and corticosteroids, and 27 patients took both these drugs and acetylsalicylic acid, three drugs with potential upper gastrointestinal side effects.

Gabapentin or pregabalin were given to 17.6% of patients. Prescribers in Italy, Germany, and Iceland used these antiepileptics in >20% of patients, compared with less than 10% in Switzerland and the U.K. (Table 3). About 20% of patients ($n = 451$) used antidepressants, including amitriptyline, which was given to 5.3% of the patients. The details for other adjuvants and drugs to treat symptoms are given in Tables 2 and 3.

Drugs Used for the Treatment of Underlying and Concomitant Diseases. Drugs and drug classes used to treat malignant and concurrent diseases, which were taken by >10% of patients, included anticancer treatment, low–molecular weight heparin and other anticoagulants, antiplatelet drugs, antibiotics, cardiovascular drugs, diuretics, and vitamins. Other drugs given to less than 10% of patients are specified in Table 2.

Use of Unnecessary, Potentially Unnecessary, Duplicate, and Antagonizing Drugs

Approximately 45% of patients used at least one drug that was categorized as an unnecessary or potentially unnecessary drug. Some patients used more than one of these medications. Unnecessary drugs were taken by 18.5% of patients, which included lipid-lowering drugs ($n = 142$; 6.2%), hormone replacement therapy ($n = 20$; 0.9%), vitamins ($n = 264$; 11.6%), and some minerals ($n = 11$; 0.5%). Potential unnecessary drugs were used by about 33% of patients and included anticancer drugs ($n = 120$; 5.3%), megestrol acetate ($n = 11$; 0.5%), drugs given for cardiovascular indications ($n = 312$; 13.7%), gastroprotective agents ($n = 660$; 28.9%), and allopurinol ($n = 45$; 2.0%).

About 6% of patients received two or more drugs that were identified as duplicate drugs. These combinations were opioid on Step II and Step III of the WHO analgesic ladder ($n = 91$; 4.0%), two benzodiazepines ($n = 34$; 1.5%), haloperidol and a phenothiazine ($n = 7$), warfarin and low–molecular weight heparin ($n = 4$), angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker ($n = 3$), hyoscine butylbromide and trospium ($n = 2$), metoclopramide and domperidone ($n = 1$), furosemide and torasemid ($n = 1$), diltiazem and verapamil ($n = 1$), and carvedilol and metoprolol ($n = 1$). Finally, metamizole was given using two different preparations ($n = 1$).

Combinations of drugs with antagonistic effects included metoclopramide or domperidone and hyoscine derivatives ($n = 17$), codeine and mucolytics ($n = 5$), mucolytics and hyoscine derivatives ($n = 3$), and loperamide and laxatives ($n = 2$).

Exposure to Clinically Relevant Pharmacodynamic DDIs

Almost half of the patients (47.7%) received at least one drug (in addition to opioids) with a potential to induce or aggravate drowsiness (Table 4); 13.1% of patients received two or more of these agents. Fifty-six patients (2.4%) were given two or three anticoagulant and antiplatelet drugs concomitantly, and 8.4% used these agents along with NSAIDs. Megestrol acetate was used in nine patients on systemic corticosteroids. Corticosteroids or megestrol acetate were used in 81 (3.5%) patients who also received antidiabetic agents (Table 4). Overall, 53% of patients were exposed to drugs that exert and often share affinity for dopamine (35%), serotonin (21.8%), and muscarinic receptors (20.3%), which increases the risk of neuropsychiatric complications (delirium, extrapyramidal symptoms, serotonin, and anticholinergic syndromes) among others. Some patients used more than one of these agents; 3.3% were given two or three dopamine antagonists (mostly metoclopramide and antipsychotics), 1.3% used two or three drugs with known serotonergic effects (mostly antidepressants), and 1.7% coadministered two or three drugs with antagonist effects

Table 4
Exposure to Drug Combinations That May Cause Clinically Relevant DDIs[6,20,21,27–48]

Coadministered Drugs	Potential Clinical Effect	Number of Patients (%)
Potential interactions of analgesics		
NSAIDs + corticosteroids	Increased risk of gastric ulceration, fluid retention	319 (14.0)
NSAIDs + LMWH, warfarin, other oral anticoagulants, ASA, and/or other antiplatelet medications	Increased risk of bleeding	192 (8.4)
NSAIDs + SSRIs	Increased risk of upper gastrointestinal bleeding	56 (2.5)
NSAIDs + antihypertensive medications	Hypotensive effect attenuated	245 (10.7)
NSAIDs + ACE inhibitors	Increased risk of nephrotoxicity	70 (3.1)
NSAIDs + bisphosphonates	Increased risk of nephrotoxicity	2 (0.1)
Paracetamol + phenytoin	Analgesic effect attenuated, increase in hepatic toxicity	3 (0.1)
Step III opioids + other medications with CNS depressant effect, i.e., Step II opioids, benzodiazepines, nonbenzodiazepine hypnotics and sedatives, neuroleptics, TCAs, mirtazapine, antihistamine drugs, hyoscine derivatives, and others	Sedation, increased risk of respiratory depression	1081 (47.7)
Tramadol + other opioids, dextromethorphan, neuroleptics, and antidepressants	Seizure threshold lowered	47 (2.1)
Tramadol + dextromethorphan and antidepressants	Increased risk of serotonin syndrome	9 (0.4)
Opioids metabolized with important contribution of CYP3A, i.e., fentanyl, oxycodone, methadone, buprenorphine + CYP3A inhibitors	Increased opioid effect, risk of overdosing	113 (5.0)
Opioids metabolized with important contribution of CYP3A, i.e., fentanyl, oxycodone, methadone, buprenorphine + CYP3A inducers	Opioid effect attenuated	35 (1.5)
Morphine + rifampin	Opioid effect attenuated	2 (0.1)
Potential interactions of other drugs used for symptom control and other clinical conditions (not listed above)		
Corticosteroids and megestrol acetate + insulin and oral hypoglycemic drugs	Risk of hyperglycemia	81 (3.5)
Corticosteroids + megestrol acetate	Increased risk of hyperglycemia and adrenal insufficiency	9 (0.4)
Corticosteroids + CYP3A4 inhibitors	Decreased clearance of corticosteroid, increased clinical effect, risk of toxicity	125 (5.5)
Corticosteroids + CYP3A4 inducers	Increased clearance of corticosteroid, clinical effect attenuated	33 (1.4)
Metoclopramide + antipsychotics	Increased risk of extrapyramidal syndrome	73 (3.3)
Metoclopramide + SSRIs and SNRIs	Increased risk of serotonin and extrapyramidal syndromes	59 (2.6)
SSRIs + other agent with serotonergic activity, i.e., other antidepressants, tramadol, and dextromethorphan	Increased risk of serotonin syndrome	22 (1.0)
Hyoscine hydrochloride and butyl bromide + other muscarinic receptor antagonists, i.e., TCAs, neuroleptics, antihistamines, and urinary antispasmodics	Excessive anticholinergic effects	12 (0.5)
Haloperidol + other drugs with a risk of Torsades de Pointes (amiodarone, azithromycin, chloroquinine, chlorpromazine, cisaprid, citalopram, clarithromycin, domperidone, erythromycin, escitalopram, methadone, and sotalol)	Prolongation of QTc interval—risk of ventricular arrhythmias (Torsades de Pointes)	25 (1.1)
Diazepam + omeprazole	Inhibition of diazepam metabolism, increased sedation	9 (0.4)
Benzodiazepines substrates of CYP3A izoenzymes (diazepam, alprazolam, clonazepam, midazolam, flunitrazepam, clorazepate, and others) + CYP3A inhibitors	Increased effect, risk of overdosing, including CNS depression	30 (1.3)
Benzodiazepines substrates of CYP3A izoenzymes (diazepam, alprazolam, clonazepam, midazolam, flunitrazepam, clorazepate, and others) + CYP3A inducers	Sedative hypnotic effect attenuated	11 (0.5)

(*Continued*)

Table 4
Continued

Coadministered Drugs	Potential Clinical Effect	Number of Patients (%)
Warfarin and other oral anticoagulants + NSAIDs, ASA, antiplatelet agents, proton pump inhibitors, sulfamethoxazole,[a] quinolones, fluconazole and other antifungal azoles,[a] metronidazole,[a] amiodarone,[a] tramadol, paracetamol, allopurinol, and statins	Increased risk of bleeding	61 (2.7)

DDIs = drug-drug interactions; CYP = cytochrome P450; ASA = acetylsalicylic acid; ACE inhibitors = angiotensin-converting enzyme inhibitors; NSAIDs = nonsteroidal anti-inflammatory drugs; TCA = tricyclic antidepressants; CNS = central nervous system; LWMH = low-weight molecular heparin; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors.
[a]Via inhibition of CYP2C9.

at muscarinic receptors (mostly antipsychotics, tricyclic antidepressants, and antispasmodics). Finally, 418 (18.3%) patients used drugs with a risk of Torsades de pointes and 39 took two or three of these agents. About 20% of patients who were treated with methadone and levomethadone or haloperidol were given at least one additional drug with a risk of Torsades de pointes. Multiple other potentially pharmacodynamic DDIs also were present (Table 4).

Exposure to Clinically Relevant Pharmacokinetic DDIs via CYP450

The patients used many drugs important to palliate symptoms that are substrates of the CYP3A4 (izoenzyme of cytochrome P450); 58.3% of patients used fentanyl, oxycodone, methadone or levomethadone, or buprenorphine, all Step III opioids that are metabolized by CYP3A enzymes (Table 4). Benzodiazepines that are substrates of CYP3A4, that is, diazepam, alprazolam, clonazepam, midazolam, flunitrazepam, and clorazepate, were used by 12.8% of patients. The other substrates of CYP3A4 used most frequently included corticosteroids, nonbenzodiazepine hypnotics, haloperidol, and calcium channel blockers; 9.2% of patients were given one or more moderate or strong CYP3A4 inhibitor (antifungal azoles, ciprofloxacin, macrolides, verapamil, diltiazem, and nelfinavir). A limited number of patients (2.4%) used a CYP3A4 inducer (carbamazepine, phenytoin, phenobarbital, modafinil, rifampin, and efavirenz; Table 5). Oxycodone, which is converted to active metabolites by CYP2D6, was used by 20.8% of patients. Paroxetine and fluoxetine (strong inhibitors) or duloxetine (moderate inhibitor) of this enzyme were used by 1.7% of patients. Detailed information about the potential CYP-related DDIs are given in Tables 4 and 5.

Discussion

In this multicenter, multinational cross-sectional study including 2282 patients with advanced cancer, we observed that the patients used a mean number of 7.8 drugs and more than one-fourth of patients used 10 or more medications. Exposure to potential DDIs was frequent, and almost half of the patients used one or more unnecessary or potentially unnecessary medication.

Our findings are consistent with most previous studies.[1–3,17–20] One exception is a study performed in a palliative care inpatient unit by Gaertner et al.,[20] where the median number of drugs prescribed was 14.[18] However, this study included all drugs even if prescribed on-demand and never administered. Furthermore, medications were registered for the complete length of the hospital stay, and not all medications were given concomitantly. In the present study, we analyzed all drugs used within the last 24 hours, including over-the-counter medications and herbal preparations, giving a number for the actual exposure to drugs and drug combinations.

