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FIRST-LINE CHEMOTHERAPY WITH ANTHRACYCLINE AND TAXANE COMBINATION IN METASTATIC BREAST CANCER

Detection of bone metastases with TRACP 5b

by

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ABSTRACT

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FIRST-LINE CHEMOTHERAPY WITH ANTHRACYCLINE AND TAXANE COMBINATION IN METASTATIC BREAST CANCER

Detection of bone metastases with TRACP 5b
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Background: In Finland, breast cancer (BC) is the most common cancer among women, and prostate cancer (PC) that among men. At the metastatic stage both cancers remain essentially incurable. The goals of therapy include palliation of symptoms, improvement or maintenance of quality of life (QoL), delay of disease progression, and prolongation of survival. Balancing between efficacy and toxicity is the major challenge. With increasing costs of new treatments, appropriate use of resources is paramount. When new treatment regimes are introduced into clinical practice a comprehensive assessment of clinical benefit, adverse effects and cost is necessary. Both BC and PC show a predilection to metastasize to bone. Bone metastases cause significant morbidity impairing the patients´ QoL. Diagnosis of bone metastases relies mainly on radiological methods, which however lack optimal sensitivity and specificity. New tools are needed for detection and follow-up of bone metastases.

Aims: Anthracyclines and taxanes are effective chemotherapeutic agents in the treatment of metastatic breast cancer (MBC) with different mechanisms of action. Therefore, evaluation of the combination of anthracyclines with taxanes was a justifiable approach in the treatment of MBC patients. We assessed the efficacy, toxicity, cost of treatment and QoL of BC patients treated with first-line chemotherapy for metastatic disease with the combination epirubicin and docetaxel. We also evaluated the diagnostic potential of tartrate-resistant acid phosphatase 5b (TRACP 5b) and carboxyterminal telopeptides of type I collagen (ICTP) in the diagnosis of bone metastases in BC and TRACP 5b in PC patients.

Results: The combination of epirubicin and docetaxel was effective in this phase II study, but required individual dose adjustment to avoid neutropenic infections, and the use of growth factors to maintain a feasible dose level. The response rate was 54 % (95 % CI 37–71) and the median overall survival (OS) was 26 months. Of the patients, 87 % were treated for infections. The treatment of adverse events required additional use of health resources mainly due to neutropenic infections, thereby raising direct treatment costs by 20 %. Despite adverse events, the global QoL was not significantly compromised during the treatment. Clinically evident acute cardiac toxicity was not observed**.** The combination of serum TRACP 5b and ICTP was at least equally sensitive and specific in detection of of bone metastases as commonly used total alkaline phosphatase (tALP) in BC patients. In contrast, TRACP 5b was less specific and sensitive than tALP as a marker of skeletal changes in PC patients**.**

Conclusions: Treatment with epirubicin and docetaxel showed high efficacy in first-line chemotherapy of MBC. The relatively high incidence of neutropenic infections requiring hospitalization increased the treatment costs. Despite adverse events, the global QoL of the patients was not significantly compromised. The combination of TRACP 5b and ICTP showed similar activity as tALP in detecting bone metastases in MBC. In contrast, TRACP 5b was less specific and sensitive than tALP as a marker of skeletal changes in PC.

Keywords: Breast cancer, prostate cancer, chemotherapy, neutropenia, treatment cost, quality of life, cardiac toxicity, bone metastases, bone markers, TRACP 5b, ICTP, tALP.

TIIVISTELMÄ

Jaana Korpela

ANTRASYKLIINI—TAKSAANI-YHDISTELMÄ LEVINNEEN RINTASYÖVÄN ENSILINJAN KEMOTERAPIASSA

TRACP 5b luustometastaasien detektoinnissa

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Tausta: Suomessa rintasyöpä on naisten ja eturauhassyöpä miesten yleisin syöpä. Näiden syöpien metastasoinutta muotoa ei juurikaan pystytä pysyvästi parantamaan, joten hoidon tavoitteena on syövästä aiheutuvien oireiden lievittäminen, elämänlaadun parantaminen tai ylläpitäminen sekä taudin etenemisen hidastaminen ja elinajan pidentäminen. Keskeisenä haasteena on löytää tasapaino hoidon tehokkuuden ja haittavaikutusten välillä. Uusien syöpähoitojen kustannusten jatkuvasti noustessa käytettävissä olevat resurssit on hyödynnettävä optimaalisesti. Hoitokäytäntöjä arvioitaessa on punnittava hoitojen hyödyt, haitat ja kustannukset. Rinta- ja eturauhassyöpä metastasoivat usein luustoon. Luustometastaasit aiheuttavat runsaasti potilaiden elämänlaatua heikentäviä komplikaatioita. Luustometastaasien diagnostiikka perustuu pääasiassa luuston röntgen- ja gammakuvauksiin**.** Niiden herkkyys ja tarkkuus eivät kuitenkaan ole optimaalisia, joten luustometastastaasien diagnosoimiseen ja seuraamiseen tarvitaan uusia menetelmiä.

Tavoitteet: Antrasykliinit ja taksaanit ovat tehokkaita solunsalpaajia metastasoineen rintasyövän hoidossa. Ne eroavat toisistaan vaikutusmekanismeiltaan. Tutkimuksessa selvitettiin näihin solunsalpaajiin kuuluvien epirubisiinin ja doketakselin yhdistelmähoidon tehokkuutta, haittavaikutuksia, hoitokustannuksia sekä hoidon vaikutusta potilaiden elämänlaatuun metastasoineen rintasyövän ensilinjan hoidossa. Tutkimme myös tartraatti-resistentin happaman fosfataasin 5b (TRACP 5b) ja kollageeni I:n karboksiterminaalisen telopeptidin (ICTP) diagnostista potentiaalia luustometastaasien diagnosoinnissa rintasyöpäpotilailla sekä TRACP 5b:n käyttökelpoisuutta eturauhassyöpäpotilailla.

Tulokset: Epirubisiinin ja doketakselin yhdistelmähoito osoittautui tehokkaaksi tässä faasi II-tutkimuksessa. Yksilöllisiä annosmuutoksia jouduttiin kuitenkin tekemään neutropeenisten infektioiden välttämiseksi sekä käyttämään kasvutekijöitä riittävän annostason ylläpitämiseksi. Hoitovaste saavutettiin 54 %:lla (95 % CI 37–71) ja kokonaiselinaika oli 26 kk. Potilaista 87 % sai hoitoa vaatineen infektion. Haittavaikutusten, erityisesti neutropeenisten infektioiden, hoito lisäsi suoria hoitokustannuksia 20 %:lla. Haittavaikutukset eivät laskeneet yleistä elämänlaatua. Kliinisesti merkittävää akuuttia sydäntoksisuutta ei todettu. TRACP 5b ja ICTP olivat yhdessä käytettynä vähintään yhtä herkkä ja tarkka menetelmä rintasyövän luustometastaasien diagnosoinnissa kuin yleisesti käytetty alkalinen fosfataasi (AFOS). Sen sijaan eturauhassyövän aiheuttamien luustometastaasein diagnostiikassa TRACP 5b ei ollut yhtä herkkä ja tarkka kuin AFOS.

Päätelmät: Epirubisiinin ja doketakselin yhdistelmähoito oli tehokas levinneen rintasyövän ensilinjan hoidossa. Hoito aiheutti suhteellisen runsaasti sairaalahoitoa vaativia neutropeenisiä infektioita, mikä lisäsi oleellisesti kokonaiskustannuksia. Haittavaikutukset eivät heikentäneet merkittävästi potilaiden yleistä elämänlaatua. TRACP 5b:n ja ICTP:n yhdistelmä oli yhtä herkkä ja tarkka rintasyövän aiheuttamien luustometastaasien detektoinnissa kuin AFOS. Sen sijaan TRACP 5b ei ollut yhtä herkkä eikä tarkka kuin AFOS eturauhassyöpään liittyvien luustometastaasien diagnostiikassa.

Avainsanat: Rintasyöpä, eturauhassyöpä, solunsalpaajahoito, neutropenia, hoitokustannus, elämänlaatu, sydäntoksisuus, luustometastasointi, luun merkkiaineet, TRACP 5b, ICTP, AFOS.

CONTENTS

ABBREVIATIONS

A	Doxorubicin
AC	Doxorubicin-cyclophosphamide combination
AD	Doxorubicin-docetaxel combination
AI	Aromatase inhibitor
AP	Doxorubicin-paclitaxel combination
AUC	Area under the curve
AT	Anthracycline-taxane combination
BAP	Bone specific isoform of alkaline phosphatase
BC	Breast cancer
BM	Bone metastasis
BMP	Bone morphogenetic protein
CAF	Cyclophosphamide-doxorubicin-5-fluorouracil combination
CECOG	Central European Cooperative Oncology Group
CEF	Cyclophosphamide, epirubicin, 5-fluorouracil combination
CHF	Cardiac heart failure
CMF	Cyclophosphamide-metotrexate-5-fluorouracil combination
CNS	Central nervous system
CR	Complete response
CT	Computed tomography
CTX	C-telopeptide of type 1 collagen crosslinks
D	Docetaxel
DPD	Deoxypyridinoline
E	Epirubicin
EC	Epirubicin-cyclophosphamide combination
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGF	Epidermal growth factor
ELISA	Enzyme-linked immunosorbent assay
EORTC	European Organisation on Research and Treatment of Cancer
EP	Epirubicin-paclitaxel combination
ER	Estrogen receptor
ErB2	Epidermal growth factor receptor 2
ESMO	European Society for Medical Oncology
ESO	European School of Oncology
FACT	Functional Assessment of Cancer Therapy
FADO	Epirubicin-docetaxel study
FGF	Fibroblast growth factor
5´-FU	5-fluorouracil
G	Gemcitabine
GCP	Good clinical practice

HER-2	Human epidermal growth factor receptor 2
HRQOL	Health-related quality of life
HRV	Heart rate variability
ICER	Incremental cost-effectiveness ratio
ICTP	Carboxyterminal telopeptide of type I collagen
IL	Interleukin
LVEF	Left ventricular ejection fraction
M	Methotrexate
MBC	Metastatic breast cancer
MI	Mitomycin
MMP	Matrix metalloproteinase
MRI	Magnetic resonance imaging
NC	No change
NCCN	National Comphensive Cancer Network
NICE	National Institute for Health and Clinical Excellence
NIH	National Institute of Health
NTX	Cross-linked N-terminal telopeptide of type 1 collagen
OPG	Osteoprotegerin
ORR	Overall response rate
OS	Overall survival
P	Paclitaxel
PC	Prostate cancer
PCb	Paclitaxel-carboplatin combination
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PgR	Progesterone receptor
PICP	Carboxyterminal propeptide of type I procollagen
PINP	Aminoterminal propeptide of type I procollagen
PR	Partial response
PTHrP	Parathyroid hormone-related protein
PYD	Pyridinoline
QALY	Quality-adjusted life year
QoL	Quality of life
Q-TWiST	Quality-adjusted Time Without Symptoms and Toxicity
RR	Response rate
RANK	Receptor activator of the nuclear factor-kappaB
RANKL	Receptor activator of the nuclear factor-kappaB ligand
tALP	Total alkaline phosphatase
TNF	Tumor necrosis factor
TGF	Transforming growth factor
TRACP 5b	Tartrate-resistant acid phosphatase 5b
TTP	Time to tumor progression
V	Vinblastine

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred to in the text by the corresponding Roman numerals I-VI.

I Salminen E, **Korpela J**, Varpula M, Asola R, Varjo P, Pyrhönen S, Mali P, Hinkka S and Ekholm E. Epirubicin/docetaxel regimen in progressive breast cancer─a phase II study. Anti-Cancer Drugs 2002;13:925–9.

II **Korpela J** and Salminen E. Neutropenic infections add significant costs to palliative chemotherapy in breast cancer. Anticancer Res. 2002; 22:1337–40.

III Salminen E, Syvänen K, **Korpela J**, Varpula M, Antila K, Varjo P and Ekholm E. Docetaxel with epirubicin─investigations on cardiac safety. Anti-Cancer Drugs 2003; 14:73–77.

IV **Korpela J**, Tiitinen SL, Hiekkanen H, Halleen JM, Selander KS, Väänänen HK, Suominen P, Helenius H and Salminen E. Serum TRACP 5b and ICTP as markers of bone metastases in breast cancer. Anticancer Research 2006; 26: 3127–3132.

V Salminen E, Ala-Houhala M, **Korpela J**, Varpula M, Tiitinen SL, Halleen JM, Väänänen HK. Serum tartrate-resistant acid phosphatase 5b (TRACP 5b) as a marker of skeletal changes in prostate cancer. Acta Oncol 2005; 44: 742–7.

VI **Korpela J**, Mali P, Kaljonen A and Salminen E. Quality of life of patients with metastatic breast cancer treated with epirubicin and docetaxel. Submitted.

1. INTRODUCTION

Breast cancer (BC) is by far the most common cancer among women with over one million new cases diagnosed annually worldwide (http://globocan.iarc.fr). Prognosis is generally good for patients diagnosed with early-stage BC with a 5-year disease-free survival rate of 89 % (Brewster *et al.* 2008). However, approximately 30 % of women diagnosed with early BC will eventually progress to or relapse with locally advanced or metastatic disease (Brewster *et al.* 2008). An additional 6–10 % will present with metastatic disease at primary diagnosis (Colozza *et al.* 2007). Although the mortality rate from BC has been declining steadily from 1990 largely due to increased awareness, earlier detection, screening programs and improved therapies, breast cancer is still the leading cause of cancer-related death in women in the US (http://www.cancer.org). It is estimated that approximately 500 000 women will die each year of BC (http://globocan.iarc.fr). Prostate cancer (PC) is the most prevalent malignancy in men with over 900 000 new cases diagnosed yearly worldwide (http://globocan.iarc.fr). In Finland, BC is the most common cancer among women and PC the most common cancer among men. In 2009, 4459 breast cancers and 4591 prostate cancers were diagnosed in Finland (http://www.cancerregistry.fi). Common features of these cancers are that they can be detected early, the majority are hormone-dependent, and a typical finding of both cancers in the disseminated disease stage is bone metastases. Once metastasized, both BC and PC remain essentially incurable.

When new cancer drugs or treatment regimes are introduced and adapted into clinical practice, they should either significantly improve overall and/or progression-free survival, or be substantially better tolerated than current drugs. Quality of life (QoL) and treatment cost analysis can provide essential information on the benefits and costs of new cancer drugs, thereby supporting decisions on their utilisation and adoption into clinical practice. Ideally, such decisions should include a comprehensive assessment of direct and indirect costs, as well as reliable measurements of clinical benefit, which take patients´ preferences and needs into account. QoL is recognised as a major outcome when evaluating new cancer therapies (Uyl-de Groot. 2006). With the ever-increasing costs of new treatments, diagnostic methods and QoL measures, a wise and balanced use of resources is paramount. Anthracyclines are among the most active chemotherapeutic agents for treatment of metastatic breast cancer (MBC). At the time this study was developed, combinations of anthracyclines and cyclophoshamide were commonly used in first-line chemotherapy of MBC, with or without 5-fluorouracil. The taxanes were introduced in the 1990s. They showed significant activity in first- and second-line MBC treatment and incomplete clinical cross-resistance to anthracyclines (Chan *et al.* 1999, Nabholtz *et al.* 1999, O'Shaughnessy *et al.* 2002, Paridaens *et al.* 2000). The combination of taxanes with anthracyclines became a reasonable next step for clinical studies in metastatic disease.