The clinical significance of this observed polypharmacy is emphasized by the finding that older patients, patients with lower performance status scores (KPS score ≤ 50), and patients treated in oncology wards or palliative care units/hospices used a higher number of medications (Table 1). Thus, those patients who are most vulnerable also used the higher number of drugs, which is consistent with the findings by Currow et al.[3] This may simply be

Table 5
Drugs With Inhibitory or Inductive Effect on Main Metabolizing Enzymes and P-gp, Used by the Study Population[6,27–30,33–44]

Drug	CYP3A4	CYP2D6	CYP1A2	CYP2C9	CYP2C19	P-gp	Other	Number of Patients (%)
Amiodarone	Weak inhibitor	Weak inhibitor		Moderate inhibitor		Inhibitor		17 (0.7)
Carbamazepine	Strong inducer			Moderate inducer		Inducer		28 (1.2)
Carvedilol						Inhibitor		25 (1.1)
Chlorpromazine		Moderate inhibitor						13 (0.6)
Ciprofloxacin	Moderate inhibitor		Strong inhibitor					66 (2.9)
Clarithromycin	Strong inhibitor					Inhibitor		13 (0.6)
Dexamethasone	Weak inducer					Inducer	UGT inducer	619 (27.1)
Diltiazem	Moderate inhibitor	Weak inhibitor				Inhibitor		11 (0.5)
Erythromycin	Moderate inhibitor					Inhibitor		1 (0.04)
Esomeprazole					Moderate inhibitor			402 (17.6)
Felodypine						Inhibitor		11 (0.5)
Fluconazole	Moderate inhibitor			Moderate inhibitor	Strong inhibitor			101 (4.4)
Fluoxetine	Weak inhibitor	Strong inhibitor		Weak inhibitor	Moderate inhibitor			13 (0.6)
Haloperidol		Possible major inhibitor						146 (6.4)
Itraconazole	Strong inhibitor					Inhibitor		4 (0.2)
Modafinil	Moderate inducer							4 (0.2)
Omeprazole					Moderate inhibitor			259 (11.3)
Paroxetine		Strong inhibitor						25 (1.1)
Phenobarbital	Likely major inducer		Weak inducer	Weak inducer	Possible major inducer			6 (0.3)
Phenytoin	Strong inducer		Moderate inducer			Inducer		11 (0.5)
Rifampin	Strong inducer			Moderate inducer	Moderate inducer	Inducer	Moderate CYP2B6 and 2C8 inducer, UGT inducer	3 (0.1)
Verapamil	Moderate inhibitor	Weak inhibitor	Weak inhibitor			Inhibitor		22 (1.0)
Voriconazole	Strong inhibitor			Weak inhibitor	Moderate inhibitor			3 (0.1)
Ticlopidine		Weak inhibitor			Strong inhibitor		Weak CYP2B6 inhibitor	11 (0.5)

UGT = UDP-glucuronosyl transferase; P-gp = P-glycoprotein.

a result of the fact that sicker patients need more treatment. However, caution is advised as many patients used medications considered to be unneeded. Furthermore, the differences in use across countries demonstrated in this study suggest that not all indications are absolutes.

The drugs and drug classes used most commonly in addition to opioids were proton pump inhibitors (62.4%), laxatives (52%), corticosteroids (49.1%), paracetamol (31.2%), NSAIDs (29.9%), metoclopramide (28%), benzodiazepines (24.1%), anticoagulants (23%), antibiotics (21.4%), anticonvulsants (21.3%), diuretics (20.1%), and antidepressants (19.8%). This distribution illustrates that, in advanced cancer pain patients, drugs used to minimize pain and other symptoms represent a large part of the total drug use. The assessment of the use of adjuvants and symptomatic medications reveals differences between countries, especially for corticosteroids, agents with high risk for serious adverse drug reactions. These differences may represent more variable practice between centers than countries. Irrespective of representing a center or country variability, the lack of a more uniform practice may be related to limited evidence-based knowledge,[49–51] resulting in treatment that is based on local practice. Recent guidelines for treatment of cancer pain[49] primarily describe the use of opioids; the findings in this study of a large variability in drug selection and doses for other analgesics argue that new guidelines also should include nonopioid analgesic therapy.

According to the literature, "medical futility" is described as "an intervention that no longer provides patients benefit, does not achieve a valuable goal, has a potential for harm, and lacks benefits to justify resources," and includes unneeded/unnecessary drugs.[25,26,52–54] Most drugs used by the study population are essential for symptom control or the treatment of other clinical conditions. However, almost 20% of patients used unnecessary drugs, one-third used potentially unnecessary drugs, and a further 7% was exposed to duplicate or antagonistic agents. This result agrees with previous studies where up to 24% of ambulatory patients with advanced cancer used at least one unnecessary drug.[25,26] In the study by Riechelmann et al.,[25] about 2% of patients used duplicate drugs, mostly benzodiazepines. Similarly, in our survey, benzodiazepines were duplicated in 34 (1.5%) patients. Additionally, we observed a number of other duplicate drugs including opioids, antipsychotics, cardiovascular medications, anticoagulants, muscarinic receptor antagonists, diuretics, D2 antagonists, and metamizole. Drug duplications may be caused by physicians who are not familiar with drugs, drugs that appear by different brand names, and prescribed by more than one physician. However, we recognize that in some cases both the categorization for a drug as an unnecessary drug or a duplicate may not reflect reality.

The use of a high number of drugs in advanced cancer and palliative care patients should raise concern of the risk of adverse drug events, including adverse drug reactions and DDIs. Previous studies have indicated a high prevalence of potential DDIs in these patients[17–21]; however, assessment is difficult, and the results are dependent on the methods used for their identification. In a study by Riechelmann et al., in 372 advanced cancer outpatients receiving supportive care exclusively, 250 potential DDIs, related to the use of phenytoin, corticosteroids, warfarin, angiotensin-converting enzyme inhibitors, NSAIDs, and some others, were identified in 31% of the patients.[19] Most of the same drugs were in a study done by Miranda et al.,[13] associated with unplanned admissions to an oncology ward because of DDIs. In the study by Gaertner et al.,[20] a total of 631 potential DDIs were found in 151 of 200 palliative care inpatients. The combinations of drugs such as scopolamine, neuroleptics, metoclopramide, antihistamines, NSAIDs, (levo-) methadone, amitriptyline, carbamazepine, and diuretics were indicated to have high potential for DDIs in the study population. However, a detailed analysis of eight patients with the highest risk for DDIs did not confirm their clinical relevance, which demonstrates the need for individual assessments. In another study performed in palliative care inpatients during the last two weeks of life, published by the same group, potential DDIs were present in 61% of 364 patients. NSAIDs, antipsychotics, antiemetics, antidepressants, insulin, glucocorticoids, and cardiovascular drugs were the most frequently implicated drugs.[21]

Thus, both the previous studies and our study confirm that drugs with a recognized potential for DDIs are frequently used, but the studies do not actually describe how often the observed DDIs impair analgesia or lead to adverse effects. Still, as reviewed by Brennan,[6] several case reports reflect that DDIs are a clinically relevant entity in cancer patients receiving palliative care.

Factors other than polypharmacy may increase the risk for DDIs, such as genetic variations that influence drug pharmacokinetics or pharmacodynamics, renal failure that may cause an accumulation of active metabolites, severe liver impairment, or a narrow therapeutic index of a drug,[6,42,43] all factors relevant for opioid treatment in cancer patients with pain. The risk for adverse effects from DDIs in patients with advanced cancer underlines the importance for palliative care physicians to regularly check patients' medication lists for drugs that are not expected to provide benefit to the patient, are duplicates, or have antagonistic actions. Possible drugs with a known great potential for DDIs (Tables 4 and 5) should be avoided if possible, and doses should be adjusted if the patient develops renal or liver impairment.

In the present study, we identified potential DDIs through a literature search and from electronic DDI databases (Table 4).[6,20,21,27–48] To identify the relevant DDIs, we included only those that have been demonstrated in humans. We may, therefore, by omitting DDIs observed in preclinical models, have underestimated the risk for DDIs. It is also noteworthy that the possible adverse effects because of drug combinations observed in this study have potentially serious consequences. Sedation, gastric ulcers, increased bleeding, cognitive impairment, Parkinson-like symptoms, anticholinergic effects, serotonin syndrome, and cardiac arrhythmias all have major implications for the patient. Several of the adverse effects resulting from polypharmacy also limit the patients' chances to obtain pain relief. One example is sedation, which limits adequate titration of opioids.

CYP3A4 is involved in the metabolism of more than half of all drugs and is the enzyme most implicated in serious DDIs (Tables 4 and 5). The variable susceptibility of drugs, including opioids, to DDIs derived from inhibition or induction of CYP450 enzymes has been recently investigated.[29,40,55–61] In the present study, a large number of patients used one of the WHO Step III opioids that are metabolized by CYP3A4 (fentanyl, oxycodone, methadone, levomethadone, and buprenorphine) and, at the same time, another CYP3A4 substrate, a CYP3A4 inhibitor, or a CYP3A4 inducer[27–30,33–43] (Table 5). During stable treatment with all medications, this comedication should not have major clinical consequences, as opioids will be titrated to effect. The more dangerous clinical situation is when drugs influencing CYP3A4 activity are introduced or stopped. Opioid metabolism may then rapidly change, and overdosing or increased pain may occur.[6] Metabolism of opioids that undergo glucuronidation (i.e., morphine, hydromorphone, buprenorphine) may be further affected by drugs that influence the activity of UDP-glucuronyl transferases; however, this is known to be of less clinical significance and was not presented separately in this article (except for the case of rifampin, Tables 4 and 5).[35,44,59] In addition, several opioids are glycoprotein P substrates.[28] Glycoprotein P is an efflux transporter protein involved in cellular uptake and excretion of drugs from the gastrointestinal and urinary tracts, which also limit penetration of many drugs (including morphine and other opioids) across the blood-brain barrier. Its activity is influenced by many drugs including rifampin, clarithromycin, itraconazole, amiodarone, cyclosporine, verapamil, ritonavir, and others, representing additional risk for DDIs.[28]

We recognize that the present study has some limitations. First, this study did not record drugs not given on a daily basis. This may give an underestimation of the drugs actually having an effect on the patients at the time of the study, which is particularly important concerning the cytotoxic drugs. Second, the assessment of unnecessary drugs was performed retrospectively. This limits the possibility to assess each patient individually for special indications. The use of a special instrument designed for assessing unneeded drugs, such as the Medication Appropriateness Index,[62] would better have described each medication. However, the retrospective assessment of unneeded drugs and the practicalities associated with using a 10-item instrument for close to 18,000 drug administrations

precluded the use of this instrument. Third, this study only assessed the number of potential DDIs and use of unneeded drugs, and therefore, we have no assessment of the frequency of the various clinical symptoms caused by polypharmacy.

In conclusion, this study demonstrates that advanced cancer patients with pain treated with a WHO Step III opioid use a high number of concomitant drugs. Nonopioids and corticosteroids are frequently used, but different patterns of use were observed between countries. Potential DDIs were identified in most patients, of which several could result in serious complications. Furthermore, many patients receive unneeded drugs. These findings demonstrate that patients with advanced cancer should be carefully followed to continuously evaluate drug therapy.

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Paper III

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ORIGINAL REPORT

Efficacy of Methylprednisolone on Pain, Fatigue, and Appetite Loss in Patients With Advanced Cancer Using Opioids: A Randomized, Placebo-Controlled, Double-Blind Trial

Ørnulf Paulsen, Pål Klepstad, Jan Henrik Rosland, Nina Aass, Eva Albert, Peter Fayers, and Stein Kaasa

See accompanying editorial on page 3210; listen to the podcast by Drs Vardy and Agar at www.jco.org/podcasts

A B S T R A C T

Purpose
Corticosteroids are frequently used in cancer pain management despite limited evidence. This study compares the analgesic efficacy of corticosteroid therapy with placebo.

Patients and Methods
Adult patients with cancer receiving opioids with average pain intensity ≥ 4 (numeric rating scale [NRS], 0 to 10) in the last 24 hours were eligible. Patients were randomly assigned to methylprednisolone (MP) 16 mg twice daily or placebo (PL) for 7 days. Primary outcome was average pain intensity measured at day 7 (NRS, 0 to 10); secondary outcomes were analgesic consumption (oral morphine equivalents), fatigue and appetite loss (European Organisation for Research and Treatment of Cancer–Quality of Life Questionnaire C30, 0 to 100), and patient satisfaction (NRS, 0 to 10).

Results
A total of 592 patients were screened; 50 were randomly assigned, and 47 were analyzed. Baseline opioid level was 269.9 mg in the MP arm and 160.4 mg in the PL arm. At day-7 evaluation, there was no difference between the groups in pain intensity (MP, 3.60 *v* PL, 3.68; $P = .88$) or relative analgesic consumption (MP, 1.19 *v* PL, 1.20; $P = .95$). Clinically and statistically significant improvements were found in fatigue (−17 *v* 3 points; P .003), appetite loss (−24 *v* 2 points; $P = .003$), and patient satisfaction (5.4 *v* 2.0 points; $P = .001$) in favor of the MP compared with the PL group, respectively. There were no differences in adverse effects between the groups.

Conclusion
MP 32 mg daily did not provide additional analgesia in patients with cancer receiving opioids, but it improved fatigue, appetite loss, and patient satisfaction. Clinical benefit beyond a short-term effect must be examined in a future study.

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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INTRODUCTION

Pain is a prevalent symptom in patients with cancer,[1] and providing pain relief is a challenge. Cancer pain is complex, involving inflammatory, neuropathic, ischemic, and compression mechanisms.[2] Pain may be caused by a mixture of these mechanisms in the individual patient, occurring at multiple sites and changing over time.[2]

Careful assessment of pain and titration of nonopioid and opioid analgesics comprise the basis of cancer pain treatment. In addition, the WHO and European Association for Palliative Care pain management recommendations state that adjuvant pain medications should be considered at each step of the WHO analgesic ladder.[3] Corticosteroids are one of the adjuvant pain medications, according to the treatment guidelines.[4-7]

Inflammation is a significant pain-modulating factor. Proinflammatory cytokines and chemokines can directly modulate neuronal activity in both the peripheral and CNSs.[8] Glia cells play a major role in pain regulation, in part by releasing proinflammatory cytokines.[9] Corticosteroids are potent anti-inflammatory drugs, inhibit a range of proinflammatory molecules,[10] and are recommended therapy as an adjunct for postoperative pain.[11] In two randomized trials, analgesic effect in patients with cancer was reported.[12,13] Corticosteroids can also mediate pain relief by reducing tumor-related edema in brain metastases[14] or by directly reducing tumor burden (eg, in prostate cancer).[15]

Corticosteroids are used in a large proportion of patients with cancer pain. A European survey of 3,030 patients admitted to palliative care programs showed that 39% used corticosteroids.[1] A Swedish survey showed that 50% of patients with cancer in palliative care received corticosteroids, and pain was the indication for treatment in 25% of the cases.[16] However, in a recently published systematic literature review, we found little evidence for an analgesic effect of corticosteroids in the treatment of cancer pain.[17] This review calls into question the widespread use of corticosteroids for cancer pain.[17]

The most common indications for starting corticosteroids in the Swedish survey were appetite loss (37%), fatigue (36%), and poor well-being (33%).[16] An expert working group of the European Association for Palliative Care stated that steroids might be effective in relieving fatigue for a short period of time, but the documentation was weak.[18] A systematic review of the treatment of cancer-associated anorexia and weight loss reported evidence to support the use of corticosteroids in short courses as an appetite stimulant.[19]

Against this background, we performed a randomized controlled trial with the primary aim of comparing the analgesic effects of oral methylprednisolone 32 mg with placebo administrated for 7 days in patients with cancer pain using opioids. Secondary aims were to evaluate the effects of corticosteroids regarding fatigue, appetite loss, satisfaction with treatment, and tolerance of this medication.

PATIENTS AND METHODS

Study Design

The study was a randomized, placebo-controlled, double-blind, parallel-group, multicenter phase III trial of oral corticosteroids in patients with cancer experiencing pain. The trial was conducted according to Good Clinical Practice guidelines, monitored independently by staff members from Oslo University Hospital, and registered in ClinicalTrial.gov on May 8, 2008. The study was approved by the Regional Committee for Medical Research Ethics and Norwegian Directorate of Health. The procedures were conducted in accordance with the Declaration of Helsinki, as revised in 1983. The technical appendix, statistical code, and complete anonymized data set are available from the corresponding author.

Patients

Patients with cancer, age $\geq$ 18 years with average pain $\geq$ 4 (numeric rating scale [NRS], 0 to 10) in the last 24 hours, with $>$ 4 weeks expected survival and receiving an opioid for moderate or severe cancer pain, were eligible for the study. Exclusion criteria were as follows: excruciating pain (average pain NRS $\geq$ 8 in last 24 hours), use of corticosteroids in the last 4 weeks, diabetes mellitus, peptic ulcer disease, concurrent medication with nonsteroidal anti-inflammatory drugs, radiotherapy or systemic cancer treatment started $<$ 4 weeks before entering the study or planned to start within the study period, spinal cord compression or need of bone surgery, and severe cognitive impairment. No changes in the current scheduled opioid medication were allowed for the last 48 hours before inclusion or throughout the study period. Patients could use additional opioid for breakthrough pain. In- and outpatients were screened for participation at five palliative care units and outpatient oncology services in Norway: Telemark Hospital, Haraldsplass Deaconess Hospital, Sørlandet Hospital, St Olav's University Hospital, and Oslo University Hospital. Written informed consent was obtained before any study-related procedures were performed.

Randomization and Masking

Computerized randomization was provided by Norwegian University of Science and Technology by personnel not otherwise involved in the study. Randomization was stratified for study center and pain related to verified bone metastases. Production of study drugs was performed at the hospital pharmacy at the Telemark Hospital Trust. Randomization was blinded for all parties until the completion of data collection.

Intervention

After baseline assessment, patients received identical-looking capsules of the study drug containing either methylprednisolone 16 mg or placebo twice daily for 7 days. Patients were contacted daily by a study nurse during the treatment period to ensure compliance with the protocol.

Instruments

Medical and sociodemographic data. Patient demographics, medications, clinical characteristics, and pain categories, as judged by clinical evaluation, were recorded at baseline (Table 1). Daily analgesic consumption, which was a secondary outcome in the trial, was recorded in a diary and converted to oral morphine equivalents.[20]

Symptom assessment. Primary end point was average pain intensity (NRS, 0 [no pain] to 10 [worst imaginable pain]), as measured by the Brief Pain Inventory[21] at day 7. Secondary outcomes were daily pain intensity at rest measured by the Edmonton Symptom Assessment System (NRS, 0 to 10), reported as area under the curve[22]; change in fatigue and appetite loss from

Table 1. Patient Demographic and Clinical Characteristics at Inclusion (N = 49)

Characteristic	Methylprednisolone (n = 26)		Placebo (n = 23)	
	No.	%	No.	%
Sex				
Female	13		11	
Male	13		12	
Age, years				
Mean	62.5		66.0	
95% CI	59.0 to 65.9		60.8 to 71.2	
Karnofsky score (0 to 100)				
Mean	66.4		65.7	
95% CI	60.8 to 72.2		59.7 to 71.6	
Cancer diagnosis				
Breast	1	4	1	5
Prostate	3	12	3	14
GI	6	23	5	23
Lung	6	23	5	23
Gynecologic	5	19	5	23
Other	7	27	4	18
Metastasis				
No	1	4	1	5
Liver	11	42	6	27
CNS	2	8	0	0
Bone	9	35	6	27
Lung	4	16	3	14
Other	15	58	18	82
Mini Mental State Examination score				
Mean	27.1		27.0	
Concomitant disease				
Total	16	62	13	59
Cardiac	4	16	4	18
Vascular	5	19	8	36
Lung	3	12	4	18
GI/hepatic	4	16	1	5
Other	8	31	10	43
Ongoing cancer treatment				
Radiotherapy	0	0	0	0
Chemotherapy	4	16	3	14
Hormonal therapy	3	12	3	14
None	19	73	17	77

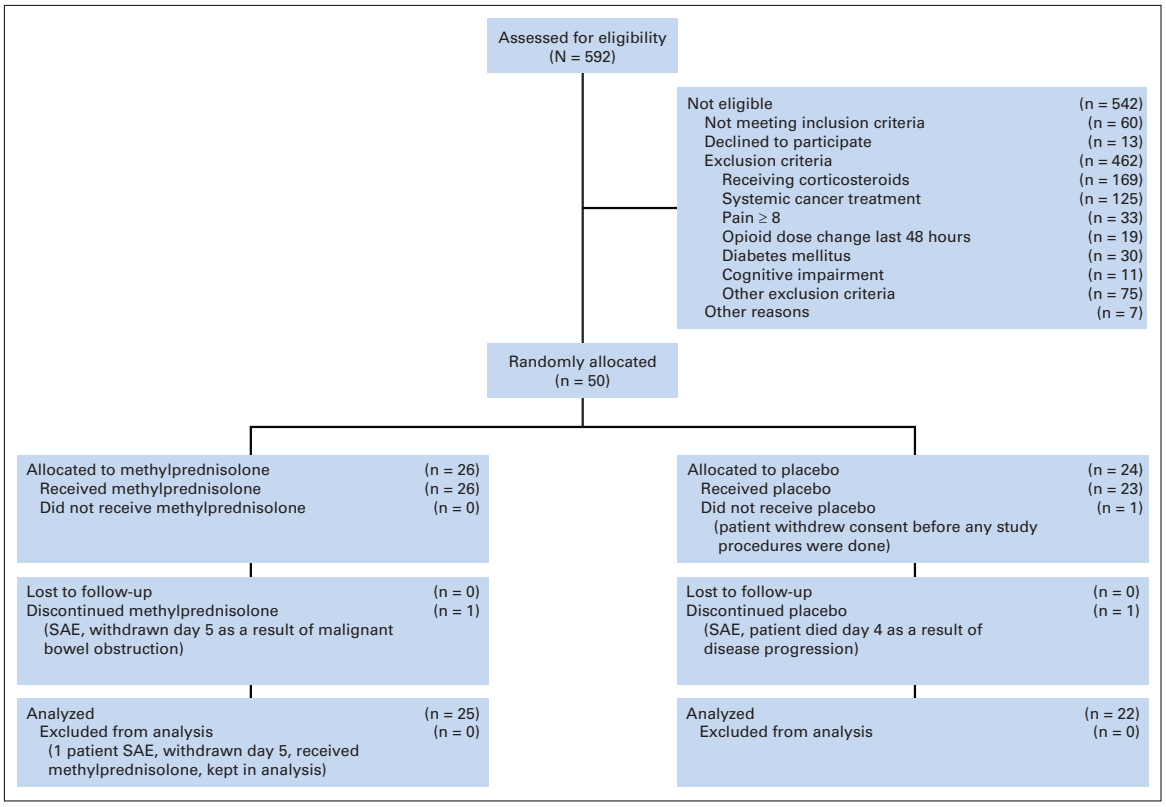

Fig 1. CONSORT flow diagram. SAE, serious adverse effect.