BC as well as PC are most likely to recur in bone. In advanced disease bone metastases will occur in 65–75 % of both BC and PC patients (Coleman. 1997). Bone metastases are the most common cause of morbidity and a potential source of serious complications such as pathological fractures, pain, hypercalcemia and spinal cord compression, thereby seriously deteoriating the patient's QoL. The diagnosis and follow-up of bone metastases usually relies on a combination of radiological or isotope imaging and laboratory tests. However, these methods have their limitations in terms of specificity and sensitivity. In addition, there are dosimetric and cost-effectiveness considerations when using nuclear-medicine-based and radiological methods repeatedly. Better tools are needed for early diagnosis of bone metastases, as well as for monitoring response to therapy. There is growing interest in the use of biochemical markers of bone remodelling in metastatic bone disease. Biochemical markers are non-invasive and easy and fast to perform and, therefore, have potential to improve the diagnosis of bone metastases.

The aim of this thesis was to assess the efficacy, toxicity, cost of treatment and QoL effects of the combination of epirubicin and docetaxel in first-line chemotherapy of MBC. In addition, the aim was to evaluate the diagnostic potential of tartrate-resistant acid phosphatase 5b (TRACP 5b) in the diagnosis of bone metastases in BC and PC patients.

2. REVIEW OF THE LITERATURE

2.1. Metastatic breast cancer as a clinical problem

Despite recent advances in primary treatment of BC, MBC remains a significant health problem. Even though the incidence of MBC is likely to decline due to increased awareness, earlier detection, screening programs and improved adjuvant therapies, the prevalence may increase since the survival time is slowly increasing (Andre *et al.* 2004, Chia *et al.* 2007, Dafni *et al.* 2010, Gennari *et al.* 2005, Giordano *et al.* 2004, Mauri *et al.* 2008). The median survival of patients is currently given as 20–28 months depending on the nature of the metastases and the tumor biology (Chia *et al.* 2007, Gennari *et al.* 2005, Giordano *et al.* 2004, Mauri *et al.* 2008). Systemic therapy in the metastatic setting has only modestly enhanced long-term outcomes, and MBC still remains essentially incurable. The goals of therapy of MBC include delay of disease progression, prolongation of overall survival time, palliation of symptoms, and improvement or maintenance of QoL (Mayer & Burstein. 2007).

Within the past two decades, the possibilities in the treatment of MBC have multiplied due to the availability of new chemotherapeutic agents (taxanes, vinorelbine, gemcitabine and capecitabine), newer hormonal agents (third-generation aromatase inhibitors and fulvestrant) and biological agents (e.g. trastuzumab, bevacizumab and lapatinib). Advances in the treatment of early-stage BC have led to increased use of adjuvant chemotherapy. As a result, the decisions regarding the treatment of patients presenting with MBC are becoming more difficult as many patients are likely to be pre-treated with a variety of adjuvant chemotherapeutic agents. Clinical trials in the first-line metastatic setting will become increasingly difficult to interpret because of the wider range of previous treatments. In addition, due to the expanding variety of treatment options, numerous treatments are given sequentially in the metastatic setting. There is currently no golden standard of treatment for the metastatic setting although during the past couple of years some general guidelines have been established.

The burden of bone metastases in BC is considerable. Bone is the primary site of metastasis. Bone is also the most common site of the first distant relapse (Coleman & Rubens. 1987). According to autopsy findings, bone metastases occur in 60–90 % of patients who die from BC (Kamby *et al.* 1988). Bone metastases cause significant morbidity such as bone pain, pathological fractures, impaired mobility, hypercalcemia, and spinal cord compression (Coleman & Rubens. 1987). Bone pain and skeletal complications have a profound impact on QoL and compromise patients´ mobility and social environment. As metastatic bone disease frequently follows a protracted clinical course, skeletal complications are a major issue (Coleman & Rubens. 1987).

The clinical behavior of MBC is often unpredictable, reflecting the biological heterogeneity of the disease. Emerging new technologies will possibly change the current practice, so

that in the future genetic profiling will lead to a better understanding of the molecular differences between clinical cases, and thus allow more individualized care than today (Brenton *et al.* 2005). More efficient treatment options are needed. In addition, better predictive markers of response to treatment are needed to avoid unnecessary adverse side effects of ineffective treatment. Given the budgetary pressures and constantly rising costs, especially of new cancer drugs, economic concerns are growing when treating a chronic disease like MBC with a variety of treatment options.

2.2. Treatment of metastatic breast cancer

In contrast to the series of guidelines and consensus statements on adjuvant treatment of early BC (Brewster *et al.* 2008, Carlson *et al.* 2006a, Carlson *et al.* 2006b), only a few consensus statements exist on medical treatment of MBC: the Central European Cooperative Oncology Group (CECOG) (Beslija *et al.* 2009), the European Society for Medical Oncology (ESMO)(Cardoso *et al.* 2010), the National Comphensive Cancer Network (NCCN, USA) (www.nccn.org), the European School of Oncology (ESO) (Cardoso *et al.* 2009), and the National Institute for Health and Clinical Excellence (NICE) (http://guidence.nice.org.uk).

The management of MBC is complex and there are no approved standards of care, particularly after first-line treatment. Advances in the treatment of MBC over the last decades have been significant, and a wide array of options exists. Treatment plans require an individualized approach. Individual treatment decisions are largely empirical, based on multiple factors including specific tumor biology, tumor growth rate, presence of visceral metastases, history of prior therapy and response to it, time to progression, risk of toxicity, age, menopausal status and performance status of the patient, other diseases and medication, need for rapid disease/symptom control, socio-economic and psychological factors, patient's preference and available resources (Beslija *et al.* 2009, Cardoso *et al.* 2010, Comen & Fornier. 2010).

Treatment options include endocrine treatment, cytotoxic chemotherapy, biological therapy (e.g. trastuzumab, lapatinib, bevacizumab), bisphosphonates, and supportive measures. Local treatment modalities, such as palliative radiotherapy and surgery, are also considered (Beslija *et al.* 2009, Cardoso *et al.* 2010, Kataja *et al.* 2008).

2.2.1. Endocrine therapy

Up to almost 80 % of BCs are hormone-dependent (Dunnwald *et al.* 2007). The presence of hormone receptors predicts response to endocrine therapy. Endocrine therapy is considered the first option in women with hormone-dependent MBC unless fast response to treatment is needed, the patient is young, the disease-free time is short, the patient has extensive visceral metastases, the disease is rapidly progressive, or the patient needs fast relief of symptoms. The recommendation is based upon the reduced toxicity of endocrine treatment as compared to chemotherapy (Wilcken *et al.* 2003).

Tamoxifen, a selective estrogen receptor modulator, has been the treatment of choice for first-line treatment of MBC in post-menopausal women for many years. The aromatase enzyme catalyses the final step in estrogen biosynthesis and was identified as an attractive target for selective inhibition. Aromatase inhibitors (AI) have been introduced since the early 1980s. Later, more potent and highly selective third generation AI:s (non-steroidal letrozole and anastrozole and steroidal exemestane) have replaced older AIs (Riemsma *et al.* 2010). Of the estrogen receptor (ER)-positive MBC:s approximately 50–60 % get clinical benefit in first-line treatment (Bonneterre *et al.* 2000, Howell *et al.* 2004, Mouridsen *et al.* 2003, Nabholtz *et al.* 2003a, Paridaens *et al.* 2003). There appears to be an advantage of treatment with AIs compared to tamoxifen in terms of clinical benefit and time to progression (TTP), but not overall survival (OS) in first-line therapy (Gibson *et al.* 2007, Milla-Santos *et al.* 2003, Mouridsen *et al.* 2003, Nabholtz *et al.* 2003a). So far, there are no randomised clinical trials comparing the efficacy of the third-generation AIs. Fulvestrant is a new type of ER-antagonist that is devoid of the partial agonist properties of tamoxifen (Osborne *et al.* 2004). According to a phase III study, fulvestrant and exemestane were equally active and well-tolerated in a reasonable proportion of post-menopausal women with advanced BC who had experienced progression or recurrence during treatment with a nonsteroidal AI (Chia *et al.* 2008). Tamoxifen, AIs and fulvestrant have different toxicity profiles, which must be taken into account when choosing endocrine treatment for the individual patient. In addition, megestrol acetate may be used after first-line hormonal treatment (Kataja *et al.* 2008).

In pre-menopausal women, tamoxifen with ovarian suppression/ablation (luteinising hormone releasing hormone analogue agonist, surgery or radiation) is the preferred option (Beslija *et al.* 2009, Utsumi *et al.* 2007). The use of aromatase inhibitors after or concomitantly with ovarian ablation is another option (Beslija *et al.* 2009, Cardoso *et al.* 2009).

If the tumor initially responds to first-line hormonal therapy, a second-line hormonal agent is chosen. After second-line endocrine therapy, there is little evidence to assist in selecting the optimal sequence of endocrine therapy, and no definitive recommendation can be given for endocrine treatment cascade (Beslija *et al.* 2009, Kataja *et al.* 2008). In addition, subsequent hormonal responses tend to be of shorter duration and, ultimately, the disease will become refractory to hormonal treatment.

2.2.2. Chemotherapy

MBC can be either initially hormone-receptor-negative or can eventually become endocrine-resistant. Therefore, during the course of their disease, most patients become candidates for chemotherapy. Chemotherapy is the treatment of choice for patients who have extensive visceral metastases or have life-threatening disease requiring early relief of symptoms.

Single-agent chemotherapy was introduced in the treatment of MBC in the 1960s. During the 1970s, the use of multiple drug regimens became common (Bergh *et al.*

2001). By the end of the 1990s, the most commonly used chemotherapeutic agents used alone or in combination were anthracyclines (doxorubicin, epirubicin), fluorouracil (5-FU), methotrexate, mitomycin, mitoxantrone, cyclophosphamine, and vinorelbine. The most common combinations used were CMF (cyclophosphamide, methotrexate, 5-FU), CAF/CEF (cyclophosphamide, doxorubicin/epirubicin, 5-FU) and AC/EC (doxorubicin/epirubicin, cyclophosphamide). The taxanes, capecitabine and gemcitabine, were introduced for advanced BC in the late 1990s. New treatment options are emerging, e.g. ixabepilone, an epothilone B analogue, a novel microtubule inhibitor (Egerton. 2010, Steinberg. 2008, Thomas *et al.* 2007) and pemetrexed, an antifolate (Robert *et al.* 2011).

Today, there are several chemotherapeutic agents that can be used alone or in combination in MBC (Table 1.). Although no clinical trial has ever demonstrated improved survival with chemotherapy over best supportive care in patients with MBC, several randomized trials have shown a modest prolongation of survival in patients enrolled in the superior treatment arm. Improved RR (response rate) or TTP have been documented for multiple agents. However, these do not always correlate with improvement in OS (Wilcken & Dear. 2008). It is of note that the interpretation of OS due to subsequent-line agents is challenging (Verma *et al.* 2011).

Table 1. Chemotherapeutic drugs which are used in treatment of metastatic breast cancer.

Anthracyclines:	**Alkylating agents:**	**Antimetabolites:**
Doxorubicin	Cyclophosphamide	Metothrexate
Epirubicin		Gemcitabine
Liposomal doxorubicin	**Platinum:**	Capecitabine
	Cisplatin	Fluorouracil
	Carboplatin	
Taxanes:		
Paclitaxel	**Vinca alkaloids**:	
Docetaxel	Vinorelbine	
Albumin bound paclitaxel (Nab-Paclitaxel)		

2.2.2.1. Anthracyclines

Anthracycline monotherapy or combination therapy has been used as first-line treatment of MBC for over 30 years. Before the era of taxanes, anthracycline-based combinations were generally shown to give higher RRs, and were considered the best choice in first-line treatment for chemotherapy-naïve patients (Fossati *et al.* 1998). Anthracyclines, particularly doxorubicin, have been the most widely used drugs for MBC. Epirubicin is an analog of doxorubicin with similar efficacy and improved toxicity profile, especially in terms of cardiotoxicity (Minotti *et al.* 2000). To manage toxicities, new formulations of anthracyclines (e.g. liposomal anthracyclines) have been developed. According to a Cochrane meta-analysis, anthracyclines can improve RR and TTP, but no advantage in terms of OS has been seen (Lord *et al.* 2004).

2.2.2.2. Taxanes

Taxanes were introduced for advanced BC in the 1990s. Paclitaxel was extracted from the bark of the Pacific yew tree already in the 1960s, but the development of the drug was difficult and relatively slow (Verweij *et al.* 1994). Docetaxel was extracted from the needles of the European yew in the 1980s. The first clinical studies in MBC using these taxanes were published early in the 1990s (Verweij *et al.* 1994). Taxanes have quickly become established as important chemotherapeutic agents in the treatment of MBC. Both taxanes bind to tubulin, stabilize the microtubule, and thereby inhibit its disassembly, leading ultimately to cell death by apoptosis. Although sharing similar mechanisms of action, paclitaxel and docetaxel have some differences in their molecular pharmacology (McGrogan *et al.* 2008) and in their pharmacokinetic and pharmacodynamic profiles (Lyseng-Williamson & Fenton. 2005). The pharmacokinetics of paclitaxel is non-linear, whereas the pharmacokinetics of docetaxel is linear (Gralow. 2005). Docetaxel is more potent on a molecular level (Lyseng-Williamson & Fenton. 2005). According to the only head-to-head comparison between single-agent docetaxel and paclitaxel, docetaxel was clinically superior in terms of TTP (5.7 vs. 3.6 months; $P < 0.0001$) and also survival (15.4 months vs. 12.7 months; $P=0.03$) (Jones *et al.* 2005).

According to a Cochrane meta-analysis, only taxanes have been shown to provide prolongation of OS in comparison to non-taxane-containing regimens although this benefit has been modest (Ghersi *et al.* 2005). However, when the analysis was limited to trials in women receiving first-line chemotherapy the difference in OS was no longer statistically significant. Also RR and TTP favor taxane-containing regimens (Ghersi *et al.* 2005). The benefit of taxanes appears to be less apparent in patients with no previous anthracycline exposure. Results of phase III single taxane studies are shown in Table 2. New formulations of taxanes (e.g. a nanoparticle formulation of paclitaxel) have been developed to reduce toxicity while maintaining efficacy (Robinson & Keating. 2006).

Today, anthracycline- and/or taxane-based regimens are preferred in first- and second-line treatment of MBC, especially in symptomatic patients and/or in rapidly progressing situations (Beslija *et al.* 2007).

2.2.2.3. Anthracycline and taxane combinations

Anthracyclines and taxanes are two of the most effective single chemotherapeutic agents in the treatment of MBC with different mechanisms of action and incomplete cross-resistance. Since the late 1990s, the combination of anthracyclines with taxanes with the aim of improving overall outcome and survival of MBC patients has been studied. At the time our study was started in 1998, very few publications existed in this area.

Only a single study has compared docetaxel and paclitaxel in combination with an anthracycline directly. Doxorubicin and docetaxel combination (AD) has been compared with doxorubicin and paclitaxel combination (AP) given every three weeks (Cassier *et al.* 2008). The response rate was 39.6 % for the AD and 41.8 % for the AP arm. After a median follow-up of 50.2 months, median progression-free survival (PFS) was 8.7 and

Table 2. Phase III clinical trials using first-line single taxanes in MBC.