baseline to day 7, both measured by the European Organisation for Research and Treatment of Cancer–Quality of Life Questionnaire C30[23]; and overall satisfaction with the intervention (NRS, 0 [no benefit] to 10 [major benefit]) measured at day 7. Fatigue and appetite loss scores were calculated according to guidelines,[24] with scores ranging from 0 to 100; a higher score represented a higher level of symptoms (ie, worse). A difference of 10, corresponding to 1 on the NRS (0 to 10) scales, was considered clinically significant.[25]

Adverse effects. The presence of adverse effects (AEs) was assessed by the investigator at day 7 through semistructured interviews (presence of edema, sleeplessness, restlessness, anxiety, muscle weakness, psychological changes, dyspepsia, mouth symptoms, and other [yes *v* no]). The complete protocol is available at http://www.ntnu.edu/prc/projects.

Statistical Analysis

The trial was designed to detect a difference in average pain intensity of 1.5 (NRS, 0 to 10) between the intervention and placebo groups measured at day-7 evaluation.[26] With a standard deviation of 1.5,[12] two-sided *t* test, power of 0.90, and significance level of .05, the estimated sample size was 22 evaluable patients in each group. A total of 50 patients were recruited to allow for dropouts.

All data are reported as means, 95% CIs, ranges, medians, or frequencies as appropriate. In the comparison between the two groups, the independent student's *t* test was used for continuous variables. In addition, regression and covariate analyses were performed to adjust for pain intensity and other differences between the groups at baseline, with the stratification factor of pain related to verified bone metastasis and study center. Mann-Whitney U test was used for noncontinuous variables. A *P* value ≤ .05 was defined as significant. SPSS statistical software (versions 15.0 and 19.0; SPSS, Chicago, IL) was used for all statistical analyses. Statistical analyses were performed according to intention-to-treat principles.

RESULTS

Study Population

A total of 592 patients with cancer and average pain intensity ≥ 4 in the last 24 hours were identified and screened for eligibility at five outpatient oncology services and palliative care programs. Fifty patients were recruited during the period from April 2008 to January 2012. The reasons for excluding patients are shown in Figure 1. The two treatment groups had some minor differences in characteristics at baseline (Tables 1 and 2). These were corrected for in the data analyses. Three patients did not complete the study period: one withdrew consent before any study procedures were performed, one died as a result of disease progression, and one was withdrawn because of malignant bowel obstruction. In addition, one patient was withdrawn because of rapidly increasing back pain at day 5. This patient received methylprednisolone 48 mg daily on an open basis because of clinical suspicion of spinal cord compression. The patient remained in the analysis, according to the principles of the intention-to-treat analysis. No patients were withdrawn or discontinued the study because of AEs.

Table 2. Pain Characteristics and Pain Medication at Inclusion (N = 49)

Characteristic	Methylprednisolone (n = 26)		Placebo (n = 23)	
	No.	%	No.	%
Pain category				
Bone	6	23	5	23
Visceral	11	42	9	41
Soft tissue	1	4	6	27
Neuropathic	5	19	1	5
Mixed	3	12	2	9
Breakthrough pain	14	54	17	77
Opioids				
Morphine	8	31	7	32
Oxycodone	9	35	10	45
Fentanyl	7	27	6	27
Other	2	8	0	0
Oral morphine equivalents (mg per day)				
Mean	269.9		160.3	
95% CI	168.0 to 371.8		90.2 to 230.5	
Nonopioids				
Paracetamol	22	85	22	100
Pregabalin	3	12	3	14
Gabapentin	6	23	0	0
Amitriptyline	1	4	2	9
Ketamine	1	4	0	0

Twenty-five patients were evaluable in the corticosteroid group, and 22 patients in the placebo group (Fig 1).

Efficacy Analyses

Treatment effect on pain relief. At day 7, there were no differences in average pain intensity (mean difference, −0.08; 95% CI, −0.97 to 1.13; corticosteroid arm, 3.6; 95% CI, 2.8 to 4.4; placebo arm, 3.7; 95% CI, 3.0 to 4.4; $P = .88$). Similarly, there were no significant differences in pain intensity between the groups when measured as change from baseline (−0.48; 95% CI, −1.43 to 0.47; corticosteroid arm, −1.16; 95% CI, −1.96 to −0.35; placebo group, −0.68; 95% CI, −1.28 to −0.08; $P = .50$; Table 3; Fig 2). Correcting for differences between groups in baseline pain intensity, allowing for covariates, reduced the difference between the groups to −0.33 (95% CI, −1.33 to 0.67).

There were no differences between the groups concerning opioid consumption. The opioid dose increased similarly in both groups (relative consumption day 7 *v* day 0: corticosteroid arm, 1.19; 95% CI, 1.00 to 1.38; placebo arm, 1.20; 95% CI, 0.90 to 1.51; $P = .95$; Table 3; Fig 3). Daily registrations of pain intensity at rest (area under curve) were also similar between the study groups (Table 3).

Regression analyses were also performed adjusting for differences in baseline characteristics between the groups (Tables 1 and 2): baseline opioid dose, presence of breakthrough pain, use of gabapentin or pregabalin, soft tissue pain, liver metastases, and other metastases. Regression analyses did not change the results. Interactions of treatment with pain categories and cancer type were explored using linear regression analyses and showed no evidence of important interactions; the β coefficients for medication and for the main effects of the prognostic factors were substantially unchanged when the interaction terms were included and excluded from the model.

Treatment effect on fatigue, appetite loss, and overall satisfaction. At day 7, there were significant improvements in fatigue and appetite loss in the corticosteroid group compared with the placebo group. Reported as change from baseline, fatigue improved 17 points (95% CI, −27 to −6) in the corticosteroid arm versus a deterioration of 3 points (95% CI, −5 to 11) in the placebo group ($P = .003$). Appetite improved 24 points (95% CI, −38 to −11) in the corticosteroid group versus a deterioration of 2 points (95% CI, −8 to 11) in the placebo group ($P = .003$). Regression analyses using the same variables as for pain intensity did not change the results (data not shown). Overall satisfaction with treatment was significantly higher in the corticosteroid group compared with the placebo group (5.4; 95% CI, 4.1 to 6.7 *v* 2.0; 95% CI, 0.7 to 3.3; $P = .001$; Table 3; Fig 2).

AEs. There were no differences between number of AEs in the corticosteroid group compared with the placebo group (average number, 1.08; 95% CI, 0.52 to 1.64 *v* 1.55; 95% CI, 0.85 to 2.24, respectively; $P = .28$; Table 4). The most frequent AEs were oral symptoms, restlessness, and sleeplessness. The two latter were more frequent in the corticosteroid group (restlessness, six *v* three; sleeplessness, four *v* three). Three serious AEs were reported during the treatment period: one in the placebo group, where a patient died at day 4 because of disease progression, and two in the corticosteroid group, where one patient was withdrawn on day 5 because of malignant bowel obstruction, and another was withdrawn on day 5 because of clinical suspected spinal cord compression. None of these were suspected to have been caused by the study medication.

DISCUSSION

This study found no evidence of any additional analgesic effect of methylprednisolone 32 mg daily for 7 days in patients with advanced cancer treated with opioids. Patients receiving corticosteroids reported less fatigue, better appetite, and better overall satisfaction with the treatment compared with the placebo group. The medication was well tolerated.

The evidence for analgesic effects of corticosteroids in patients with cancer was recently evaluated in a systematic literature review published by our research group.[17] Four randomized controlled trials were identified, but only one of these performed an adequate assessment of outcomes,[12] and the quality of evidence was rated low. Accordingly, only a weak recommendation was made: "Evidence supports that a moderate dose of corticosteroid, such as methylprednisolone 32 mg, may contribute to analgesia and seems to be well tolerated."[17(p104)] In addition, concern about serious AEs associated with continued high-dose treatment with corticosteroids was raised.

In a cross-over study by Bruera et al,[12] a difference in pain intensity of 13 (visual analog scale, 0 to 100) in favor of the corticosteroid period compared with the placebo period was found (CIs not provided). The intervention was similar to that in our study: methylprednisolone 16 mg twice daily. However, the two studies differ in some respects. In our study, patients used on average 222 mg oral morphine equivalents at baseline, had advanced cancer disease, and a mean Karnofsky performance score of 66, approximately equal to an Eastern Cooperative Oncology Group performance status of 2.[27] In the study by Bruera et al, the 28 evaluated patients used propoxyphene equaling approximately 36 mg of oral morphine equivalents,[28] and patients had a mean Eastern Cooperative Oncology Group performance status of 3.5. This indicates that the two studies represent two different cancer pain populations.

Table 3. Primary and Secondary Outcomes

Outcome	Methylprednisolone (n = 25) Mean	Methylprednisolone (n = 25) 95% CI	Placebo (n = 22) Mean	Placebo (n = 22) 95% CI	P*
Average pain intensity†‡					
Day 0	4.76	4.33 to 5.19	4.36	3.88 to 4.85	.21
Day 7	3.60	2.79 to 4.41	3.68	2.99 to 4.37	.88
Mean difference	−1.16	−1.96 to −0.35	−0.68	−1.28 to −0.08	.50
Morphine consumption (OMEs), mg§					
Day 0	273.8	167.8 to 379.8	165.8	93.1 to 238.5	.09
Day 7	318.6	192.3 to 444.8	188.2	103.2 to 273.2	.08
Mean difference	44.8	−16.0 to 105.6	22.4	−5.6 to 50.4	.51
Relative difference (day 7/day 0)	1.19	1.00 to 1.38	1.20	0.90 to 1.51	.95
Pain intensity at rest (day 1 to 7)‡§‖					
AUC	19.9	14.4 to 25.4	17.9	12.2 to 23.6	.60
Fatigue§‖¶					
Day 0	77.1	68.3 to 85.9	67.2	56.3 to 78.1	.15
Day 7	60.4	49.7 to 71.2	70.5	61.4 to 79.6	.16
Mean difference	−16.7	−27.0 to −6.3	3.3	−4.5 to 11.1	.003
Appetite loss§‖¶					
Day 0	73.3	60.2 to 86.5	63.6	50.8 to 76.5	.28
Day 7	49.3	34.9 to 63.7	65.2	51.9 to 78.4	.10
Mean difference	-24.0	−37.5 to −10.5	1.5	−8.1 to 11.2	.003
Patient satisfaction with treatment‡§	5.4	4.05 to 6.70	2.0	0.71 to 3.29	.001

Abbreviations: AUC, area under the curve; OME, oral morphine equivalent.
*t test.
†Primary outcome.
‡Numeric rating scale, 0 to 10.
§Secondary outcome.
‖Higher score in symptom assessment represents higher level of symptom (ie, worse).
¶Eastern Cooperative Oncology Group performance status, 0 to 100.

We observed a beneficial effect from corticosteroids on appetite loss and fatigue. A Cochrane review from 2010 found no research on corticosteroids with fatigue as the primary outcome.[29] In 2013, Yennurajalingam et al[30] published a randomized controlled trial with fatigue as the primary end point. Participants were outpatients with advanced cancer. The study demonstrated a significant improvement of 5.9 points (Functional Assessment of Chronic Illness Therapy–Fatigue subscale, range, 0 to 52) in the corticosteroid

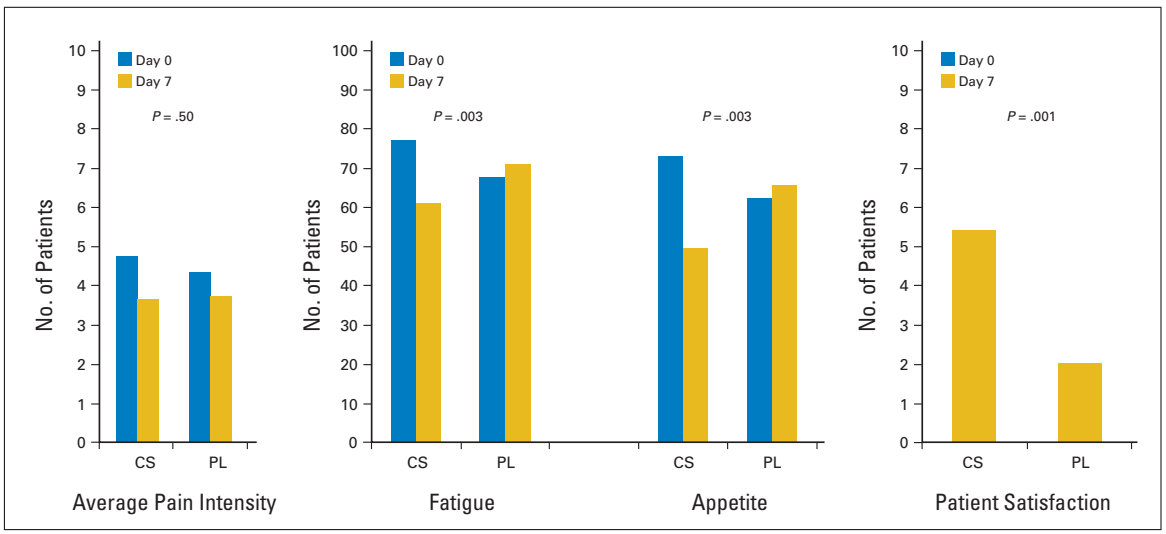

Fig 2. Main results: average pain intensity in last 24 hours (numeric rating scale [NRS], 0 to 10), fatigue and appetite (European Organisation for Research and Treatment of Cancer–Quality of Life Questionnaire C30, 0 to 100) on days 0 and 7, and patient satisfaction (NRS, 0 to 10) on day 7. CS, corticosteroid; PL, placebo.

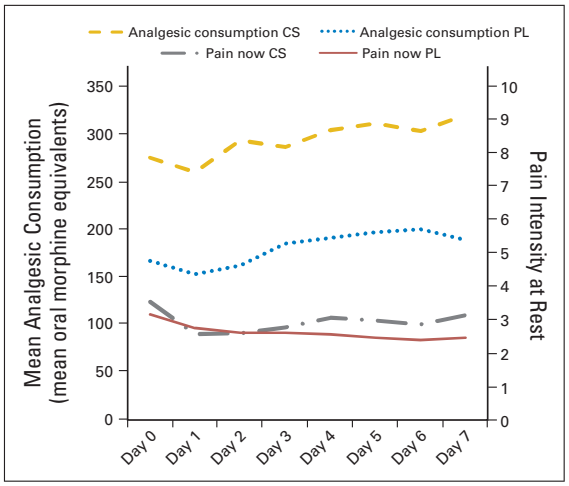

Fig 3. Mean analgesic consumption and pain intensity at rest (numeric rating scale, 0 to 10) as measured day by day. CS, corticosteroid; PL, placebo.

group receiving dexamethasone 4 mg twice daily compared with the placebo group. The improvements were significant after both 8 and 15 days. Both the corticosteroid doses used as well as the results demonstrated are comparable to the findings in our study. Several randomized controlled trials have demonstrated a short-term positive effect on appetite loss[12,13,30-33]; only one study did not demonstrate this effect.[34]

The number of AEs was low in our study, with no difference between the two groups. This finding coincides with the studies by Bruera et al[12] and Yennurajalingam.[30,34] It is generally agreed that corticosteroid toxicity is related to the total cumulative dose of corticosteroids as well as the duration of their use.[7,35] AEs accumulate with long-term use, and development of cushingoid habitus with moon face and skin atrophy, osteoporosis, hyperglycaemia, increased risk of infection, and neuropsychological effects[36] may interfere with health-related quality of life in this patient group. Furthermore, corticosteroids are known to promote muscle atrophy[37,38] and myopathy.[39]

Table 4. AEs

	Methylprednisolone (n = 25)		Placebo (n = 22)	
Predefined AE Category	No.	%	No.	%
Oral symptoms	6	24	7	32
Restlessness	6	24	3	14
Psychic change	2	8	3	14
Anxiety	2	8	3	14
Edema	1	4	5	23
Muscle weakness	1	4	3	14
Sleeplessness	4	16	3	14
Dyspepsia	3	12	4	18
Other	2	8	3	14
Total	27		34	
Mean No. of AEs	1.08		1.55	
P		.28		

Abbreviation: AE, adverse effect.

These effects may, in long-term use, counteract the positive effects on fatigue and appetite. Indeed, the trial by Bruera et al indicated that the appetite-stimulating effect of corticosteroids diminishes over time. This underlines the need for larger long-term studies. Nevertheless, the reported results support a short-term trial of corticosteroids in patients with cancer-related fatigue or loss of appetite.

To our knowledge, ours is the first randomized, controlled, double-blind study investigating the analgesic properties of corticosteroids in a population of patients with advanced cancer using opioids. Although the majority of patients included had metastatic disease, the number of dropouts and amount of missing data were low. All outcomes for pain intensity and analgesic consumption showed in a consistent way that there were no differences between the intervention and control groups. It was known that a large proportion of the patient group screened already used corticosteroids or had received systemic cancer treatment. Therefore, it was necessary to screen a large number of patients to reach the target of 50 eligible patients. The recruitment period was 45 months. This may have introduced a possible selection bias. The corticosteroid group had higher levels of pain intensity, morphine consumption, fatigue, and loss of appetite at baseline compared with the placebo group, although none of these differences were statistically significant. Regression analyses did not change the results.

Our trial did not show any analgesic effects from corticosteroids. The small sample size is reflected by the wide 95% confidence limits. However, the clinical difference of interest was above the upper bound of the 95% CI, which confirms that there is unlikely to have been a clinically useful effect. The outcomes of fatigue and appetite loss showed both clinically and statistically significant improvement. This suggests that the lack of analgesic effect in the study was not a small-sample effect and supports the main conclusion. However, the sample size was too small to perform a subgroup analysis, which could have been of clinical interest.

Lack of analgesic effect in the this study should not preclude the use of corticosteroids in cancer pain syndromes where specific mechanisms of action from these drugs are effective. Examples of such mechanisms are reduction of edema in patients with cerebral metastases and tumor reduction in patients with lymphoma.

In conclusion, our study found no evidence of an analgesic effect of methylprednisolone 32 mg daily in patients with advanced cancer treated with opioids. Thus, this study provides no support for cancer pain in general as an indication for starting treatment with corticosteroids. Patients who received corticosteroids had clinically significant reduced fatigue and increased appetite, as well as a significantly higher level of treatment satisfaction, suggesting a symptomatic benefit from the treatment. Clinical benefit beyond short-term effects must be examined in a future study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Ørnulf Paulsen, Pål Klepstad, Peter Fayers, Stein Kaasa
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Collection and assembly of data: Ørnulf Paulsen, Jan Henrik Rosland, Nina Aass, Eva Albert
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Manuscript writing: All authors
Final approval of manuscript: All authors

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GLOSSARY TERMS

chemokines: cytokines that are responsible for chemotactic responses. Chemokines are heparin-binding proteins, which play a role in a variety of biologic processes, the most important being leukocyte chemotaxis. Their classification as C, CC, CXC, and CX3C is based on the position of cysteine residues that form two disulfide bonds. Typically, chemokines mediate their effects through G protein–coupled seven-transmembrane domain receptors, which belong to four families on the basis of their affinity for a given chemokine–CXCR1 to CXCR5, CCR1 to CCR9, XCR1, and CX3CR1.

cytokines: cell communication molecules that are secreted in response to external stimuli.

Eastern Cooperative Oncology Group performance status: criteria used by doctors and researchers to define the progression of a patient's disease, assessing how the disease affects daily living habits, and to assist in the determination of the appropriate treatment and prognosis.

Karnofsky performance score: a standard way of measuring the ability of patients with cancer to perform ordinary tasks. Karnofsky performance scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities. The Karnofsky performance score may be used to determine a patient's prognosis, measure changes in a patient's ability to function, or decide whether a patient could be included in a clinical trial.

stratification factor: a factor used to separate data into subgroups to determine whether that factor is significant.

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Are Corticosteroids Effective in All Patients With Cancer-Related Pain?

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Corticosteroids are commonly used in cancer medicine. Many chemotherapy regimens, especially those used in the treatment of hematologic malignancies, often include corticosteroids, sometimes at high-doses. Often the impact of the sudden cessation after 5 days of high-dose corticosteroids was the major adverse effect reported by patients. Even more recently, corticosteroids were included in the treatment of prostate cancer, prompting some to ask whether corticosteroids were active agents in this disease.[1] While not included in many newer chemotherapy regimens, corticosteroids are often administered at significant doses as antiemetics for moderately and highly emetogenic chemotherapy regimens. In fact, the optimal value of 5-HT_3 antagonists as antiemetics seems strongly related to their concurrent use with corticosteroids. In addition, the use of prednisone in combination with calcitonin was standard practice for management of hypercalcemia, before the development of bisphosphonates.