Reference	Regimen mg/m²	N	ORR (%)	TTP	Survival (months)
Nabholtz (Nabholtz *et al.* 1999)	D 100 vs. MI 12 + V 6	392	30.0 vs . 11.6 (p<0.0001)	19w vs. 1w (p=0.001)	11.4 vs. 8.7 (p=0.0097)
Chan (Chan *et al.* 1999)	D100 vs. A75	326	47.8 vs. 33.3 (p=0.008)	26w vs. 21w (p=ns)	15 vs. 14 (p=ns)
Sjöström (Sjostrom *et al.* 1999)	D 100 vs. M200 + F600	283	42 vs. 21 (p<0.001)	6.3m vs. 3.0m (p<0.001)	10.4 vs. 11.1 (p=0.79)
Paridaens (Paridaens *et al.* 2000)	P 200 (3w) vs. A 75	331	25 vs. 41 (p=0.003)	PFS 3.9 m vs. 7.5 m (p<0.001)	15.6 vs. 18.3 (p=0.38)
Sledge (Sledge *et al.* 2003)	P175 (3w) vs. A 60 vs. A50+P150 (3w)	739	34 vs. 36 vs. 47 (P vs. A p=0.84, A. vs. A+P p=0.007; P vs. A+P p=0.004)	6.0m vs. 5.8m vs. 8.0m (P vs. A, p =0.68; A vs. A+P, p =0.003; P vs. A+P, p=0.009)	22.2 vs. 18.9 vs. 22.0 (p=ns)
Jones (Jones *et al.* 2005)	D 100 vs. P 175 (3w)	449	32 vs. 25 (p= 0.10)	5.7m vs. 3.6m (p=0.0001)	15.4 vs. 12.7 (p=0.03)
Albain (Albain *et al.* 2008)	G1250+P175 (3w) vs. P175 (3w)	266	41.4 vs. 26.2 (p=0.0002)	6.14m vs. 3.98m (p=0.0002)	18.6 vs .15.8 (p=0.0489)
Fountzilas (Fountzilas *et al.* 2009)	P+Cb (3w) vs. D+G vs P (1w)	416	38 vs. 46 vs. 49 (p=0.20)	11.5m vs. 10.4m vs. 11.5m (p=0.57)	29.9 vs. 26.9 vs. 41.0 (p=0.037)
Joensuu (Joensuu *et al.* 2010)	D80 vs. D80+G1000	237	65 vs. 58 (p=0.30)	11.7m vs. 11.3m (p=0.72)	28 vs. 27 (p=0.60)

D=docetaxel, P=paclitaxel, A=doxorubicin, MI= mitomycin, V=vinblastine, M=methotrexate, F=5-fluorouracil, PCb= paclitaxel and carboplatin, G=gemcitabine, ORR= overall response rate, PFS= progression free survival, 1w=weekly, 3w= 3-weekly, w= weeks, m=months, ns = not significant.

8.0 months, respectively (P= 0.977). Median OS was 21.4 and 27.3 months, respectively (P =0.081). Hematological toxicity was significantly more frequent in the AD arm than in the AP arm ($P < 10^{-6}$), as well as grades 3-4 asthenia (P = 0.03). Neuropathy occurred more frequently in the AP arm (P = 0.03). QoL score differences between the groups or compared to baseline scores were not statistically significant.

Combination of paclitaxel and anthracyclines in first-line treatment of MBC (Table 3.)

In the EORTC 10961 (European Organization for Research and Treatment of Cancer) trial, the combination of doxorubicin and paclitaxel (AP**)** was compared with doxorubicin and cyclophosphamide (AC) (Biganzoli *et al.* 2002). There were no statistically significant differences between the two groups in terms of RR, PFS, or OS. The median OS was 20.6 versus 20.5 months in the AP and AC arms, respectively. The Central Europe and Israel Paclitaxel Breast Cancer Study Group phase III trial compared AP to cyclophosphamide, doxorubicine and 5-fluorouracil (CAF). There was a statistically significant difference in favor of AP in terms of RR, median TTP and OS (Jassem *et al.* 2001). The long-term follow-up analysis of this study confirmed the advantage of AP over CAF with regard to TTP and OS. At a median follow-up of 69 months, the difference in median TTP, and OS in favor of the AP arm remained significant: median TTP 8.1 vs. 6.2 months (P = 0.036) and OS 23.0 vs. 18.3 months (P= 0.005), respectively) (Jassem *et al.* 2009). The Eastern Cooperative Ongology Group (ECOG 1193) compared doxorubicin and paclitaxel combination with single doxorubicin and paclitaxel (Sledge *et al.* 2003). Patients received single agents crossed over to the other agent at progression. The combination arm showed higher RR and slightly longer TTP, but despite these results, combination therapy with AP did not improve either survival or QoL compared to sequential single-agent therapy.

There are not many phase III trials examining the combination of epirubicin and paclitaxel. In one phase III trial, epirubicin and paclitaxel (EP) combination was compared with epirubicin and cyclophosphamide (EC) combination (Langley *et al.* 2005). Overall response rates (ORR) were 65 % for the EP group and 55 % for the EC group (P = 0.015). However, no statistically significant change was seen in PFS and OS. These data failed to demonstrate any additional advantage of using EP rather than EC as first-line chemotherapy for MBC in taxane-naïve patients (Langley *et al.* 2005).

The sequential administration of epirubicin and paclitaxel has been compared with the concomitant combination of epirubicin and paclitaxel (Conte *et al.* 2004). The sequential administration of epirubicin and paclitaxel at full doses was found to be as active as their combination.

Table 3. Phase III trials of first-line anthracycline-paclitaxel combinations.

Reference	Regimen mg/m²	N	ORR (%)	TTP	Survival (months)
Jassem (Jassem *et al.* 2001)	A50 + P200 (3w) vs. C 500 +A 50 + F 500	267	68 vs. 55 (*p*=0.032)	8.3 vs. 6.2 (*p*=0.034)	23.3 vs. 18.3 (*p*=0.013)
Biganzoli (Biganzoli *et al.* 2002)	A60 + P175(→200) (3w) vs. A60 + C600 (→750)	275	58 vs. 54 (*p*=ns)	PFS: 6 m vs. 6 m	20.6 vs .20.5 (*p*=ns)
Sledge (Sledge *et al.* 2003)	A60 vs. P175 (3w) vs. A50 + P150 (3w)		36 vs. 34 vs. 47 (A vs. P, *p*=0.84; A vs. AP, *p*=0.007; P vs. AP, *p*=0.004)	5.8m vs. 6.0m vs. 8.0 m (*p*=0.68, *p*=0.003, *p*=0.009)	18.9 vs. 22.2 vs. 22.0 (*p*=ns)
Langley (Langley *et al.* 2005)	E75 + P200 (3w) vs. E75 + C600	705	65 vs. 55 (*p* = 0.015)	PFS 7.0m vs. 7.1m (*p* = 0.41)	13 vs .14 (*p*=0.8)

D=docetaxel, P=paclitaxel, A=doxorubicin, E= epirubicin, C=cyclophosphamide F=5-fluorouracil, ORR= overall response rate, PFS=progression-free survival 3w= 3-weekly, m=months, ns = not significant.

Combination of docetaxel and anthracyclines in first-line treatment MBC

The combination of doxorubicin and docetaxel (AD) has been shown to improve RR and TTP with no difference in OS when compared with doxorubicin and cyclophosphamide (AC) combination in a phase III trial (Nabholtz *et al.* 2003b). AD has also been compared with CAF. Median TTP and median OS were significantly longer for patients on AD compared with CAF (TTP: 8.0 vs. 6.6 months, respectively, *P* = 0.004; and OS: 22.6 vs. 16.2 months, respectively, *P*= 0.019). In addition, the RR was significantly higher in patients on AD compared with CAF (58 % vs. 37 %, respectively, *P* = 0.003) (Bontenbal *et al.* 2005).

By 2010, the combination of epirubicin and docetaxel has been studied in several mainly phase II studies (Table 4). There are only few publications of phase III trials (Blohmer *et al.* 2010, Mavroudis *et al.* 2010, Pacilio *et al.* 2006). The phase III trials of combinations of docetaxel and anthracyclines are shown in Table 5.

Table 4. Phase II trials of first-line epirubicin-docetaxel combinations.

Author	Regimen mg/m²	N	ORR (%)	TTP (months)	Survival (months)	QoL (Y/N)	Economic evaluation (Y/N)
Pagani (Pagani *et al.* 2000)	E90, D75	68	57	4.5	nr	N	N
Mavroudis (Mavroudis *et al.* 2000)	E70,D90	54	66	11.5	nr	N	N
Sessa (Sessa & Pagani. 2001)	E90, D75	70	66	4.5	nr	N	N
Viens (Viens *et al.* 2001)	E60-100, T75	62	69	9.1	22.7	N	N
Milla-Santos (Milla-Santos *et al.* 2001)	E130, D100	32	88	16.3	20.1	N	N
Yeo (Yeo *et al.* 2002)	E75, D75	46	83.7	11.0	24.2	Y	N
Polyzos (Polyzos *et al.* 2003)	E60, D80	69	65	10	24	N	N
Bonneterre (Bonneterre *et al.* 2004)	E75, D75	70	59	7.8	34	N	N
Morales (Morales *et al.* 2004)	E75, D75	133	67	10.8	19.5	N	N
Fabi (Fabi *et al.* 2004)	E90, D90	25	79	11	36	N	N
Im (Im *et al.* 2005)	E75, D75	40	60.5	8	15.8	N	N
Hainsworth (Hainsworth *et al.* 2006)	E90, D60	30	50	12	18	N	N
Gamucci (Gamucci *et al.* 2007)	E25, D25 (weekly)	43	60	11	28	N	N
Malinovszky (Malinovszky *et al.* 2007)	E75, D75	333	61	9	18	N	N
Seo (Seo *et al.* 2009)	E75 ,D75	32	41.9	12	41	N	N

D= docetaxel, E= epirubicin, ORR= overall response rate, nr= not reported, Y=yes, N=no

Table 5. Phase III trials of first-line anthracycline-docetaxel combinations.

Reference	Regimen mg/m²	N	ORR (%)	TTP	Survival (months)
Nabholtz (Nabholtz *et al.* 2003b)	A50 + D75 vs. A60 + C600	429	59 vs. 47 (*p*=0.009)	37.3w vs. 31.9w (*p*=0.014)	22.5 vs. 21.7 (*p*=0.26)
Bontenbal (Bontenbal *et al.* 2005)	A50 + D75 vs. F500 + A50 + C500	216	58 vs. 37 (*p*=0.003)	8.0m vs. 6.6m (*p*=0,004)	22.6 vs. 16.2 (*p*=0.019)
Pacilio (Pacilio *et al.* 2006)	D100 vs. D80 + E75	51	72 vs. 79 (*p*=ns)	PFS 9 vs. 11 (*p*=ns)	18 vs. 21 (*p*=ns)
Blohmer (Blohmer *et al.* 2010)	E75 + C600 vs. E 75 + C75	240	42 vs. 47 (*p*=0.63)	PFS: 10.1m vs.10.3m (*p*=0.38)	19.9 vs. 30.0 (*p*=0.21)
Mavroudis (Mavroudis *et al.* 2010)	E75 + D 75 vs. D75 + C950	166	51 vs. 53 (*p*=0.8)	10.6m vs. 11.0m (*p*=0.7)	37.6 vs. 35.7 (*p* = 0.744)

D=docetaxel, P=paclitaxel, A=doxorubicin, E=epirubicin, C= cyclophosphamide, ORR= overall response rate, PFS=progression-free survival, ns = not significant, w= weeks, m=months

2.2.2.4. Combination of taxanes with other chemotherapeutic agents in first-line chemotherapy of metastatic breast cancer

Taxane-based therapy is considered standard care for anthracycline-pretreated taxane-naïve MBC patients. Both docetaxel and paclitaxel have been used alone or in combination with newer agents in several phase III trials in anthracycline-pretreated patients (Morabito *et al.* 2007). One first-line randomized phase III trial has demonstrated improved OS with polychemotherapy compared to single-agent therapy in anthracycline-pretreated MBC patients. Albain *et al*. (2008) compared paclitaxel/gemcitabine combination with single paclitaxel. The OS was 18.6 vs. 15.8 months (*P*=0.049), respectively. Increased grade 3 to 4 neutropenia, fatigue and neuropathy were observed in the combination group (Albain *et al.* 2008). Founzilas *et al*. 2009 have compared 3-weekly (3w) paclitaxel and carboplatin with docetaxel and gemcitabine and with weekly paclitaxel (1w) as first-line treatment for MBC patients treated with anthracycline-based adjuvant chemotherapy. Trastuzumab was given to patients with human epidermal growth factor receptor 2 (HER-2) over-expressing tumors. Median survival times were 29.9, 26.9 and 41.0 months (P = 0.037), respectively. In terms of survival and toxicity, single paclitaxel appeared to be the most preferable choice (Fountzilas *et al.* 2009). Joensuu *et al*. (2010) have compared alternating administration of docetaxel and gemcitabine with single-agent docetaxel as first-line treatment of advanced breast cancer. There was no significant difference in RR, TTP, and survival between the groups but fewer adverse effects occurred during gemcitabine cycles. (Joensuu *et al.* 2010) A recent phase III trial compared docetaxel plus epirubicin with docetaxel plus capecitabine. The regimens had similar efficacy. Median TTP was 10.6 and 11.0 months, respectively. RR was 51 % and 53 %, respectively. The differences were not statistically significant (Mavroudis *et al.* 2010). When gemcitabine,

epirubicin and paclitaxel were compared with CEF, no significant differences in terms of efficacy were observed, but treatment-related toxicity was higher in the gemcitabine arm.(Zielinski *et al.* 2005).

2.3. Toxicity of anthracyclines and taxanes

The clinical usefulness of anthracyclines is limited by toxicity that may preclude adequate dosing and rechallenge on relapse, or lead to drug resistance. High cumulative doses increase the probability of cardiotoxicity, while individual doses are often limited by myelosuppression. Alopecia, severe acute nausea, vomiting and mucositis are additional adverse effects of doxorubicin that may limit their use in therapy. Pegylated liposomal doxorubicin is less cardiotoxic and causes less nausea, vomiting and myelosuppression; instead, the incidence of skin toxicity has been higher (O'Brien *et al.* 2004).

Adverse effects of both paclitaxel and docetaxel treatment are common. Alopecia is the most frequent side effect of both drugs. Skin toxicity consisting of erythema, desquamation and skin exfoliation and/or nail toxicity is mainly seen with docetaxel, while rashes are sometimes seen with paclitaxel. Nausea and/or vomiting can be counteracted by prophylactic use of antiemetics. Diarrhea and mucositis are usually mild, the latter occurring more frequently with docetaxel. Arthralgia and myalgia appear to be more common with paclitaxel. Fluid retention is unusual: more common with docetaxel, being related to cumulative dose. (Verweij *et al.* 1994) Both taxanes cause neurotoxicity manifested as polyneuropathy. The most common feature is a distal predominantly sensory neuropathy, and this appears to be related to dose level and cumulative dose. Motor neuropathy is believed to be much less common, and weakness is usually mild (Kuroi & Shimozuma. 2004).

Myelosuppression is the major dose-limiting toxicity of both anthracyclines and taxanes. Neutropenic sepsis, chemotherapy-associated anemia and thrombocytopenic hemorrhage are potentially life-threathening complications of chemotherapy and can have a significant impact on QoL. Neutropenia (<2,000 neutrophils/mm3) occurs in most patients given taxanes. The incidence of grade 4 neutropenia approximates 50–55 % (Verweij *et al.* 1994). Anemia and thrombocytopenia are less frequent and less pronounced than neutropenia (Verweij *et al.* 1994). Due to the overlapping toxicity profiles of anthracyclines and taxanes in terms of myelosuppression, combinations of these two groups have resulted in increased incidence of myelosuppression and febrile neutropenia (Biganzoli *et al.* 2002, Bontenbal *et al.* 2005, Nabholtz *et al.* 2003b).

Doxorubicin/paclitaxel combination has been compared with doxorubicin/docetaxel combination (Cassier *et al.* 2008). The study showed differences in the toxicity profiles between the treatment arms. Grade 3–4 asthenia (P=0.03), as well as hematological toxicity, was more frequent in the docetaxel than in the paclitaxel arm ($P < 10^{-6}$). Neuropathy occurred more frequently in the paclitaxel arm ($P = 0.03$). Increased incidence of arthralgia, myalgia and neuropathy has been reported with epirubicin/

paclitaxel and doxorubicin/paclitaxel combinations when compared with anthracycline/cyclophosphamide combination (Biganzoli *et al.* 2002, Jassem *et al.* 2001, Langley *et al.* 2005).

Pegylated and non-pegylated liposomal doxorubicin have shown high antitumor activity with acceptable toxicity when combined with docetaxel (Alexopoulos *et al.* 2004, Morabito *et al.* 2004, Schmid *et al.* 2009, Sparano *et al.* 2009). Neutropenia, palmar-plantar-erythrodisesthesia, asthenia and mucositis have been the most relevant side effects (de la Fouchardiere *et al.* 2009).

Sequential administration of anthracyclines and taxanes has shown reduced haematological toxicity, especially febrile neutropenia, compared with concomitant administration, essentially maintaining comparable antitumoral efficacy (Alba *et al.* 2004, Conte *et al.* 2004) although it appears that combination therapy is associated with improved RR and TTP (Cardoso *et al.* 2009).

2.3.1. Cardiotoxicity of anthracyclines and taxanes

Cardiotoxicity is a significant complication of cancer treatment especially in early stage disease. Cardiotoxicity remains an issue also in a palliative setting, although the focus shifts from avoiding long-term sequelae to more immediate problems that might compromise survival or QoL (Barrett-Lee *et al.* 2009).

The incidence and severity of cardiotoxicity depend on the type of drugs used, dose and schedule employed, cumulative dose, combination of other cardiotoxic drugs, and prior chest-wall radiation therapy. Patient-dependent risk factors include age, pre-existing vascular risk factors such as hypertension, diabetes and known underlying heart disease (Bovelli *et al.* 2010). Cardiac events associated with chemotherapy vary in incidence, in severity from mild to fatal, and in timing from acute (during or shortly after treatment), subacute (within days of weeks after chemotherapy) to chronic, arising several years after cancer treatment (Altena *et al.* 2009). Cardiac events associated with chemotherapy may consist of arrhythmias, mild blood pressure changes, electrocardiogram (ECG) changes, thrombosis, myocarditis, pericarditis, myocardial infarction, cardiomyopathy, cardiac left ventricular failure, and congestive heart failure (Albini *et al.* 2010, Zuppinger & Suter. 2010). In a metastatic setting, acute and subacute cardiac toxixicy are more important than late toxicity.

Anthracycline-induced cardiotoxicity has been recognized for more than 30 years and remains an important consideration even today (Cardinale *et al.* 2010, Gianni *et al.* 2009, Zuppinger & Suter. 2010). It is currently believed that doxorubicin-induced cardiac damage takes place from the earliest administration of the drug, and that toxicity is cumulative and dose-dependent (Mordente *et al.* 2009). The pathophysiology of anthracycline-induced cardiomyopathy remains controversial and incompletely understood. Overproduction of reactive oxygen species can probably be held responsible for anthracycline acute cardiotoxicity, while intramyocardial formation of secondary

alcohol metabolites might play a key role in promoting the progression of cardiotoxicity toward end-stage cardiomyopathy and congestive heart failure (Mordente *et al.* 2009). Once the critical threshold level of myocardial damage has been reached, cell death ensues (Ewer & Lippman. 2005). Doxorubicin cardiotoxicity is exponentially dose-dependent and increases dramatically when cumulative doses exceed about 500 mg/m^2 (Barrett-Lee *et al.* 2009). Lifetime cumulative doxorubicin dose should be limited to 450–550 mg/m^2 . However, age has been shown to be an important risk factor for doxorubicin-related cardiac heart failure (CHF) following a cumulative dose of 400 mg/m^2, with older patients (age >65 years) being 2.25 times more likely to experience CHF compared to younger patients (Swain *et al.* 2003). It has recently been recommended that already at a cumulative dose of 300 mg/m^2 further exposure should be reduced to limit potential cardiotoxicity (Aapro *et al.* 2011). For elderly patients even lower limits would be more appropriate (Aapro *et al.* 2011).

Epirubicin is an epimer of doxorubicin. It has been suggested for a long time that epirubicin is less cardiotoxic than doxorubicin because lower levels of secondary alcohol metabolites are produced by epirubicin (Minotti *et al.* 2000). A Cochrane Review has confirmed a lower rate of CHF, with no difference in RR and survival observed in patients treated with epirubicin compared with doxorubicin (van Dalen *et al.* 2006). A maximum cumulative dose of 900 mg/m^2 is considered the standard (Barrett-Lee *et al.* 2009). In a Danish study, 1097 patients were treated for MBC with several epirubicin-based regimens. The maximum cumulative dose of epirubicin acceptable from the standpoint of cardiotoxicity was shown to be less than has been assumed before. The risk of cardiotoxicity increased by 40 % for each 100 mg/m^2 increase in cumulative dose, and by 30 % with each decade of age. The acceptable dose depended on a range of factors, including tumor burden, predisposition to heart disease and treatment history (including mediastinal irradiation, endocrine therapy for metastatic disease and prior treatment with CMF). Age was a major factor affecting the maximum acceptable cumulative dose. For a 40-year-old patient with no predisposition to heart disease and no risk factors related to treatment history, the cumulative dose of epirubicin acceptable from the point of view of cardiotoxicity was 890 mg/m^2, i.e. close to the 900 mg/m^2 which is often cited. However, the acceptable cumulative dose was only 732 mg/m^2 if the patient was aged 70 years. For a 40-year-old patient with no treatment-related risk factors but a predisposition to heart disease, the acceptable maximum dose was 806 mg/m^2. However, the acceptable cumulative dose was reduced by 200 mg/m^2 in a comparable patient aged 70 years (Ryberg *et al.* 2008).

Strategies to prevent anthracycline-induced cardiomyopathy include limiting the total cumulative dose, use of doxorubicin analogues such as epirubicin, and novel delivery systems such as liposomal doxorubicin (Bovelli *et al.* 2010, Ewer *et al.* 2004, O'Brien *et al.* 2004, Stavridi & Palmieri. 2008)**.** Liposomal anthracyclines achieve lower cardiotoxicity by changing tissue distribution and by decreasing the rate of drug release (Theodoulou & Hudis. 2004).

The most frequent cardiovascular events reported during paclitaxel administration have been declines in heart rate and blood pressure (Rowinsky *et al.* 1991). Ekholm *et al*. (2000) have reported that autonomic modulation of the heart rate is impaired after paclitaxel therapy (Ekholm *et al.* 2000). On further investigation, patients without significant cardiac risk factors frequently had asymptomatic sinus bradycardia (approximately 30 %). Heart block and conduction abnormalities have occurred infrequently and have often been asymptomatic. Cardiac rhythm disturbances and chest pain during paclitaxel infusion have been reported, but the causal relationship of paclitaxel to atrial and ventricular arrhythmias and cardiac ischemia has not been evident because many patients have had other conditions known to be associated with cardiac events. Nevertheless, the incidence of severe cardiac events has been low (Arbuck *et al.* 1993, Bovelli *et al.* 2010).

Taxanes interfere with the metabolism and excretion of anthracyclines and potentiate anthracycline-induced cardiotoxicity, especially at high, cumulative anthracycline doses. More specifically, pharmacokinetic studies have shown an interaction between paclitaxel and doxorubicin, increasing the hepatic clearance of the doxorubicin metabolite doxorubinol (Gianni *et al.* 1995, Nabholtz. 2003). The highest cumulative dose of doxorubicin that can be safely administered in combination with paclitaxel is as low as 360 mg/m^2. To reduce cardiotoxicity, doxorubicin should be given before paclitaxel (Conlin & Seidman. 2007, Giordano *et al.* 2002).

In clinical trials, docetaxel has not been associated with increased cardiotoxicity when combined with doxorubicin, probably due to low doxorubicin doses (Bird & Swain. 2008, Nabholtz *et al.* 2003b). No pharmacokinetic interaction between docetaxel and doxorubicin has been shown. However, it has been shown that even docetaxel can stimulate doxorubinol formation in combination with doxorubicin in human heart cytosol *in vitro,* a fact which instigates caution against combining docetaxel with cumulative doses of doxorubicin higher than those adopted in available clinical trials (Salvatorelli *et al.* 2006).

Combination treatments with epirubicin and taxane seem to be less cardiotoxic (Gennari *et al.* 1999, Grasselli *et al.* 2001). A cumulative epirubicin dose limit of 990 mg/m^2 in combination treatments with paclitaxel has been proposed, but the incidence of CHF seems to be increased in patients with additional cardiac risk factors (Gennari *et al.* 1999). Baldini *et al*. (2004) have evaluated the cardiac safety of two different schedules of epirubicin and paclitaxel in advanced BC patients in a phase III trial. Patients received epirubicin 90 mg/m^2 plus paclitaxel 200 mg/m^2 every three weeks for eight courses (arm A), or epirubicin 120 mg/m^2 every three weeks for four courses, followed by four courses of paclitaxel 250 mg/m^2 every 3 weeks (arm B). They demonstrated that the risk of CHF or impairment in cardiac function correlated only with the cumulative dose of epirubicin; no impact on cardiotoxicity was attributed to high-dose paclitaxel (Baldini *et al.* 2004). In clinical trials, docetaxel has not been associated with increased cardiotoxicity when combined with epirubicin (Bird & Swain. 2008).

2.4. Quality of life in oncology

2.4.1. Quality of life terminology

The World Health Organization has defined health in 1948 not only as absence of disease but also as presence of physical, mental and social well-being. In general, the term quality of life encompasses all aspects of patients´ well-being, whereas health-related quality of life (HRQoL) is more specific and involves only those aspects of life which are more directly affected by healthcare interventions. However, the term QoL is more popular in the oncological literature and is extensively used instead of HRQoL. In this thesis, the term QoL is used accordingly. QoL as a concept refers to the effect of a disease and its therapy upon a patient´s physical, mental and social well-being as perceived subjectively by the patient himself. It is a multidimensional construct that includes several key dimensions. The minimum dimensions in QoL measurements include physical functioning, disease- and treatment-related symptoms, and physiological and social functioning (Velikova *et al.* 1999).

2.4.2. Use of quality of life assessments

In cancer clinical trials the traditional biomedical endpoints have been tumor response, disease-free survival, and OS. However, as cancer treatment research has progressed, it has become evident that these endpoints alone may not be sufficient for informed decision making among different treatment options (Sprangers. 2010). The quality of the survival is important from the patients´ point of view, and in this setting, the Quality-adjusted Time Without Symptoms and Toxicity (Q-TWiST) has been found to have an important application (Radice & Redaelli. 2005).

When treating MBC, the objective of the treatment is not to cure; the main purpose of the treatment is to delay disease progression, control symptoms, and improve/maintain the QoL (Morrison & Meier. 2004). The side-effects of treatment should never exceed the expected positive effects: small gains must be weighed against side-effects to justify its use. QoL assessments are of major importance when comparing two palliative treatments, especially when one treatment arm is suspected to be associated with significantly more morbidity with no expected differences in cure/survival, or when survival/disease-free survival or cure are expected to differ in the treatment arms at the expense of major toxicity, or when evaluating cost-effectiveness (Roila & Cortesi. 2001). It is important to note that QoL studies are not simple extensions of toxicity scales. Toxicity scales measure only the maximum toxicity but do not take the duration into account as QoL instruments do. Furthermore, there is less effect on QoL from acute than chronic or late toxicity. For example, patients with debilitating neuropathy often have poor QoL even though they have good control of their cancer (Roila & Cortesi. 2001). Collection of the data from formal QoL instruments broadens the parameters of benefit beyond response and survival, and allows more accurate determination of the supportive and ameliorative interventions needed by the patients.

The prognostic value of self-rated QoL in terms of survival is still somewhat controversial. Most of the studies in which QoL domains have been found to be prognostic have included patients with advanced disease (Coates *et al.* 2000, Efficace *et al.* 2004, Kramer *et al.* 2000a, Lee *et al.* 2010, Montazeri. 2009, Shadbolt *et al.* 2002). The earlier the assessments are made during the disease course, the less prognostic the results are (Osoba. 2007a).

In addition, the QoL as a health-related outcome is widely recognized as an important component of economic evaluations (e.g. cost-utility and cost-effectiveness analysis) (Bagust *et al.* 2001, Tappenden *et al.* 2006, Uyl-de Groot. 2006).

2.4.3. Quality of life instruments

Because of the complex nature of BC, it is evident that no single instrument is comprehensive and sensitive enough to detect clinically significant changes in all outcomes across all phases of care with acceptable responder and provider burden. Accordingly, several different QoL instruments have been used in BC studies.

The two most common validated QoL instruments used in international cancer trials are the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ C-30) (Aaronson *et al.* 1993) and the Functional Assessment of Cancer Therapy (FACT) (Cella *et al.* 1993). The EORTC has been primarily used in Europe and FACT in North America (Gunnars *et al.* 2001). The EORTC-QLQ C-30 puts more emphasis on symptoms and health status, whereas FACT focuses more on psychosocial aspects. The EORTC QLQ C-30 is a general cancer instrument that can be complemented with disease- and treatment-specific questionnaires for different types of cancer (Aaronson *et al.* 1993). The EORTC QLQ C-30 includes physical, functional, cognitive, emotional, social, and global domains, as well as various signs and symptoms (Aaronson *et al.* 1993). Functional assessment of cancer therapy general (FACT-G) comprises a core questionnaire containing 27 questions to which site- or treatment-specific subscales covering all common solid tumors and treatments are added. Physical, functional, emotional, social well-being, and symptoms are covered (Cella *et al.* 1993).

2.4.4. Quality of life of patients with advanced breast cancer

Among the QoL studies in cancer patients, BC has received most attention, probably for several reasons. First, BC is one of the most common types of cancers. Secondly, early detection and treatment of BC have improved, and the survivors now live longer, so studying QoL in this setting is important. Thirdly, BC affects women's identities as mothers and partners, thereby affecting the whole family (Montazeri. 2008). QoL of MBC patients has been studied less that of early stage BC.

BC patients often experience physical symptoms and psychosocial distress that adversely affect their QoL (Anderson *et al.* 2008). At the time of recurrence, high levels of psychological morbidity have been reported, especially among younger women

(Turner *et al.* 2005). Pain, fatigue, sleep disturbance, arm morbidity, and menopausal symptoms are the most common symptoms reported by BC patients (Montazeri. 2008). Especially younger patients suffer from poor sexual functioning that negatively affects their QoL (Montazeri. 2008). In general, the QoL of BC patients depends on the stage of the disease, patients with metastatic disease reporting the lowest QoL values. The main cause of the reduction in QoL has been pain and discomfort, as well as anxiety and depression (Lidgren *et al.* 2007a). Approximately 40 % of women with advanced BC have been found to have psychiatric and psychological disturbance, substantially affecting the QoL of these women (Grabsch *et al.* 2006). Other common features are dissatisfaction with their body image (25 %) and feeling unattractive (30 %) (Grabsch *et al.* 2006).

Several studies have evaluated the QoL of BC patients receiving systemic therapies including chemotherapy and hormonal therapy. Almost all QoL studies have indicated that BC patients receiving chemotherapy experience several side effects and symptoms that negatively affect some aspects of their QoL. Specifically, chemotherapy has been associated with fatigue, nausea, and peripheral neuropathy. In addition, chemotherapy has been found to be related to cognitive impairment (Argyriou *et al.* 2010). Also hormonal therapies have been found to have a negative impact on QoL (Costantino. 2002). QoL data regarding tamoxifen are limited, although tamoxifen has not been associated with significant psychological distress. QoL studies comparing the third-generation AIs with tamoxifen or megestrol acetate show that the AIs produce a more favorable QoL, mostly due to a lower incidence of thromboembolism and vaginal bleeding (Costantino. 2002). In general, in the majority of studies, no significant QoL differences among treatment groups in MBC trials have been reported (Bottomley & Therasse. 2002, Fountzilas *et al.* 2009, Hakamies-Blomqvist *et al.* 2000). Treatment side effects do not usually significantly deteoriate QoL. It has been reported that physical functioning and treatment toxicity explain only 16 % of the variance of global QoL, maybe mostly due to the psychic work that patients are forced to apply to the sense of hope that the treatment offers (Hakamies-Blomqvist *et al.* 2001).