There have been many questions raised as to the value of corticosteroids in cachexia and appetite stimulation. Although studies have shown mixed results, it has been the experience of many physicians that corticosteroids may be beneficial in patients with refractory cachexia for stimulation of appetite and improvement in quality of life. However, the use of corticosteroids was recommended for short (maximum 2 weeks), periods as longer duration of treatment may increase the likelihood of adverse effects including deterioration in muscle strength.[2]

Corticosteroids are used commonly when it is felt that inflammation may be contributing to the patient's symptoms. For brain metastases and spinal cord compression, corticosteroids have always been an effective option to relieve edema. Some have suggested that a response to corticosteroids in brain metastases and metastatic cord compression may even indicate the disease's response to radiotherapy, but with little evidence to support the claim. Corticosteroids are listed as emergent therapy for cord compression and superior vena syndrome often with dramatic responses. Clinical experience suggests that corticosteroids might also be highly effective for liver capsular pain and for pain-related to nerve compression. However, in a recently published systematic literature review, there was little evidence for an analgesic effect of corticosteroids in the treatment of cancer pain.[3]

Recommendations for the use of corticosteroids in cancer and palliative care have since been supported by reports and guidelines from various organizations.[4] A study of corticosteroid use in Swedish patients with cancer demonstrated that corticosteroids were used commonly; 50% of patients with cancer in the palliative care setting received corticosteroids.[5] The most common indications for starting corticosteroids in this survey were appetite loss (37%), fatigue (36%), and poor well-being (33%) while pain was an indication in 25%. A recent report from New Zealand[6] showed that of almost 1,200 patients receiving care from seven inpatient hospices, two thirds had received at least one course of corticosteroids during that care. The reasons for corticosteroids were a nonspecific indication (40%), neurologic symptoms (25.3%), and soft-tissue infiltration symptoms (14.4%). Detailed information was recorded for a sample of 260 patients with the agent of choice being dexamethasone with a median dose of 8 mg (dose range, 1 mg-40 mg). Corticosteroids were prescribed for a median duration of 29 days per course. Abrupt stopping occurred in 72 (23.2%) cases; of these 35 (49%) had been on a course of corticosteroids for more than 3 weeks. Corticosteroid-prescribing guidelines, including cessation titration, were only available in one hospice. Adverse effects were recorded in 82 (32%) but only 52% of the 260 had regular monitoring, thus suggesting that adverse events were in fact much more common than reported.

But do corticosteroids make a difference? The study by Norwegian investigators in the article that accompanies this editorial[7] uses high level evidence from a randomized, double-blind, placebo-controlled trial. Using well-validated tools, they measured the effect of methylprednisone (16 mg twice daily) on pain, fatigue, and appetite over a 1-week period. The study showed no difference in pain scores between the two groups when measured as absolute or percentage differences, and this negative finding was not changed by regression analysis. The study did find significant differences in appetite stimulation, fatigue, and overall satisfaction in favor of the corticosteroid group.

Will this level of evidence change practice in use of corticosteroids in oncology? Perhaps it will, but not necessarily in the direction expected. All could agree that the study provides evidence to support the use of short course of methylprednisone with the goal of improving appetite and fatigue in the short term. Fatigue and appetite are significant issues for patients with advanced cancer and a common cause of distress for both patients and families. However, based on other evidence,[2,6] caution needs to be taken with balancing adverse effects and benefits when corticosteroids are used for longer than a week in this setting.

Another important consideration involves a careful examination of the population treated in this study, to ensure that the results are generalizable to most patients treated in daily practice. The average morphine dose for patients with cancer has been quoted as being 60 mg/d.[8] The average morphine equivalent dose for this study was 220 mg per day and the medications were morphine, oxycodone, and fentanyl. No methadone was used in these patients, possibly a reflection of practice in Norway, while it is a commonly used drug in the United States for patients needing higher doses of opioids, especially those with neuropathic pain. Patients had to have stable pain for at least 48 hours before study entry, although they could be taking extra doses for breakthrough pain. Most patients with severe pain (pain scores > 7) were excluded from enrollment on the study. There were nonstatistically significant differences in the presence of neuropathic pain in the active care group with both higher opioids doses and greater use of gabapentin. To show how atypical this population may be, the study took some four years to accrue given difficulties in enrolling, and many patients were excluded if they in fact had had a previous dose of corticosteroids so we may in fact have some selection bias. The authors note all of these issues in the discussion, and acknowledge an earlier study by Bruera,[9] in which an average daily opioid dose of 20 mg/d was associated with a beneficial effect of corticosteroids on pain.

So, what is the bottom line? Short courses of corticosteroids seem to have an impact on fatigue and appetite and may continue to be useful in pain relief in patients on lower doses of opioids who have a possible inflammatory component to their pain. However, this study suggests that we not rely on corticosteroids as a coanalgesic in patients with cancer who have used them previously, and who are receiving higher doses of opioids. Other approaches for pain relief are clearly needed to better serve our patients experiencing cancer-related pain.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Are Corticosteroids Effective in All Patients With Cancer-Related Pain?

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Paper IV

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Title: The Relationship Between Pro-inflammatory Cytokines and Pain, Loss of Appetite and Fatigue in Patients with Advanced Cancer

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Abstract

Background: Systemic inflammation is associated with quality of life and symptoms in patients with advanced cancer. The aims of this study were to examine the relationships between inflammatory biomarkers and pain, appetite and fatigue; and to explore whether baseline biomarkers were associated with changes in pain, appetite and fatigue following treatment with corticosteroids.

Material and Methods: A secondary explorative analysis was done on a trial examining the analgesic properties of corticosteroids in patients with advanced cancer. Inclusion criteria were: >18 years, taking strong opioids; cancer diagnosis; pain ≥4 (numerical rating scale 0-10). Serum was extracted and levels of inflammatory biomarkers were assessed. Symptoms were assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30. The relationship between PROMs and inflammatory biomarkers was examined using Spearman Rho-Rank and multiple regression analysis.

Results: Data were available on 49 patients. Levels of sTNF-r1, IL-6, IL-18, MIF, MCP-1, TGF-β1, IL-1ra, and CRP and Erythrocyte sedimentation rate (ESR) were elevated; IL-1β, IL-2, IL-4, IL-8, IL-10, IL-12(p70), interferon-γ, MIP-1α, and TNF-α were below level of detection. Correlations were observed between appetite and IL-6, and CRP, and fatigue and IL-1ra (r_s: 0.380-0.413, p< .01). There was no association between pretreatment biomarkers and effect from corticosteroid treatment.

Conclusion: In patients with advanced cancer and pain, there are correlations between pro-inflammatory cytokines and appetite and fatigue. . Inflammatory biomarkers were not associated to pain or to the efficacy of corticosteroid therapy. Further research examining the attenuation of the systemic inflammatory response and possible effects on symptoms would be of interest.

Introduction:

Systemic inflammation is identified as the seventh "hallmark of cancer"(1); necessary for tumour genesis, maintenance and progression of the cancer state. Symptoms like pain, wasting, fatigue, cognitive impairment, anxiety and depression are frequent and often co-occur in cancer patients. Together with symptoms' similarity with cytokine-induced sickness behavior, this led to the theory that they might share a common cytokine-based neuroimmunologic mechanism (2, 3).

In health, equilibrium exists between pro- and anti-inflammatory cytokines. Through an intricate interplay with mutually dependent positive and negative feedback mechanisms, cytokines are key mediators and provide homeostasis and immune control as part of the innate immune system (4). The complex tumor-host interactions that exist in the setting of advanced cancer result in disturbance of this equilibrium. Data from patients with advanced cancer show a cytokine pattern that suggests a state of simultaneous immunostimulation and immunosuppression where pro-inflammatory cytokines predominate, finally resulting in increased concentrations of Macrophage Migration Inhibitory Factor (MIF), Tumour Necrosis Factor α (TNF-α), interleukin (IL) -6, IL-8, IL-10, IL-18, and Transforming Growth Factor β (TGF-β) in patients with advanced cancer (4).

Clinical data have confirmed an association between serum concentrations of inflammatory biomarkers and symptoms in patients. To illustrate, elevated C-reactive protein (CRP) is associated with pain, anorexia, dyspnoea, and fatigue in patients with cancer (5, 6). In patients with lung cancer undergoing concurrent chemoradiation therapy, serum concentrations of soluble receptor 1 for tumor necrosis factor (sTNF-r1) and IL-6 were related to an increase in the mean score for all 15 recorded symptoms and five most severe symptoms, respectively (7). Cancer related fatigue was associated with biomarkers IL-6, IL-1 receptor antagonist (IL-1ra) and neopterin (8). Increased levels of IL-6 were also found to be associated with major depression in patients with lung cancer (9) and pancreatic cancer (10), the latter found the cytokines IL-1β, IL-4, and IL-12(p70) to be associated with pain intensity and TGF-β with fatigue. Trials have explored associations between inflammatory gene

variants and symptoms. For instance was gene variants for IL-8 and IL-10 associated with pain, depressed mood and fatigue in patients with lung cancer (11).

Associations with specific biomarkers have not been consistent between trials, which may in part be due to use of cross-sectional designs, inconsistency in measurements (12) and non-homogenous cancer patient populations. Despite this inconstancy, there is now a persuasive argument that systemic inflammation, notably key pro-inflammatory cytokines and acute phase proteins (e.g. CRP), influence symptoms in patients with cancer.

In clinical practice, anti-inflammatory drugs are used for symptom control (13). Corticosteroids have been shown to improve appetite and fatigue in patients with advanced cancer (14-16). The mechanisms of action are not well defined, but are thought to be as a result of effects on systemic inflammation.

The current study was a secondary exploratory analysis of a biobank from a randomized, controlled trial assessing the analgesic effects of methylprednisolone 32 mg daily in patients with advanced cancer (16).

The primary aim of this study was to examine the relationship between inflammatory biomarkers (cytokines and markers of the inflammatory response) and pain, appetite and fatigue in patients with advanced cancer receiving opioids. A secondary aim was to explore whether baseline biomarkers were associated with changes in pain, appetite and fatigue following treatment with corticosteroids.

Materials and methods

Overall Design

A secondary explorative analysis was undertaken on a trial examining the analgesic efficacy of corticosteroids in patients with advanced malignant disease and cancer pain using opioids (16). In this randomized, controlled trial, forty-nine patients were randomized to methylprednisolone 16 mg twice daily or placebo; 25 were evaluated in the corticosteroid arm, 22 were evaluated in the

placebo arm. 13 patients randomized to placebo received corticosteroids on an open basis after the intervention period. Patient reported outcome measures (PROMs) from these patients were included in the analyses at follow up after corticosteroid treatment. Ethical approval was given and all patients provided written informed consent to analysis of their data in line with the present study. Eligible patients met the following criteria: >18 years, taking strong opioids; cancer diagnosis; pain ≥4 (numerical rating scale 0-10); expected survival > 4 weeks.

Inflammatory biomarkers were assessed at baseline, i.e. before corticosteroid treatment. Patient reported outcome measures, PROMs, were assessed at baseline and at follow up after 7 days of corticosteroids using the European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire C30 (EORTC QLQ-C30) (17). The EORTC QLQ-C30 scores were calculated according to the EORTC scoring manual (18), scores ranges from 0 to 100; a higher score correspond to a better health-related quality of life in the function scales ("better"), whereas a higher score representing higher levels of symptoms ("worse") in the symptom scales.