It is usually assumed that the number and severity of symptoms caused by the tumor burden will be decreased by chemotherapy, and that there is a direct relationship between the tumor load and its symptomatic effect on the patient (Efficace *et al.* 2004). Accordingly, tumor response ought to correlate with palliative benefit. To support this, a direct comparison of QoL parameters in MBC patients under palliative chemotherapy or supportive care was made: the results favored the use of palliative chemotherapy in terms of QoL improvement in MBC patients in good clinical condition (Karamouzis *et al.* 2007). In addition, various studies have shown that the improved QoL has been associated with the clinical efficacy of chemotherapy and with tumor response (Hopwood *et al.* 2008, Modi *et al.* 2002). According to Zimmermann *et al*. (2010), the most important determinants of QoL in patients with advanced cancer are age, performance status, survival time, and treatment status. Compared to patients receiving cancer treatment, those awaiting new treatment had poorer emotional well-being. Also

those on surveillance or those whose treatment had been stopped had poorer existential well-being, probably reflecting less psychological support and hope (Zimmermann *et al.* 2010).

2.5. Pharmacoeconomics

Given the budgetary pressures and constantly rising treatment costs, economic evaluation of new, expensive cancer treatments is becoming increasingly important (Meropol & Schulman. 2007). The constantly rising costs have shifted the attention of evaluation of treatment effects using endpoints to other than just clinical efficacy. Policy-makers and regulatory authorities require information on the cost and cost-effectiveness of the treatment. The economic impact of cancer-related interventions has received increased attention because of the high cost of many new cancer drugs, and also due to their relatively modest benefits in the metastatic treatment setting (Greenberg *et al.* 2010).

During recent decades, there has been a growing number of publications on economic evaluation in health care. However, so far there has been great variation in the methodology and reporting of the results. The methods used for assessing and quantifying treatment outcomes in terms of costs and utility differ widely among studies, making comparisons across studies difficult (Grusenmeyer & Wong. 2007, Uyl-de Groot. 2006). International comparisons of economic evaluations are difficult due to differences in the health-care systems, treatment modalities, general cost levels, and currencies. In addition, the quantification of costs is challenging and, given the pricing complexities of the health-care market, the quantification of true costs is difficult and also depends on the perspective of the study (hospital perspective, societal perspective). Even the time horizons differ between the studies (e.g. three vs. six months´ duration of initial or terminal care).

Different types of cost analysis have been used in medicine: cost identification, cost minimization, cost-effectiveness, and cost-utility (Hillner. 1996). Cost-identification analysis simply collects all the costs of a given treatment. Cost-minimization analysis assumes that the effectiveness of the therapies being compared are equal and only analyzes the lowest cost of two or more different treatments. Cost-effectiveness analysis measures the benefit of a health-care intervention in units of medical effect. In order for cost-effectiveness estimates to be meaningful, the incremental costs imposed by new health technology over the current standard treatment are usually compared against the incremental effects it delivers, typically over the lifetime of the patient. The benefit measures employed commonly include OS, quality-adjusted survival, progression-free survival, quality-adjusted progression-free survival, tumor response, and adverse events avoided (Tappenden *et al.* 2006). The decision maker must finally establish a cut-off level at which acceptable cost per effect is determined. Cost-utility analysis estimates the impact of a health intervention on the quality and length of life (Uyl-de Groot. 2006). Quality-adjusted life year (QALY) gained calculations are frequently used. QALY is

defined as a measure of a person's length of life weighed by a valuation of their health-related QoL. The results of the QoL questionnaire in the QALY calculation is converted into a number between 0 and 1 which reflects overall QoL representing health utility. The value 0 is equivalent to being dead and 1 represents the best possible health state. However, some health states are regarded as being worse than 0 and are given a negative value. Utility values may be elicited from the patients themselves or from the general public. The best and easiest way of getting the utility data is to include a valuation instrument within the QoL instrument (Uyl-de Groot. 2006). To assess this extra cost of a new intervention compared to existing treatments, the incremental cost-effectiveness ratio (ICER) can be used. This measures the additional cost per QALY of the new intervention compared to the existing intervention. According to the National Institute for Health and Clinical Excellence (NICE, UK), if the ICER of a treatment is more than £ 20,000–30,000 per QALY, then it would not be considered cost-effective.

The application of economic principles to medicine does not mean that less money should be spent on cancer treatment, but that scarce resources are spent on care that delivers the greatest possible health benefits.

2.5.1. Treatment costs of advanced breast cancer

The economic burden of cancer is significant globally. According to the NIH estimate, the overall costs of cancer in the US in 2010 are US$ 263.8 billion: US$ 102.8 billion for direct medical costs, US$ 20.9 billion for indirect morbidity costs (cost of lost productivity due to illness) and US$ 140.1 billion for indirect mortality costs (cost of lost productivity due to premature death) (http://www.cancer.org/Cancer Facts and Figures 2010). On the basis of limited information, BC represents an important part of the total financial resources, a figure of 20–25 % of the total cost of cancer in the US is estimated (Radice & Redaelli. 2003).

In BC, both the direct and indirect costs are dependent on the stage of the disease. The major proportion of the lifetime costs in BC comprises the initial and terminal care, mainly due to the large amount of hospitalisation in these phases (Lidgren *et al.* 2007b, Will *et al.* 2000). In Finland, the mean cost per patient for stages I, II, III and IV at diagnosis were € 5,091, € 11,087, € 14,495 and € 12,573, respectively, and the ratios of means for stages II, III and IV compared to stage I were 1.9, 2.5 and 2.1, respectively (P<0.001) (Kauhava *et al.* 2004). The mean costs per survival day for stages I through IV were € 3.5, € 9, € 16 and € 67.2, respectively, and the ratios of means were 2.6, 4.6 and 19.2, respectively (P<0.001) (Kauhava *et al.* 2004). Similar studies have been performed in the US, Australia, the UK, and Canada. Despite the marked differences in the actual costs between the studies, a common feature is that the costs of stages III and IV tend to be higher than those of stages I and II, although the result in the UK study was not as clear due to the low number of stage IV cancers (Butler *et al.* 1995, Legorreta *et al.* 1996, Will *et al.* 2000, Wolstenholme *et al.* 1998). The health care costs for treatment of disseminated BC in Sweden have been estimated by Dahlberg *et a*l.

(2009). According to their study, the mean direct cost of disseminated BC from the date of diagnosis of dissemination until death was € 93,700 (95 % CI € 78,500 - € 109,600) which is considerably higher than previously shown in Sweden or elsewhere (Dahlberg *et al.* 2009). Drugs and hospitalizations were the largest single cost sources. In a Finnish study, it was estimated that about one third of the costs for fatal breast cancer could be avoided through mammography screening (Kauhava *et al.* 2006).

Treatment of febrile neutropenia is costly, because it typically involves hospitalization. Estimates of the direct costs of managing febrile neutropenia vary substantially. They depend on various factors, including care setting, severity of the episode, and the country. Lathia *et al.* (2010) have quantified the direct medical costs of treating febrile neutropenia in Canada. They reported high treatment costs mainly due to hospitalization (Lathia *et al.* 2010). The total mean direct medical costs per febrile neutropenia episode was Can$ 6,324 +/- 4,783 in 2007 (Canadian dollars) (Lathia *et al.* 2010). The mean cost due to hospitalization was Can$ 4,657, whereas the cost of antibiotics was Can$ 258, and of granulocyte-colony-stimulating factors Can$ 354. Bennett and Calhoun (2007) have estimated both the direct and indirect costs in the US. The direct cost of treatment of febrile neutropenia in BC patients treated in an outpatient setting was US$ 1,094 per episode, and US$ 10,354 in an inpatient setting. In the inpatient setting, hospitalization accounted for over 75 % of the costs. Indirect costs were estimated to be US$ 1,530 and US$ 2,832, respectively (Bennett & Calhoun. 2007). In Spain, the estimated cost of an episode of febrile neutropenia was € 3,519 (Mayordomo *et al.* 2009). This is in line with estimates from the UK, where the estimated cost was £ 3,330 (http://www.nice.org.uk). The data regarding the cost-effectiveness of using hematopoetic growth factors as primary prophylactic therapy against febrile neutropenia are somewhat conflicting (Esser & Brunner. 2003, Lathia *et al.* 2010, Trueman. 2009).

A few economic evaluations comparing docetaxel and paclitaxel in MBC have been made. According to a Canadian population-based retrospective analysis, docetaxel is more effective than paclitaxel at a cost of Can$ 2,434 for each additional month gained (Vu *et al.* 2008). According to a study from the UK, the ICER value for docetaxel was £ 12,032/QALY versus 3-weekly paclitaxel, £ 4,583/QALY versus weekly-paclitaxel, and £ 14,694/QALY versus nano albumin-bound three-weekly paclitaxel (Benedict *et al.* 2009). Docetaxel compared with three-weekly paclitaxel was estimated to have a cost-effectiveness ratio that falls within the acceptable threshold in the UK. The study also suggests that docetaxel may be cost-effective versus once-weekly paclitaxel and nano albumin-bound paclitaxel, although there was more uncertainty around these findings (Benedict *et al.* 2009). Calculations in Spain showed that, compared to weekly paclitaxel, docetaxel therapy is cost-effective for treating metastatic breast cancer patients based on a € 30,000/QALY threshold (Frias *et al.* 2010).

2.6. Biochemical markers of bone metastases in breast and prostate cancer

Both BC and PC show a predilection to metastasize to bone. Bone is the primary site of metastasis in both cancers. According to autopsy findings, bone metastases occur in 60–90 % of patients who die from BC (Kamby *et al.* 1988), and in >80 % of patients who die from PC (Bubendorf *et al.* 2000).

Bone is connective tissue composed of organic matrix, mineral and bone cells. The organic matrix consists predominantly of collagen fibers and the mineral consists of calcium and phosphate deposited on these fibers. There are four types of cells in the bone, namely, osteoblasts, osteocytes, osteoclasts, and bone lining cells. Bone is constantly undergoing bone remodelling, which is a complex process involving resorption of bone by the osteoclasts and bone formation by the osteoblasts. Osteoclasts resorb bone by attaching themselves to the matrix and secreting enzymes that digest the matrix and dissolve the bone mineral. Osteoblasts secrete both type I collagen and the non-collagenous proteins of the organic matrix, and regulate the mineralization of this matrix. Normally there is a balance between the amount of bone resorbed and the amount of bone formed. (Hill. 1998) Regulation of normal bone remodeling occurs via the receptor activator of the nuclear factor-kappaB (RANK)/ RANK ligand (RANKL)/ osteoprotegerin (OPG) pathway, which is disrupted in metastatic bone disease (Sterling *et al.* 2011). This triad regulates osteoclast maturation, differentiation, and survival. Excessive bone resorption is prevented by the decoy receptor OPG, produced by osteoblasts. OPG inhibits the binding of RANK to RANKL and thus inhibits the recruitment, proliferation, and activation of osteoclasts (Neville-Webbe & Coleman. 2010).

Bone metastases have been characterized as osteolytic or osteoblastic/sclerotic. This classification represents two extremes of a continuum in which dysregulation of the normal bone remodeling process occurs. The ´coupling´ between bone resorption and bone formation is disturbed, making affected bones vulnerable to complications. Patients can have both osteolytic and osteoblastic metastasis or even mixed lesions containing both elements. Most BC bone metastases are predominantly osteolytic lesions, although at least 15–20 % are predominantly osteoblastic lesions (Coleman & Seaman. 2001). In contrast, PC bone metastases are osteoblastic in nature. However, the presence of osteolytic bone lesions in the osteoblastic cases may account for the increase in observed fractures in PC (Roudier *et al.* 2008).

The molecular basis of the preferential growth of cancer cells in the bone microenvironment has been an area of active investigation. The precise molecular mechanisms underlying this process still remain to be elucidated. It has been increasingly recognized that the unique characteristics of the bone niche provide homing signals to cancer cells, and create a microenvironment conducive for the cancer cells to colonize. Bone metastases depend on the dynamic crosstalk between metastatic cancer cells, cellular components

of the bone marrow microenvironment and the bone matrix (osteoclasts and osteoblasts) (Ibrahim *et al.* 2010).

When growing in the bone microenvironment, BC cells produce cytokines and hormones, e.g. parathyroid-hormone-related protein (PTHrP), interleukins (IL-1, IL-8, IL-11, IL-15, IL-17), transforming growth factor β (TGF-β), and tumor necrosis factor α (TNF-α) that enhance osteoclast activation and bone resorption via RANKL-dependent and RANKL-independent mechanisms. Bone resorption by osteoclasts releases growth factors and cytokines, e.g. TGF-β, from the bone matrix, which in turn further stimulate tumor growth and bone destruction. The production of growth factors such as fibroblast growth factors (FGFs), bone morphogenetic proteins (BMPs), and TGF-β by metastatic tumor cells also stimulate osteoblast activity, leading to increased bone formation. The result of increased osteoblast proliferation and activity results again in induction of osteoclast activity and bone resorption by increased expresson of RANKL in osteoblastic stromal cells. RANKL activates RANK on osteoclast precursors and promotes cellular maturation in the presence of macrophage-stimulating factor. As the bone resorption increases, the bone formation and resorption fall out of balance resulting in bone destruction (Akhtari *et al.* 2008, Chirgwin & Guise. 2000, Kakonen & Mundy. 2003, Sterling *et al.* 2011, Suva *et al.* 2011, Zhang *et al.* 2010). Similarly, the complex interactions between tumor cells, bone cells and bone matrix constitute a vicious cycle of osteoblast-mediated bone metastasis (Ibrahim *et al.* 2010). PC cells produce osteogenic factors, e.g. platelet-derived growth factors (PDGFs) and bone morphogenetic proteins (BMPs), which activate osteoblasts to deposit new matrix for bone formation. This unmineralized matrix enriched with growth factors and noncollagen proteins provides more fertile soil for the tumor cells. Newly formed bone may provide additional factors attracting PC cells, allowing them to survive and proliferate in the bone environment, thereby activating more osteoblasts. In addition, osteoblasts in turn control osteoclast activity through the expression of cytokines such as RANKL, the key activator of osteoclast differentiation (Boyle *et al.* 2003). Thus, osteoblasts can create more space in the bone for dominantly osteoblastic lesions by activating osteoclasts (Ye *et al.* 2007).

The diagnosis the bone metastases usually relies on imaging methods including plain radiographs, radionuclide bone scans, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET). However, all these methods have their limitations in terms of specificity and sensitivity. Especially the monitoring of skeletal disease progression and assessment of treatment response of bone metastases is hindered by a lack of effective and rapid methods. Bone scintigraphy is considered the mainstay method in the initial diagnosis (Costelloe *et al.* 2009). In the follow-up, the flair-phenomenon, an apparent recrudescence of disease seen on imaging, is a significant source of false positives (Clamp *et al.* 2004). Moreover, radiographs have limited sensitivity in the diagnosis and follow-up of skeletal metastases. It has been estimated that approximately 50 % of cortical bone must be destroyed before lytic metastases will become detectable by X-rays. Although CT scans are superior to radiographs, CT scanning is also relatively insensitive in showing small intramedullary lesions, and it has

the disadvantage of limited skeletal coverage. Bone scintigraphy findings are sensitive but non-specific. MRI and FDG-PET scanning are accurate techniques that are somewhat limited by their high cost. (Coleman. 1998, Grankvist *et al.* 2011, Suter *et al.* 2007)

Biochemical markers are non-invasive and easy and fast to perform. Bone markers can be divided into bone-resorption and bone-formation markers, representing the activity of osteoclasts and osteoblasts, respectively (Table 6.). The majority of bone-resorption markers are products of collagen degradation. Other markers of bone resorption are osteoclastic enzymes, tartrate resistant acid phosphatase and catepsin K. Bone formation markers are either by-products of bone formation or osteoblastic enzymes (Clemons *et al.* 2006).

Table 6. Markers of bone resorption and formation. Modified from Chao 2010 (Chao *et al.* 2010)

	Resorption	**Formation**
Serum	Calcium	tALP
	ICTP	BAP
	N-telopeptide (NTX)	Osteocalcin
	C-telopeptide (CTX)	C-terminal peptide of type I procollagen (PICP)
	RANKL/osteoprotegerin (OPG)	N-terminal peptide of type I procollagen (PINP)
	TRACP 5b	
	Galactosyl hydroxylysine	
Urine	Calcium	
	Hydroxyproline	
	NTX	
	CTX	
	Pyridinoline (PYD)	
	Deoxypyridinoline (DPD)	

2.6.1. Bone-resorption markers

Tartrate-resistant acid phosphatase 5b

Tartrate-resistant acid phosphatase 5b (TRACP 5b) activity in serum is a marker of bone resorption (Halleen *et al.* 2000, Halleen *et al.* 2001, Halleen. 2003). TRACP 5b is derived from osteoclasts (Janckila *et al.* 2002) (Figure 1.). It has been suggested that TRACP 5b indicates ongoing bone-resorption activity at the time of sample collection (Chu *et al.* 2003). The biological and analytical variability is low (Halleen *et al.* 2000, Halleen *et al.* 2001). In addition, TRACP 5b activity does not show marked dependence on food intake or diurnal rhythm (Halleen *et al.* 2001, Hannon *et al.* 2004). TRACP 5b activity is not affected by liver or kidney function (Hannon *et al.* 2004, Shidara *et al.* 2008, Yamada *et al.* 2008), which is an important issue concerning patients with, e.g. additional liver metastases or renal dysfunction.

Serum TRACP 5b levels are affected by changes in both pathological and physiological bone turnover, i.e. TRACP 5b is not specific to pathological bone resorption. Increased TRACP 5b concentrations have been detected in conditions with increased bone resorption such as post-menopausal age and osteoporosis (Halleen *et al.* 2001). In addition, TRACP 5 b levels have been shown to increase in BC and PC with bone metastasis (Capeller *et al.* 2003, Chao *et al.* 2004, Halleen *et al.* 2001, Jung *et al.* 2004, Lyubimova *et al.* 2004, Martinetti *et al.* 2002). However, it has been proposed that TRACP 5b might not be sensitive enough to detect oligometastatic disease (Chao *et al.* 2005). Serum TRACP 5b has been shown to decrease during bisphosphonate therapy (Capeller *et al.* 2003, Fagerlund *et al.* 2008, Hannon *et al.* 2004, Lyubimova *et al.* 2004, Martinetti *et al.* 2002, Mehlhorn *et al.* 2008, Nenonen *et al.* 2005, Tauchert *et al.* 2009, Terpos *et al.* 2003a, Terpos *et al.* 2003b, Voskaridou *et al.* 2003). TRACP 5b has been shown to have potential in predicting metastatic bone fractures (Gerdhem *et al.* 2004).

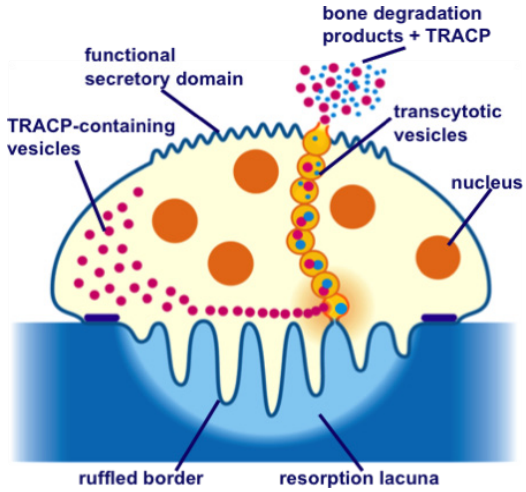

Figure 1. Transport of TRACP 5b in resorbing osteoclasts. Courtesy of Professor Kalervo Väänänen.

Carboxyterminal telopeptide of type I collagen

Carboxyterminal telopeptide of type I collagen (ICTP) is a cross-linked product of collagen I degradation that is generated by matrix metalloproteinases (Sassi *et al.* 2000) (Figure 2.). Increased concentrations of ICTP have been shown to be closely associated with increased pathological bone resorption in clinical conditions such as rheumatoid arthritis, multiple myeloma, and cancer bone metastases, but to be rather insensitive to changes in physiological bone collagen turnover (Garnero *et al.* 2003, Sassi *et al.* 2000). Several studies have shown increased levels of ICTP in both BC and PC patients with bone metastasis (Demers *et al.* 2000, Kataoka *et al.* 2006, Koopmans *et al.* 2007, Lein *et al.* 2007, Ulrich *et al.* 2001, Zissimopoulos *et al.* 2009). There are studies which indicate that preoperatively elevated serum ICTP could be a prognostic factor in BC

(Keskikuru *et al.* 1999, Keskikuru *et al.* 2002). The clinical specificity for discriminating BC patients with bone metastases from those without has been shown to be reasonably good, but the sensitivity may not be sufficient for early identification of patients with subclinical bone recurrence in a clinical practice setting (Ulrich *et al.* 2001). However, according to a more recent study, ICTP could serve as a marker for early diagnosis of bone metastases in BC patients, although the sensitivity in this study was reasonably low (49 %) as well (Zissimopoulos *et al.* 2009). ICTP has also shown potential in monitoring treatment response in bone metastases from BC (Blomqvist *et al.* 1996). A retrospective study has indicated that follow-up measurement of serum ICTP could be useful in the early assessment of bone metastases in patients with PC: however, bone formation markers showed better distinction between patients with and without disease progression (Koopmans *et al.* 2007). ICTP may provide valuable information regarding the progression and skeletal complications of bone metastasis in men with metastatic PC undergoing bisphosphonate therapy (Lein *et al.* 2007, Lein *et al.* 2009).

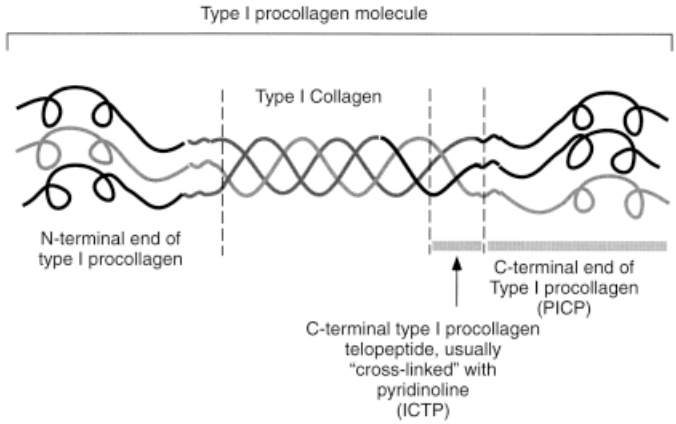

Figure 2. Type I procollagen molecule. Reprinted by permission from Macmillan Publishers Ltd: Kidney International 1999.

Cross-linked aminotelopeptide and carboxytelopeptide

Cross-linked aminotelopeptide (NTX) and carboxytelopeptide (CTX) are degradation products of type I collagen that can be measured in serum and urine. NTX and CTX are also present in tissues other than bone, and therefore non-skeletal processes may influence their levels (Herrmann & Seibel. 2008). In clinical practice, measurements of NTX and CTX are used in a range of metabolic and malignant bone diseases (Herrmann & Seibel. 2008). Many studies indicate that these peptide markers are potential tools for detecting skeletal lesions attributable to BC and PC (Cloos *et al.* 2004, Kanakis *et al.* 2004, Kiuchi *et al.* 2002, Koizumi *et al.* 2003, Leeming *et al.* 2006b, Tamada *et al.* 2001). Various isoforms of CTX have been shown to perform differently in detection of bone metastases. The αα-CTX isoform is a promising marker for the diagnosis of skeletal invasion in breast cancer patients (Leeming *et al.* 2006a). Serum and urinary levels of

both CTX and NTX respond to bisphosphonate therapy, and this response seems to be associated with clinical outcome (Coleman *et al.* 2005, Lein *et al.* 2007, Lipton *et al.* 2008). Due to the interindividual variability of NTX and CTX they cannot substitute traditional diagnostic tools such as bone scintigraphy. In addition, NTX and CTX levels are also elevated in postmenopausal women, thus limiting their utility in this patient group (Herrmann & Seibel. 2008, Reginster *et al.* 2001, Schneider & Barrett-Connor. 1997). The NTX and CTX levels are also elevated in different metabolic bone diseases such as osteoporosis (Reginster *et al.* 2001).

Receptor activator of the nuclear factor-kappaB ligand and osteoprotegerin

The molecular triad, which includes RANKL, its receptor RANK, and the endogenous soluble RANKL decoy receptor OPG, has emerged as an important determinant of bone metabolism (Pivonka *et al.* 2010). The serum levels of RANK, RANKL and OPG can be determined by means of enzyme-linked immunosorbent assay (ELISA). Despite some discrepancies in the literature, RANKL/OPG levels do not seem to offer universally applicable diagnostic tools for detection of bone metastases (Brown *et al.* 2001, Jung *et al.* 2003, Jung *et al.* 2004, Leeming *et al.* 2006b, Lipton *et al.* 2002). Mountzios et al. (2010) have recently evaluated the effect of treatment with the biphosphonate zoledronic acid on RANKL/OPG, and assessed the possible correlations of marker-level changes with skeletal morbidity and clinical outcomes in BC and PC patients. The RANKL/OPG ratio was upregulated in patients with BC, and it tended to decline after treatment with zoledronic acid, whereas PC patients presented with profound elevation of OPG only that persisted after treatment. The markers were not able to predict skeletal morbidity or clinical outcomes independently of well-established prognostic clinical parameters (Mountzios *et al.* 2010).

2.6.2. Bone-formation markers

Total alkaline phosphatase

Total alkaline phosphatase (tALP) is a bone-formation marker. Osteoblasts are naturally rich in alkaline phosphatase and the release of enzyme into circulation during bone formation gives some indication of osteoblast activity (Coleman. 1998). Due to its wide availability and to inexpensive detection methods, tALP is still widely used to screen for bone metastases in clinical practice even though the sensitivity is not very high. Clinical interpretation is complicated by the fact that increased levels of tALP may reflect either bone or liver disease. Once liver disease is ruled out, tALP provides a good impression of osteoblast activity. To improve specificity, monoclonal antibodies to the bone-specific isoform of alkaline phosphatase (BAP) have been developed. Due to its higher specificity, BAP has been increasingly preferred (Fohr *et al.* 2003). However, even BAP is not specific to pathological bone turnover, and is affected, e.g. by osteoporosis (Lumachi *et al.* 2009).

N-terminal and C-terminal peptides of type I procollagen

Type I collagen is the major structural organic component of bone tissue. It is synthesized as a large protein, type I procollagen. The extension domains at both ends of this procollagen are known as the amino- and carboxy-terminal propeptide domains of type I procollagen (PINP and PICP, respectively). Once the procollagen is secreted into the extracellular matrix prior to the formation of collagen fibrils, the extension domains are cleaved off and released into the circulation. In patients with BC, a decreased serum PICP:PINP ratio appears to signify a more aggressive phenotype with a higher propensity to bone metastases (Jukkola *et al.* 1997). However, due to the low sensitivity of these markers, they are not used in diagnosing bone metastases in clinical practice (Fontana & Delmas. 2000).

3. AIMS OF THE STUDY

The aims of this study were:

1. To evaluate the efficacy, toxicity and QoL effects of epirubicin-docetaxel combination in first-line chemotherapy of metastatic breast cancer in a phase II study (I, III, IV, VI).

2. To study the cost of management of adverse events of epirubicin-docetaxel treatment in metastatic breast cancer (II).

3. To evaluate the diagnostic potential of serum tartrate-resistant acid phosphatase 5b (TRACP 5b) in diagnosis of bone metastases in breast and prostate cancer (IV, V).

4. PATIENTS AND METHODS

4.1. Patients

Studies I, II, III and VI

Thirty-eight women with histologically confirmed MBC were enrolled in the phase II FADO (epirubicin-docetaxel) study from June 1998 to March 2000. The number of patients was statistically estimated as appropriate for a phase II study as shown in the statistical methods.

Eligibility criteria included the presence of progressive measurable or evaluable disease, age 18–75 years, ECOG performance status ≤2, white blood cell count >3000/mm^3, platelet count ≥130 000/mm^3, and liver function <3 times the normal value. Previous adjuvant and neoadjuvant chemotherapy, or hormone treatment as adjuvant or treatment of metastatic disease, was allowed as was prior radiotherapy. A history of angina pectoris, cardiac disease or hypertension was allowed if the patient was stable on medication and had a normal LVEF (>50% by echocardiography).

Exclusion criteria included brain or leptomeningeal involvement and active infection. Thirty-four of the 38 patients were included in the cardiac safety study. Four patients did not take part in the cardiac study due to logistical difficulties. Thirty-one of the patients were included in the QoL study. Only Finnish-speaking patients were included in the QoL study, three Swedish-speaking patients were excluded. In addition two patients failed to fill out the QoL questionnaire at baseline and one patient filled out the form one day after the first cycle, these patients were excluded from the QoL assessment. One patient was non-evaluable for response and was therefore excluded.

Study IV

Serum samples were collected from 187 BC patients who had histologically confirmed BC attending the follow-up in the Department of Oncology in Turku University Hospital in 1999-2005 in a larger breast cancer study assessing prognostic factors (ESRI/Salminen E.). The serum samples were stored at –70˚C. The clinical data were collected from the patients' files.

Study V

Serum samples were collected from 130 patients with a histologically confirmed diagnosis of PC attending the Department of Oncology in Turku University Hospital in the period January 2000 to January 2003 (Prostate 2000-study/Salminen E.). The serum samples were stored at –70˚C. The clinical data were collected from the patients' files.

Ethical aspects

The studies were approved by the joint ethical committee of Turku University Hospital and the University of Turku. Satakunta Central Hospital also gave approval for the FADO protocol and the study was conducted according to good clinical practice (GCP) and the ethical standards laid down in the Helsinki Declaration. The FADO study was approved by the National Agency for Medicine (Lääkelaitos). All patients in all three studies provided written informed consent

4.2. Methods

4.2.1. Chemotherapy protocol (I, II, III, VI)

The patients were treated with epirubicin (75 mg/m^2, 15-minute i.v. infusion) followed one hour later by docetaxel (75 mg/ m^2, one-hour infusion) every three weeks. Premedication of prednisolone (40 mg) was given orally the night before treatment and continued twice daily on days 1–3. A prophylactic anti-emetic was given according to routine practice (5HT-blocker prior to chemotherapy infusion). Midcycle counts were taken on day 10–11. The aim was to give eight cycles to responding/stable patients. The starting dose of 75 mg/m^2 for both epirubicin and docetaxel was reduced by 25 % if the patient was hospitalized due to febrile neutropenia, required antibiotics, or developed prolonged neutropenia. The dose was further tailored by reducing both drugs if necessary in order to avoid febrile neutropenia requiring hospitalization. No limitations were given concerning the use of granulocyte growth factors.

4.2.2. Follow-up, response and survival (I, II, III, VI)

Patient evaluation at baseline was based on physical examination, laboratory tests, bone scan, computed tomography/ultrasound of metastatic and/or suspected organs, chest radiograph, ECG, 24-h Holter monitoring, and detection of LVEF by echocardiography. Subsequent evaluation comprised physical examination and re-imaging of disease areas, ECG recording and echoradiography, and 24-h Holter at cycles 4 and 8. When clinically indicated, the investigations were repeated during follow-up.