The inflammatory markers and cytokines selected for this study included high sensitivity C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), IL-1β, IL-1ra, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12(p70), IL-18, Interferon-γ, TGF-β1, MIF, TNF-α, Macrophage Inflammatory Protein-1α (MIP-1α), Monocyte Chemoattractant Protein-1 (MCP-1) and soluble Tumor Necrosis Factor receptor-1 (sTNF-r1). sTNF-r1 was chosen as it reflects TNF-α-activity, and as TNF-α is among the most unstable cytokines (8, 19). The cytokines were chosen on the basis of previous research on cancer related inflammation and symptoms (7, 20, 21). The sera underwent two freeze-thaw cycles.

High sensitivity CRP was performed at Fürst laboratories, Oslo. The cytokine analyses were performed at Norwegian University of Life Sciences, Ås, using multiplex technology (Multiplex System, Bio-Rad Laboratories Inc., Austin, Texas) where serum cytokine concentrations are measured in high-sensitivity assays. All samples were assayed in duplicate and performed according to

manufacturer's instructions by laboratory personnel blinded to the rest of the data. Bio Rad Human Inflammation panels 6 plex kit containing IL-8, IL-12(p70), IL-2, IL-10, interferon-γ, and sTNF-r1; Bio Rad human group 1 and 2 9 plex kit containing IL-1β, IL-1ra, IL-4, IL-6, MCP-1, MIP-1α, TNF-α, IL-18, and MIF; and Bio Rad singleplex kit TGF-β1 were used. In one patient one of the parallels in the 6 plex kit showed extreme values as compared to the other parallel and the other biomarkers in the same patient. This parallel was therefore excluded from the analysis. Except from this, no significant variation was noted between duplicates for any sample. The intra-assay coefficient of variation (CV) was <10%. Cytokine / chemokine concentrations were interpolated from an appropriate standard curve. If the biomarker concentration was below the lowest point on the standard curve, we used the lowest value.

Statistical analyses

As this was a secondary exploratory analysis no formal sample size calculation was performed. Where appropriate, all data are reported as means with 95 % confidence intervals (CIs), ranges, medians with interquartile ranges (IQRs), or frequencies. As the cytokines were not normally distributed, Spearman Rho-Rank was applied for the correlation analyses. Based on previous research (22), gender, BMI, and age were explored as possible confounding factors in a multiple regression model. Gender and BMI were significantly associated with biomarkers in the fatigue, appetite, physical function, and role function scales, but did not change the results (data not shown). Associations between pre-treatment inflammatory biomarker and change in pain, appetite, and fatigue following corticosteroid use were explored using multiple regression analyses. Gender and BMI were included as covariates. In order to give some protection for multiple testing, a significance level was set to $p = .01$. SPSS v21.0 (Chicago, IL) was used for all statistical analyses.

Results

Patient demographics, pain characteristics and analgesic use, are shown in Table 1 (n=49). The mean age was 63.9 years (CI: 61.2 – 66.8), mean Karnofsky Performance Status score (KPS) was 66 (CI: 62 -

70), median survival was 86 days (IQR: 39 – 197), mean body mass index (BMI) was 23.0 (CI: 21.6 – 24.5), and mean opioid consumption 259 mg / day (oral morphine equivalents) (CI: 178-339) (Table 1). Data were available on 49 patients at baseline and on 38 patients at follow up after receiving methylprednisolone (n=34), dexamethasone (n=2) or prednisolone (n=2). Mean dexamethasone equivalent dose was 5.5 mg/day (23).

Mean PROMs at baseline (EORTC QLQ-C30 0-100) are shown in Table 2. Mean EORTC QLQ-C30 scores were above 65 points for pain, fatigue and appetite indicating severe symptom intensity. Role, physical, and social function and global health were below 45 points, indicating impairment in these function domains and health related quality of life.

Table 3 shows the median serum concentration of inflammatory biomarkers (cytokines, CRP and ESR) at study baseline. IL-1β, IL-2, IL-4, IL-8, IL-10, IL-12(p70), TNF-α, Interferon-γ, and MIP-1α values were below the lower limit of detection. Median CRP and ESR were 44 and 42, respectively, and cytokines IL-1ra, IL-6, IL-18, MCP-1, MIF, sTNF-r1 and TGF-β1 were increased as evidence of systemic inflammation.

Table 4 shows relationship between biomarkers and pain, appetite, fatigue at study baseline. Moderate correlations were demonstrated between appetite and CRP and IL-6; and fatigue and IL-1ra ($r_{s=}$ .38 - .41, $p < .01$). Pain was not significantly correlated to biomarkers. For the other EORTC symptom parameters there were observed low correlations.

For the EORTC function domains, strong correlations were found between physical function and CRP, IL-6 and sTNF-r1; role function and CRP, IL-6, ESR, sTNF-r1 ($r_s > .50$, $p < .001$). Moderate correlations were found between physical function and ESR, and IL-18; role function and IL-18 and MIF; and cognitive function and TGF-β1 ($r_s = .40 - .50$, $p < .01$).

Table 5 shows the relationship between serum concentrations of biomarkers at baseline and improvement in PROMs following treatment with corticosteroids. Serum-concentration of MCP-1

was correlated with pain intensity (β= -.383) (explained variability R^2=0.13, *p*= .016) and sTNF-r1 was correlated with appetite (β= -0.430) (explained variability R^2=0.16, *p*= .012) after corticosteroid treatment, not significant when allowing for multiple comparisons.

The relationships between individual inflammatory markers are shown in table 6. Strong correlations were found between CRP and ESR, and IL-6; sTNF-r1 and IL-18, and MIF; IL-6 and IL-1ra, and MIF; and MCP-1 and IL-18, all correlations r_s > .50 (p < .001). A number of moderate correlations were observed (r_s = .39 - .50, p < .01)

Discussion

The present study demonstrates that biomarkers of the systemic inflammatory response are related to appetite and fatigue in patients with advanced cancer with pain. Appetite was correlated with IL-6 and CRP and fatigue was correlated with IL-1ra. Pain was not correlated with biomarkers. No significant predictors for effect on corticosteroid treatment were identified.

The inflammatory biomarker panel with increased serum concentrations of IL-6, IL-8, MIF, sTNF-r1, and TGF-β1 correspond with the cytokine pattern in patients with advanced cancer described by Lippitz (4). It is also consistent with previous reports that systemic inflammation is related to multiple quality of life and symptoms parameters (6, 24). In this study, IL-6 and CRP were related to deteriorating appetite. Animal studies have proposed a link to systemic and regional expression of the pro-inflammatory cytokines IL-1, TNF-α and IL-6 (25). In cancer patients, associations have been found between appetite loss and gene polymorphisms coding for TNF-α (26), IL-1β (27), and IL-10 (28). In patients with advanced cancer, serum-concentrations of IL-1β, IL-6 and IL-8 were associated with lack of appetite (29).. . In our data, IL-6 was the most prominent biomarker for appetite with explained variability R^2=0.16.

Regarding cancer related fatigue, the literature suggests that fatigue is linked to inflammatory, metabolic, neuroendocrine, and genetic biomarkers (12). However, results for individual biomarkers

are inconsistent (12). In patients with advanced disease, positive association has been shown between fatigue and CRP (6, 24, 30, 31) although this association did not persist after correction for covariates in another trial (32). IL-1ra and IL-6 were associated with fatigue in advanced cancer (30); although this was not confirmed for IL-6, IL-1β, IL-8 or TNFα in another trial (29).

The present study observed a moderate correlation (r= 0.413) between fatigue and the anti-inflammatory cytokine IL-1ra. IL-1ra is a physiological inhibitor of IL-1β, its production is stimulated by IL-1β and IL-6 (33). IL-1ra is expressed in higher concentrations in serum as compared to IL-1β, which has a short half-life and degrades during storage (34). Thus, IL-1ra serves as an activity marker of IL-1 activity (22, 35).

In patients with advanced cancer, intensity of fatigue have been associated with other symptoms, in particular pain, dyspnoea, anorexia, psychological distress, and insomnia (36). Fatigue is commonly described in symptom clusters with pain (37, 38). The parent trial was a pain intervention trial. Pain intensity was associated with fatigue in the trial, r_s = .38 (p< .01) (results not tabulated). In a regression model, pain and IL-1ra were both independently associated with fatigue with explained variability of R^2=0.12 and R^2=0.13, respectively.

In the treatment of IL-6-mediated Castleman's disease, trials on blockade of IL-6 activity (39, 40), and case report on IL-1ra-treatment (41) were effective in decreasing disease activity and in alleviating fatigue. Data indicate that treatment with recombinant IL-1ra may alleviate fatigue in patients with rheumatoid arthritis and Sjogren's syndrome (42, 43).

In the case of pain, the positive associations between pain and CRP (5, 6, 24) reported previously was not observed in the present trial. Moreover, intervention trials assessing corticosteroids effects on cancer pain have also shown conflicting results. The parent trial found no evidence of an analgesic effect (16) of methylprednisolone 32 mg daily for cancer pain. A second trial found only a temporary effect of systemic corticosteroids on pain (15, 44). This is in contrast to a previous cross-over trial

(45), in which 28 patients with predominantly bone localized pain (n=16), visceral (n=7) or nerve compression pain (n=5) and low level of opioids showed response in pain intensity and analgesic consumption to methylprednisolone 32 mg daily. This suggests that cancer pain might be less associated to systemic inflammation than appetite and fatigue. However, it may also indicate that subgroups of cancer pain exist which may have better corticosteroid response. Cancer induced bone pain might be one of these. In this respect, and worthy of mention, was that patients who had elevated pre-treatment serum-concentration of MCP-1 were more likely to have an improvement in pain following treatment with corticosteroids (Table 4) (explained variability R^2=0.13 *p*=0.016, not significant when allowing for multiple comparisons). Correcting for the presence of cancer induced bone pain did not influence these values.

This observation corresponds to previous work that MCP-1 plays a role in chronic pain facilitation via its receptor, C-C chemokine receptor type 2 (CCR2) (46, 47). Animal data show that MCP-1 expression in spinal neurons also is increased in animals with cancer induced bone pain. Moreover, MCP-1 induced and anti-MCP-1 or CCR2 agonist attenuated hyperalgesia in animals with bone cancer when applied intrathecally (48, 49). Corticosteroids decrease MCP-1 (50). Furthermore, experimental animal studies suggest that locally applied sustained release methylprednisolone improve hyperalgesia in rats with compression radicular pain, improvement was associated with decreased number of infiltrating macrophages at the sciatic nerve, and reduced MCP-1 expression in the nerve (51). In patients with cancer pain, MCP-1 was one of five cytokines that was significantly correlated to pain relief in a study on acute changes in cytokine serum concentrations during three hours of opioid pain treatment (52). Based on this basic science work, the observation that MCP-1 might be a biomarker of pain response from corticosteroids is interesting and should be tested in future studies.

A number of correlations were observed between biomarkers and EORTC function domains, in particular for deteriorating physical and role functions which were associated with CRP, IL-6, sTNF-r1, ESR, IL-18, and MIF. Multiple regression analysis showed that CRP was the most strongly associated

biomarker for role function and IL-6 for physical function with explained variability $R^2_{adjusted}$=0.34 and 0.28, respectively. Role function comprise two items, i.e. ability to perform work or to pursue hobby activities, while physical function items focus on physical capability and strength. The items are closely related (53) and do probably explain the same construct. Moreover, the poor role function may also be related to high intensity of cancer related fatigue in this cohort. We identified two studies that reported a multidimensional assessment of fatigue in patients with advanced cancer. The trials observed associations with cytokines IL-1ra or IL-6, respectively, in the physical fatigue subscale only and not with the mental dimensions of fatigue (54, 55). The EORTC fatigue-item has shown to correlate more strongly with the physical than the mental fatigue subscale of the Fatigue Questionnaire in palliative care patients (56). Fatigue, but not pain intensity, was significantly associated with role function in our data, r_s = .54 (p< .001) (results not tabulated).

A correlation was also demonstrated between cognitive function, i.e. difficulty in concentrating and remembering things, and the anti-inflammatory cytokine TGF-β1. Data from patients with breast cancer suggests that IL-1β, IL-6, IL-8 and TNF-α contribute to chemotherapy-associated cognitive impairment (57). Cognitive symptoms are frequent in patients receiving cytokine-based immunotherapies like Interferon-α and IL-2 (58) However, association between TGF-β1 and cognitive function is not previously described in clinical trials to our knowledge.

In the multiple regression analysis, appetite was independently associated with IL-6 and CRP; and fatigue independently associated with IL-1ra. Further, only role function was independently associated with CRP and IL-6. This supports the clinical observations seen in the primary trial where appetite and fatigue were statistically and clinically significantly improved following anti-inflammatory treatment with methylprednisolone (16). Moreover, it also corresponds to findings from another trial which showed that dexamethasone improved fatigue and physical well-being (15). Similarly, appetite, fatigue, and role function were the only items in the EORTC QLQ-C-30 independently associated with systemic inflammation in a recent large study. (24). Taken together,

these data which represent both cross-sectional data and intervention trials support systemic inflammation as a plausible causal factor in appetite, fatigue, and role function.

There are arguments to move towards assessing the clinical usefulness of specific inhibitors of inflammation to treat or prevent symptoms caused by innate immune reactions in cancer. This will also provide further information regarding the possible role of cytokines in the pathophysiology of these symptoms. As for today, for example recombinant IL-1ra (anakinra) is a viable therapeutic option and intervention trials on IL-1ra administration for chronic fatigue syndrome are underway (59).

We recognize that the present study has some limitations. Firstly, we included a limited number of patients, which makes the analyses susceptible to imprecise estimates and type II errors. Secondly, we did not obtain blood samples after the intervention period and therefore we cannot compare PROMs with changes in cytokine concentrations after corticosteroid treatment. Finally, the time of sampling was not strictly standardized. Cytokines' diurnal rhythm could influence the results as for instance IL-1, IL-6, TNF-α, and interferon-γ are linked to melatonin and peak early in the morning (8, 34).. However, to our knowledge, this is the first study that assesses associations between inflammatory biomarkers and PROMs in the setting of an interventional trial with corticosteroids.

Conclusion:

Symptoms in patients with advanced cancer have been regarded as related to the underlying tumor bulk and its associated sequelae. However, the role of the tumor-host interaction is likely to play an important part in the symptom development and certain symptoms may be related to individual cytokines implicated in the pro-inflammatory response (60).

We report an association between inflammatory markers IL-6 and CRP and appetite, and IL-1ra and fatigue in cancer patients with advanced disease. Additionally, independent associations between role function and CRP and IL-6 were prominent. Whether or not these cytokines are responsible, in

isolation or in unison with others, for the development or the progression of symptoms remains unclear and is outwith the remit of the current study. However, the demonstration of the importance of systemic inflammation in likelihood of response to anti-cancer therapy (61), may be a paradigm that can be applied to symptoms. Our findings provide further weight to the argument that the systemic inflammatory response influences symptoms, specifically anorexia and fatigue in cancer patients. Studies testing this hypothesis are needed and may have the potential to improve symptom control in patients with advanced cancer.

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Table 1: Demographics:

		Number of patients (n=49)	**Mean**	**Median**	**CI**
Gender	Female	24			
	Male	25			
Age	Years		63.9	64.8	61.2 – 66.8
Weight	kg		68.3	67.0	63.8 – 72.9
BMI[a]	kg/m^2		23.0	22.3	21.6 – 24.5
Ethnicity	Caucasian	49			
KPS[b]			66	70	62 – 70
Survival (days)			185	86	39 – 197 (IQR)[c]
Cancer diagnosis	Gastrointestinal	14			
	Lung	11			
	Gynaecological	10			
	Prostate	6			
	Breast	2			
	Other	8			
Metastases	Liver	17			
	Bone	15			
	Lung	7			
	CNS	2			
	Other	33			
	No metastases	2			
Oral opioid dose mg/24h			230	135	165 – 296
Baseline opioid (OME)[d] mg					
	Morphine SR	15	185	80	58.2 – 311.8
	Oxycodone	19	148	110	98 – 198
	Fentanyl	13	368	420	215 – 522
	Other	2	459	459	-4198 - 5115
Corticosteroid medication		n=38			
	Methylprednisolone	34			
	Dexamethasone	2			
	Prednisolone	2			
Dexamethasone equivalent dose (mg)			5.5		Range :1.5-8

[a]BMI: Body mass index, [b]KPS: Karnofsky Performance Status Score, [c] IQR: Interquartile range, [d]OME: Oral Morphine Equivalents

Table 2: EORTC QLQ-C30 at baseline:

	Mean	**Median**	**CI**
Physical function	39.3	40	33.8-44.8
Role function	24.8	16.7	18.4-31.2
Emotional function	73.9	75.0	67.0-80.8
Cognitive function	68.8	66.7	60.7-76.8
Social function	44.1	50.0	35.5-52.7
General health	40.5	41.7	34.8-46.1
Fatigue	72.7	77.8	66.1-79.2
Appetite loss	68.0	66.7	59.3-76.8
Pain	78.9	83.3	74.1-83.7
Nausea vomiting	31.0	16.7	23.0-39.0
Dyspnoea	47.6	33.3	39.1-56.1
Sleep	27.8	33.3	18.6-37.0
Constipation	46.5	50.0	34.8-58.3
Diarrhoea	22.2	0,0	13.0-31.4

CI: 95 % confidence interval

Table 3: Biomarkers and observed serum concentrations

Inflammatory marker	Concentration (pg/mL) median	Interquartile range (IQR)	LLOQ[a]
CRP	44	19.8 – 122.5	
ESR	42	18 – 83.8	
IL-1ra	21.7	21.7 – 126.8	21.7
IL-6	2.33	2.33 – 26.0	2.33
IL-18	103.2	73.4 – 164.3	1.1
MCP-1	64.1	46.9 – 107.3	1.5
MIF	134.9	85.4 – 334.2	4.8
sTNF-r1	10917	7223 – 15257	27.1
TGF-β1	45145	36714 – 52636	1.2

[a]LLOQ: Lower limit of quantification

Table 4: EORTC QLQ-C30 items at baseline and correlations to cytokine serum concentrations

EORTC Item Day 0	Fatigue	Appetite	Pain	Physical function	Role function	Emotional function	Cognitive function	Social Function	Quality of life	Nausea Vomiting	Dyspnoea	Sleep	Constipation	Diarrhea
CRP	0.262	0.380*	0.163	-0.553**	-0.891**	0.147	-0.175	-0.313	-0.332	0.129	0.277	0.215	0.346	-0.174
ESR	0.082	0.265	0.296	-0.466*	-0.527**	0.253	-0.148	-0.133	-0.316	- 0.034	0.185	0.008	0.308	-0.286
sTNF-r1	0.171	0.219	0.201	-0.552**	-0.521**	0.300	-0.108	-0.121	-0.307	0.023	0.166	0.046	0.149	-0.115
IL-1 ra	0.413*	0.336	0.158	-0.378	-0.346	0.107	0.031	-0.211	-0.255	-0.064	0.336	0.157	0.132	-0.057
IL-6	0.198	0.406*	0.198	-0.510**	-0.594**	0.162	-0.191	-0.223	-0.195	0.096	0.293	0.206	0.269	-0.280
MCP-1	0.183	0.318	0.094	-0.199	-0.229	0.227	-0.141	-0.344	0.005	-0.142	0.057	0.069	-0.022	0.225
IL-18	0.134	0.275	0.147	-0.447*	-0.428*	0.280	0.104	-0.322	-0.119	-0.032	0.179	-0.049	-0.079	0.064
MIF	0.146	0.039	0.199	-0.326	-0.408*	0.241	-0.105	-0.059	-0.067	-0.165	0.219	0.028	-0.012	-0.154
TGF-β1	0.017	0.017	0.203	-0.192	-0.238	-0.254	-0.425*	-0.220	-0.289	-0.202	-0.155	0.385	0.171	0.135

*= $p<0.01$, **=$p<0.001$ Blood samples for ESR (n=1), CRP (n=3) and for cytokines (n=6) were missing

Table 5: Fatigue, appetite and pain intensity and response to corticosteroid therapy

	Fatigue			Appetite			Pain intensity		
	β	(Sig)	R^2	β	(Sig)	R^2	β	(Sig)	R^2
CRP	0.070		.00	0.161		.02	-0.071		.00
ESR	-0.062		.00	-0.038		.00	-0.174		.03
sTNF-r1	-0.180		.03	-0.430	(0.012)	.16	-0.337	(0.033)	.10
IL-6	0.069		.00	-0.098		.01	-0.205		.04
MCP-1	-0.095		.01	-0.204		.03	-0.383	(0.016)	.13
IL-18	-0.148		.02	-0.036		.00	-0.291		.08
MIF	-0.075		.01	-0.167		.03	-0.334	(0.034)	.10
TGF-β1	-0.096		.01	-0.158		.02	0.020		.00

β = standardized beta. Multiple regression analysis: fatigue day 7 dependent; fatigue day 0, gender, and BMI as covariates.

Biomarkers CRP, IL-6, IL-18, MCP-1, MIF, and TGF-β1 were log-transformed. Blood samples were missing for for CRP (n=3) and for cytokines (n=6)

Table 6: Correlations between the analysed cytokines

	CRP	ESR	sTNF-r1	IL-1ra	IL-6	MCP-1	IL-18	MIF
CRP	1							
ESR	0.702**	1						
sTNF-r1	0.383	0.452*	1					
IL-1ra	0.317	0.280	0.206	1				
IL-6	0.686**	0.489*	0.370	0.545**	1			
MCP-1	-0.002	0.003	0.380	0.202	0.283	1		
IL-18	0.394*	0.409*	0.589**	0.488*	0.449*	0.516**	1	
MIF	0.308	0.403*	0.634**	0.316	0.538**	0.500*	0.305	1
TGF-β1	0.250	0.087	0.122	-0.123	0.161	0.152	-0.186	0.253

*=p< .01, **=p< .001