Response was defined according to WHO criteria (Miller *et al.* 1981) after cycle 3 and at close of treatment. Complete response (CR) and partial response (PR) were re-evaluated after four weeks at the end of the treatment. Patients were reviewed every three months with radiological evaluation of disease status when symptoms occurred or at six-month intervals until relapse. CR was defined as loss of disease with no evidence of tumor as indicated by imaging or clinically. In patients with PR, the tumor load was reduced by more than 50 %. No change (NC) was defined as reduction in tumor size of less than 50 % or increase in tumor size of less than 25 %. In progressive disease (PD), the tumor size grew more than 25 % despite the treatment. The duration of response was calculated from the first demonstration of response to a documented disease progression. Clinical

benefit was calculated for responding and stable patients (CR, PR and NC) maintaining the same status for at least six months.

The survival was calculated from the initiation of epirubicin-docetaxel treatment till death by any cause or till 30.9.2001 and again till 15.1.2006. The study was monitored by Finn-Medi.

4.2.3. Cardiac monitoring (III)

Cardiac function was evaluated at baseline with physical examination, chest radiograph, ECG, assessment of LVEF by bidimensional echocardiography (standardized interpretation by excluding inter-investigator variability using methods of complete reproducibility: Acuson Sequoia® or Toshiba® Powervision equipment) and 24-hour ambulatory ECG monitoring. The 24-hour monitoring was started the day before the first cycle and continued throughout the treatment day. The 24-hour ambulatory ECG was recorded during normal activity with the patients' normal sleep–wake rhythm. The ambulatory ECGs were recorded either with a Marquette 8500 (General Electric Company, Marquette, USA) or Marquette SEER®MC solid-state recorder (General Electric Company, Marquette, USA). The duration of the recordings was 24–36 hours. The two-channel recordings were analysed with a MARS®8000 Arrhythmia Review Station (Marquette Electronics Inc, Milwaukee, Wisconsin, USA). Heart rate variability (HRV) was assessed in the frequency and time domain. Spectral analysis was used to quantify the periodic components of HRV. Spectral power of HRV was calculated with fast Fourier transformation algorithm. Power spectra were quantified in three frequency bands: very-low-frequency power (VLF) from 0.0033 to 0.04 Hz, low-frequency (LF) power from 0.04 to 0.15 Hz, and high-frequency power (HF) from 0.15 to 0.40 Hz. VLF variability is associated with sympathetic vasomotor regulation. LF variability relates to baroreflex activity and is modulated by both sympathetic and parasympathetic control. HF variability is vagally mediated. Mean R-R interval, standard deviation of R-R intervals and root mean square of successive differences in R-R intervals were calculated to assess HRV in the time domain. ECG, echocardiography and 24-hour ambulatory monitoring were reassessed at cycles 4 and 8. The endpoints were: (i) development of cardiac arrhythmia or impairment of HRV, (ii) decrease in LVEF, and (iii) development of CHF.

4.2.4. Quality of life evaluations (VI)

QoL was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire EORTC QLQ-C30 version +3 (Aaronson *et al.* 1993) and the QLQ-BR23 Breast module (Sprangers *et al.* 1996). The patients filled in the EORTC QLQ-C30 forms at baseline, just before the second and eighth cycle and three months after the last cycle. EORTC QLQ-C30 raw scores were calculated according to guidelines, yielding a range of 0─100. A high score on the functional or global QoL scale represents a better level of functioning and a high score on the symptom scale or item represents more symptoms. According to Osoba *et al.* (1998), a difference of 5 to 10

points on a 0 to 100 scale is considered a small clinically significant change, a difference of 10 to 20 points a moderate change, and changes greater than 20 points would be interpreted as large changes in QoL (Osoba *et al.* 1998).

4.2.5. Assessment of treatment costs (II)

The crude chemotherapy costs consisted of the costs of chemotherapy drugs, antiemetics, and corticosteroids. The health resources utilization analysis included the costs of all additional hospitalizations, drugs, blood transfusions, and the use of hematopoietic growth factors. The cost assessment was based on hospital prices. The time frame used was from the beginning of the treatment to three months after the last cycle. The analysis did not include additional laboratory tests or X-rays because the practice of using these varies, depending on the hospital policy and the experience of the doctor thus, not directly reflecting the toxicity of the treatment. Data on the use of medical resources were extracted from the hospital records. The costs were calculated in Euros at year 2000 values.

4.2.6. Detection of bone metastases (IV, V)

The presence of bone metastases was verified by reviewing skeletal scintigrams and X-rays. TRACP 5b activity was measured using an in-house immunoassay (Halleen *et al.* 2000). ICTP was measured by a commercially available competitive radioimmunoassay (Orion Diagnostica, Espoo, Finland). Total ALP was determined using a kit manufactured by Roche Diagnostics GmbH (Mannheim, Germany). The measurements were performed with Hitachi 917 equipment (Hitachi Ltd, Tokyo, Japan). PSA was determined using the TF-IRMA method (AutoDELFIA Wallac Finland Oy, Turku, Finland).

4.2.7. Statistical analysis

The number of patients was statistically estimated as appropriate for a phase II study. It was planned to enrol up to 40 evaluable patients. According to statistical estimations, up to 30 patients would ensure 65.7–94.3 % for 95 % confidence intervals. After 24 patients, an interim analysis was performed consisting of primary treatment responses and severe adverse (grade 3–4) effects. It was estimated that with a RR of 80 %, 24 patients would ensure 64.0–96.0 % for 95 % confidence intervals. The survival analysis was estimated using the Kaplan-Meier technique. (Study I)

Analysis of variance for repeated measurements was performed using the BMDP statistical package (2V) to study changes in the heart rate, number of extrasystoles, and HRV. Log transformations were performed for non-Gaussian data (Study III).

The Chi-square and Fisher exact tests were used in comparison of categorical patient characteristics. The *t*-test or Wilcoxon rank sum test was used to compare numerical variables. Logistic regression was used to analyze the association between BM with several bone markers. Standard deviation of the explanatory variable was used as the

unit to calculate odds ratios (OR). The main criteria for assessing model discriminative ability was the nonparametric estimate of the area under (AUC) the receiver-operating characteristics (ROC) curve (Hanley & McNeil. 1982), and the sensitivity and specificity. When comparing the areas under ROC curves, we used the methods described by Hanley and McNeil (Hanley & McNeil. 1983). Analysis of variance (2-way ANOVA) was used to study the effect of hormone treatment and skeletal metastases on the logarithmically transformed TRACP5b, tALP and PSA. Pearson correlation was calculated to test the linear relationship between the (ln) duration of hormone treatment and (ln) serum markers. Linear regression analysis was used to describe an observed significant relationship. Statistical computations were performed using the SAS System for windows version 8.2 and SPSS (Version 12.0, SPSS Ins., Chicago, IL, USA). (Studies IV and V)

The comparisons of QoL scores at different time points were carried out with analysis of variance for repeated measurements**.** The analyses were performed using the MIXED procedure (SAS system for Windows XP version 9.1.3 2003) which offers a sophisticated tool for analysis of follow-up data with possible missing data during follow-up (Littell R, Milliken GA, Stroup W, Wolfinger RD. SAS® system for Mixed Models. Cary, NC: SAS Institute, Inc, 1996). A *P*-value of less than 0.05 was considered statistically significant. (Study VI)

5. RESULTS

5.1. Patient and disease characteristics

The patient characteristics of study I are shown in Table 7. The median age was 51 years (range 35-72 years), with seven patients (18 %) aged over 60. The median ECOG performance status was 1 (range 0-2). Twenty-three patients (61 %) had received adjuvant chemotherapy with CMF and two with CEF, i.e. only two patient were pre-treated with anthracycline. One patient was treated with luteinising hormone releasing hormone analogue and another with letrozole for metastatic disease. Twenty-nine (76 %) patients had received postoperative radiotherapy to the chest wall, 18 (47 %) of whom to the left side. Six patients had arterial hypertension, one patient had coronary artery disease. Seventeen (45 %) patients had metastases in one organ only. Twenty-one (55 %) patients had bone metastasis.

In study IV, the mean age was 58 (range 31–87) in the group without bone metastasis and 61 (range 38–89) in the bone metastasis, group and the median time from primary diagnosis was 149 (range 20–10,045) days and 1967 (range 30–6542) days, respectively. Patient characteristics of studies IV and V are shown in Tables 8 and 9.

Table 7. Patient characteristics in study I.

	N	**%**
Number of patients	38	
Age, mean	51	
Range	35-72	
ECOG PS	1	
Range	0-2	
Prior treatment		
- CMF	23	61
- CEF	2	5
- Antiestrogen	6	16
Postoperative radiotherapy	29	76
Hypertension/cardiovascular disease	7	18
Number of organs involved		
1	17	45
2	12	32
≥ 3	9	24
Disease sites		
- Bone	21	55
- Liver	12	32
- Lungs	19	50
Receptors		
Er+/PgR+ or Er+/PgR- or Er-/PgR+	27	71
Er-/PgR	11	29

ECOG PS= Eastern Cooperative Oncology Group performance status

Table 8. Patient characteristics, comparison of breast cancer patients without (BM-) and with (BM+) bone metastases.

Characteristics	**BM- (N=141)**	**BM+ (N =46)**	***P*-value**
	N (%)	N (%)	
Post-menopausal	110 (78)	43 (93)	0.0088*
Previous therapy			
No previous therapy	65 (46)	3 (7)	<0.0001*
Chemotherapy	43 (30)	25 (54)	0.004*
Radiotherapy	53 (38)	29 (63)	0.003*
Endocrine treatment	31 (22)	28 (61)	<0.0001*
Present systemic therapy			
Chemotherapy	16 (11)	8 (17)	0.288*
Endocrine therapy (excluding aromatase inhibitor)	30 (21)	26 (57)	<0.0001*
Aromatase inhibitor	4 (3)	11 (24)	<0.0001**
Bisphosphonates	3 (2)	16 (35)	<0.0001**
No metastases	123 (87)	0 (0)	
Local progression only	5 (4)	0 (0)	
Visceral metastases	13 (9)	31 (67)	

Statistical methods: *Chi-square, **Fisher exact test

Table 9. Patient characteristics (study V), comparison of prostate cancer patients without (BM-) and with (BM+) bone metastases.

Characteristics	**BM-**	**BM+**	***P*-value**
Number of patients	105	25	
Mean age (range)	69.4 (48–80)	70.5 (57-88)	
Hormone treatment given (%)	43 (41 %)	21 (84 %)	*P*<0.001
Median Gleason (range)	5 (2–9)	7 (5–10)	*P*=0.001
Median PSA (μg/l) (range)	1.5 (0.1–270.0)	39.0 (1.7–3700)	*P*<0.001

5.2. Response, survival, and toxicity (I, II, III, VI)

All patients completed at least three cycles of treatment, 36 (95 %) completed at least six cycles and 33 (87 %) the maximum of eight cycles. The patients received altogether 287 cycles of chemotherapy. For all patients, the median cumulative dose of docetaxel was 462 mg/m^2 (range 199–600 mg/m^2), and that of epirubicin 476 mg/m^2 (range 199–740 mg/m^2). Thirty-seven patients were evaluable for efficacy. Objective responses (CR/PR) were observed in 20/37 patients, giving an overall response rate of 54 % (95 % CI 37–71) including five (13 %) complete responses. Twenty-six patients (68 %; 95 % CI 53–84) had clinical benefit, i.e. responding and stable patients (CR, PR and NC) maintaining the same status for at least six months. Four patients (11 %) had early progression.

After a minimum follow-up of 12 months, 32 patients (84 %) had relapsed, primarily 21 (55 %) at the original disease sites, seven (18 %) at new sites, and five (14 %) in the CNS. Median TTP was 12 months and after a minimum follow-up time of 12 months the median survival was 26 months**.** The survival of the patients in the QoL study was reassessed after a mean follow-up of 79.9 months. At that point (15.1.2006) four patients were still alive and the mean survival was 40.8 months.

Haematological toxicity is shown in Table 10. Neutropenia was the main hematological toxicity. Altogether 87 % of the patients had infections during the treatment. The major non-hematological grade 3/4 adverse effects included alopecia (97 %), neuromotor affects (10 %), nausea/vomiting (8 %), and fatigue (8 %) (Table 11).

Table 10. Patients experiencing major (grade 3/4) hematological toxicity and infections requiring antibiotics.

Toxicity	**Number (%)**
Neutropenia (< 0.5 x10^9/l)	30 (79)
Leukopenia (< 1.0 x10^9/l)	23 (61)
Thrombocytopenia (<100 x10^9/l)	4 (11)
Anemia (<100 g/l)	13 (34), 5 required blood transfusions
Patients requiring antibiotics	33 (87)
No. of infection cycles	73/287 (25)
No. of neutropenic infection cycles	36/287 (13)

Table 11. Patients experiencing major non-hematological toxicity.

Toxicity	**Grade 1/2 N (%)**	**Grade 3/4 N (%)**
Alocpecia	1 (3)	37 (97)
Fluid retention ≥ 3 kg	13 (34)	-
Weight loss ≥ 3 kg	7 (18)	-
Nausea/vomiting	35 (92)	3 (8)
Neurosensory	16 (42)	1 (3)
Neuromotor	19 (50)	4 (11)
Fatigue	17 (45)	3 (8)
Diarrhea	21 (55)	1 (3)
Mucositis/stomatitis	20 (53)	1 (3)
Skin/nail	13 (34)	-

5.3. Cardiac safety (III)

Clinically evident cardiac toxicity was not observed during the treatment or follow-up (mean 34 months, minimum above 25 months) in any patients. The median value for LVEF was 64 % before treatment, 66 % at the 4th cycle, and 68 % at the 8th cycle. Four patients developed an asymptomatic decrease in LVEF of > 10% (12 %, 95% CI 3.3–27 %). One patient experienced a fall below the normal level of 50 %, most likely due to

pulmonary embolism. This fall was reversible and the LVEF normalized during follow-up. All patients with a decrease in LVEF had predisposing factors to cardiac adverse effects such as chest radiotherapy, high age, previous anthracycline, or cyclophosphamide chemotherapy. Chest radiographs for all 34 patients showed no cardiac enlargement/pulmonary congestion during or after treatment until study close. There were no changes in HRV as measured either by spectral analysis or by time domain. The treatment did not increase the number of extrasystoles.

5.4. Quality of life (VI)

Thirty-one patients filled out the questionnaire at baseline before the first cycle, twenty-four just before the second, and twenty-five before the eighth cycle. Only seven patients filled in the questionnaire at three months after the last cycle. Statistically and clinically significant changes in the QoL study were as follows. After the first cycle, the emotional functioning improved a little (change of mean by 7.7 points) and the concerns about the future were modestly relieved (change of 17 points). The physical functioning decreased slightly after the first cycle (8 points). The cognitive functioning also decreased slightly (6.7 points). Body image declined modestly (16.1 points). Systemic therapy side effects, such as eye and mouth symptoms, headache and menopausal symptoms, increased significantly (22 points) especially at the beginning of the treatment, and similar changes could be seen throughout the treatment regimen. Distress related to hair loss increased significantly by 75 points. The global QoL remained unchanged.

5.5. Treatment costs (II)

The crude treatment cost of eight cycles of chemotherapy was € 12,416 per patient, including epirubicin, docetaxel, antiemetics, and corticosteroids. The vast majority of treatment-related adverse effects that led to additional health resource utilization consisted of febrile neutropenia, milder infections, neutropenia without fever, and stomatitis. During the treatment period, 235 hospital days were required for treating infections. Granulocyte colony-stimulating factor was prescribed for 27 patients (71 %) to prevent/curtail neutropenic infections. I.v. antibiotics were required after 34 cycles. Five patients required blood transfusions. Additional treatment costs added € 2,499 per patient. The majority of additional treatment costs consisted of hospitalization (60 %) and the use of granulocyte colony stimulating factor (32 %).

5.6. TRACP 5b and ICTP as markers of bone metastases in breast cancer (IV)

When serum concentrations of all studied markers (TRACP 5b, ICTP, tALP) were analyzed with univariate logistic regression analysis, all three markers exhibited a

statistically significant association with the presence of bone metastasis, even when patients treated with bishosphonates and/or aromatase inhibitors were excluded. Analysis of the odds ratios for risk of BM corresponding to an increase of one SD in serum marker concentrations is shown in Table 12. When comparing the AUCs of the serum markers, the differences were not statistically significant. In the multivariate regression analysis, all three markers remained statistically significant predictors of bone metastases when all patients were included. However, when patients with bisphosphonates and/or aromatase inhibitors were excluded, TRACP 5b did not remain a significant predictor for bone metastases. In the multivariate analysis with the three markers combined (TRACP 5b, ICTP and tALP) the detection power for BM was slightly improved. There was no statistically significant difference between the AUC of the combination of TRACP 5b and ICTP and that of tALP. The sensitivity and specificity were estimated by finding the lowest cut-off values for each marker, with a minimum sensitivity of 85 % as a cut-off and the best possible value for specificity. The results with all patients included are shown in Table 13.

Table 12. Association of TRACP 5b, ICTP and tALP with bone metastases in logistic regression analysis (Korpela *et al.* 2006).

		All patients			Without patients on bisphosphonates and/or aromatase inhibitors		
	Predictor	OR[1]	(95 % CI)	*P*-value	OR[2]	(95 % CI)	*P*-value
Univariate analysis	TRACP 5b	6.5	(3.6–13.6)	<0.001	3.6	(2.1–7.0)	<0.001
	tALP	16.7	(6.4–54.0)	<0.001	4.5	(2.5–9.2)	<0.001
	ICTP	8.1	(4.1–18.8)	<0.001	3.2	(2.1–5.4)	<0.001
Multivariate analysis	TRACP 5b	2.9	(1.4–6.6)	0.007	1.6	(0.8–3.6)	0.194
	tALP	5.3	(1.5–21.4)	0.012	2.6	(1.3–6.0)	0.013
	ICTP	2.9	(1.3–7.2)	0.012	1.8	(1.1–3.2)	0.026

1) Corresponds to increase of one SD (TRACP 5b SD=2.24, ALP SD=161, ICTP SD=4.54)
2) Corresponds to increase of one SD (TRACP 5b SD=1.71, tALP SD=77.5, ICTP SD=2.65)

Table 13. Sensitivity and specificity of TRACP5b, ICTP and tALP for bone metastases in BC.

Cut-off value	Sensitivity	Specificity
TRACP5b 3.65 U/l	87 %	69 %
ICTP 4.2 µg/l	87 %	53 %
tALP 145 U/l	87 %	50 %
TRACP 5b (3.65 U/l) and ICTP (4.2 µg/l)	78.3 %	82 %

5.7. TRACP 5b as marker of bone metastases in prostate cancer (V)

When comparing the AUCs of TRACP 5b, tALP and PSA, tALP showed superior accuracy (AUC=0.98) in comparison with TRACP 5b (AUC=0.84) and PSA (AUC

0.84) in the detection of skeletal metastases. Table 14 shows a comparison of the clinical sensitivity and specificity of TRACP 5b, tALP and PSA at cut-off points giving the best sensitivity and specificity combination.

Table 14. Sensitivity and specificity of TRACP 5b, tALP and PSA for prostate cancer.

Best cut -off value	N	Sensitivity (95 % CI)	Specificity (95 % CI)
TRACP 5b 4.89 U/l	130	76 % (55–91)	89 % (83–95)
tALP 224 U/l	104	96 % (78–100)	91 % (83–96)
PSA 23 µg/l	124	65 % (43–84)	81 % (74–89)

The effect of androgen deprivation on the markers was specifically assessed. There was a trend towards higher TRACP5b values with longer duration of androgen deprivation (r=0.246, P=0.050) and with tALP (r=0.253, P=0.076).

Six patients in the BM+ group had been treated with bisphosphonates. Their median TRACP 5b value was 8.4 U/l, which was slightly but not significantly elevated compared to the median value of 6.3 U/l in the 19 patients not treated with bisphosphonates (p=0.514). The other markers were likewise not significantly altered by bisphosphonates.

6. DISCUSSION

At the time this study was developed, combinations of anthracyclines and cyclophosphamide were commonly used as first-line chemotherapy, with or without 5-fluorouracil, in the treatment of MBC. Taxanes were introduced in the 1990s and showed significant activity in first- and second-line treatment of MBC and incomplete cross-resistance to anthracyclines. The combination of these two types of agents became a logical next step.

6.1. Efficacy and toxicity

The RR and TTP in our study are comparable to those of other epirubicin-docetaxel phase II studies, but the mean survival was high. However, the variation in phase II trials is large due to small sample size, heterogeneity of the study population and tumor characteristics. Additionally, second and following line treatments influence overall survival (Burzykowski *et al.* 2008). More resent phase III studies have confirmed the benefit of taxane-antrasycline combinations, with superiority of combination over sequential treatment in terms of RR and TTP, but without significant overall survival advantages (Cardoso *et al.* 2009).

In line with the previous studies, the toxicity of combination therapy in the present study was quite high, even though no treatment-related mortality was observed. Especially the incidence of neutropenic infections was high. Dose reductions were needed more often than initially expected, as colony-stimulating factors were not routinely used. The doses of epirubicin and docetaxel in our study were based on earlier phase II studies (Dieras. 1997, Salminen *et al.* 1999). In view of this frequent incidence of neutropenic infections, lowering the doses to 50 mg/m2 or the use of prophylactic colony-stimulating factors should be considered. A more recent study examined different doses of epirubicin-docetaxel combination in Japanese MBC patients (Ichinose *et al.* 2008). According to their study, a combination of 60 mg /m^2 of both drugs is recommended for patients without prior chemotherapy, and 50 mg/m^2 doses for chemotherapy-pretreated patients. However, as polychemotherapy gives only modest improvement of overall survival, if any, sequential treatment of single taxane and antrasycline is nowadays more widely used due to better toxicity profile, especially febrile neutropenia, the only exception being when rapid response is needed (Alba *et al.* 2004, Beslija *et al.* 2007, Cardoso *et al.* 2009, Carrick *et al.* 2009, Conte *et al.* 2004, Jones *et al.* 2006). Colony-stimulating factors are recommended with combination of taxanes and antrasyclines, if the risk of neutropenic infections is substantially increased.

6.2. Cardiac safety

Cardiovascular toxicity is one of the best known complications of cancer treatment and can arise already during or shortly after treatment, or even several years later. At the time

this study was performed, there were only a few studies combining anthracyclines and taxanes, and even fewer studies combining epirubicin with docetaxel.

Several methods have been developed to track early cardiac dysfunction. Commonly used methods are ECG, echocardiography, radionuclide angiography, MRI, and serial measurement of plasma biomarkers (Monsuez *et al.* 2010). Even today, all these methods have their limitations. There are no level one evidence-based methods for early detection of cancer treatment-induced cardiovascular toxicity, and despite the clear need, evidence-based guidelines to screen and follow-up treatment-induced cardiotoxicity are still missing (Altena *et al.* 2009, Carver *et al.* 2007, Jannazzo *et al.* 2008). Assessment of LVEF is commonly used to detect subtle impairment of contraction, which usually reflects ongoing cardiotoxicity that will presumably progress with subsequent administration. However, LVEF can underestimate actual cardiac damage because it is insensitive to early, subclinical cardiotoxicity and gives limited information on diastolic function. Diastolic dysfunction precedes a drop in systolic function in many patients (Lester *et al.* 2008). So far, little evidence is available to define a role for ECG in the assessment of potential cardiotoxicity. Several cohort studies suggest that prolongation of corrected QT interval could be an early marker of cardiotoxicity (Nakamae *et al.* 2000), but the prediction of late cardiac disease is not established. LVEF is a commonly used indicator for chemotherapy-induced cardiotoxicity in clinical practice. Based on the previous literature and common clinical practice, we chose to estimate LVEF, HRV, and 24-hour ambulatory ECG in the assessment of cardiac toxicity.

Epirubicin-docetaxel combination did not decrease LVEF during the treatment in the present study, which is in line with the literature. In the previous studies, docetaxel has not been associated with increased cardiotoxicity when combined with anthracyclines (Bird & Swain. 2008, Nabholtz *et al.* 2003b). When anthracyclines have been combined with paclitaxel, the risk of congestive heart failure or impairment in cardiac function has been correlated with the cumulative dose of the anthracycline rather than that of the taxane (Baldini *et al.* 2004, Giordano *et al.* 2002). Decrease in HVR has been reported after high dose antracycline chemotherapy (Tjeerdsma *et al.* 1999). This might be an early indicator of cardiotoxicity and the development of CHF. However, no decrease in any of the HRV parameters was detected in the present study. Although patients with unstable cardiac disease and patients with abnormal LVEF (<50% by echocardiography) were excluded from this study, our results are in line with the literature in that epirubicin-docetaxel treatment does not induce acute cardiotoxicity (Bird & Swain. 2008, Gamucci *et al.* 2007, Morales *et al.* 2004, Pagani *et al.* 2000, Seo *et al.* 2009, Sessa & Pagani. 2001, Viens *et al.* 2001). Today, as the combination of epirubicin and docetaxel is increasingly used in an adjuvant setting with or without trastuzumab and radiotherapy, the question of cardiotoxicity is becoming even more crucial. During the period when this study was performed, trastuzumab was not used in routine clinical practice. Trastuzumab binds to HER-2 and blocks epidermal growth factor receptor 2 (ErB2) signalling required for the growth, repair, development, and survival of cardiomyocytes (Negro *et al.* 2004). It has been shown that the risk for congestive heart failure is modestly increased with

trastuzumab treatment, and the risk cardiac toxicity is increased with the concurrent treatment with anthracyclines (Suter *et al.* 2007). With the increasing number of long-term survivors, timely recognition of cancer-treatment-related consequences is of major importance. Evidence-based methods for early detection of cancer treatment-induced cardiotoxicity are needed.

6.3. Quality of life

We assessed the QoL prior to the consequent cycle, not on the day of the infusion, because in this way it reflected the QoL between the cycles in the home environment. In the present study two-sided effects were seen on the QoL. During the treatment period, the patients experienced some positive effects on their QoL: anxiety about the future decreased and emotional functioning improved. However, the improvement in emotional functioning might merely reflect the fact that in a life-threatening situation something was being done irrespective of what it was, so it could simply be an indication of hope (Ramirez *et al.* 1998).

However, during the treatment, the QoL declined in terms of systemic chemotherapy side effects such as headache, eye and mouth symptoms, menopausal symptoms, and feeling unwell. In addition, the QoL declined in respect to physical functioning, body image, and being upset by hair loss. Hair loss is one of the most unpleasant side effects associated with chemotherapy treatments. It causes emotional disturbances and constantly reminds the patient of the disease.

Cognitive functioning also declined slightly. Subjective cognitive functioning and objective tests measuring cognitive functioning do not always correlate. Subjective cognitive decline often correlates with anxiety, depression or fatigue (Castellon *et al.* 2004, van Dam *et al.* 1998); true decline in cognitive functioning is possible as there is also evidence of cognitive changes associated with chemotherapy (Vardy *et al.* 2008). There are some worrying findings that treatment-related cognitive dysfunction is progressive as opposed to the clinical lore suggesting that treatment-related cognitive dysfunction should dissipate over time (Wefel *et al.* 2010). The negative changes in QoL in this study could be seen throughout the treatment. However, the negative effects did not adversely influence the global QoL. Previous studies assessing the QoL with other anthracycline and taxane combinations have also failed to show any significant change in the overall impact on QoL, which may reflect the difficulties encountered with the data collection and interpretation as discussed below (Ghersi *et al.* 2005).

Perhaps due to methodological difficulties, QoL studies are still rather often missing in clinical trials (Wilcken & Dear. 2008). Relatively few studies have reported the effect of taxanes on QoL among women treated for MBC (Bottomley *et al.* 2004, Cassier *et al.* 2008, Hakamies-Blomqvist *et al.* 2000, Hopwood *et al.* 2008, Jassem *et al.* 2001, Jones *et al.* 2005, Kramer *et al.* 2000b, Nabholtz *et al.* 1999, Nabholtz *et al.* 2003b, O'Shaughnessy *et al.* 2002, Svensson *et al.* 2010, Twelves *et al.* 2004, Yeo *et al.* 2002).

Most of these studies have compared treatments where either docetaxel or paclitaxel is included alone or in combination in one of the treatment groups. Despite the different toxicity profiles of the chemotherapeutic agents, only minor or no differences among the different treatment groups were found in terms of QoL (Bottomley *et al.* 2004, Hakamies-Blomqvist *et al.* 2000, Jassem *et al.* 2001, Kramer *et al.* 2000b, Nabholtz *et al.* 1999, Nabholtz *et al.* 2003b, Svensson *et al.* 2010). In addition, no significant differences have been found in terms of QoL when docetaxel and paclitaxel have been compared when used alone (Jones *et al.* 2005) or in combination (Cassier *et al.* 2008).

To our knowledge, prior to our study, only Yeo *et al*. (2002) have reported the effects of the epirubicin-docetaxel combination on QoL in MBC (Yeo *et al.* 2002). Instead of a validated QoL questionnaire they used a linear analog self-assessment covering three major aspects, namely, the emotional, the physical, and symptomatic functioning. Yeo *et al.* report of deterioration of QoL in all three aspects after the third cycle of chemotherapy, after which there appeared to be some improvement. However, the QoL did not return to baseline level with the exception that there was a trend towards improved emotional functioning at the end of the treatment**.** Our assessment was more comprehensive and detailed, using validated QoL questionnaires**.** Due to the differences in the methods it is somewhat difficult to compare the results. In terms of physical functioning, our results are quite similar, but we found no statistically significant changes in terms of pain, nausea, or appetite. However, the results concerning emotional functioning were different during the treatment; in both studies, there was a trend towards better emotional functioning at the end of the treatment.

The major limitation of our QoL study, in addition to the small sample size, is the number of missing questionnaires and wrong timing. The most common reason for missing data was administrative factors and the patients whose disease was in progression (four patients). In the literature, many other authors have shown that institutional and administrative factors tend to be more influential than patient factors at least until performance status deteriorates (Bottomley *et al.* 2004, Hopwood *et al.* 1994, Hopwood *et al.* 1998). The dropout of the patients with progressive disease is of major concern because it distorts the results. The number of dropouts overestimates the effect of therapy on QoL, as patients with progressive disease and poor performance tolerated treatments poorly**.** Missing data form one of the greatest methodological challenges in cancer QoL research (Gotay *et al.* 2005).

Optimal timing of the QoL assessments is crucial. The optimal timing depends on the research hypothesis, the natural course of the disease, the treatment regimen, and the anticipated effects of the therapy (Klee *et al.* 2000). Especially in the case of cyclic chemotherapy it is of major importance to carefully plan the optimal timing, since one has to differentiate between cancer-related symptoms, acute side effects, chronic side effects and symptoms not related to cancer (Gunnars *et al.* 2001, Klee *et al.* 2000). We collected our QoL data just before the chemotherapy cycles. We were interested in the longer term QoL during the treatment period, rather than in the effects of the peak toxicity

on QoL. Thus, the timing of questionnaires just before the following chemotherapy cycle may underestimate the highest acute treatment toxicity, which is most significant 1–2 days after the infusion.

The general interpretation of QoL data is more difficult than interpretation of objective endpoints such as survival time, objective response rates, or toxicity, as the concept of QoL is inherently multidimensional and subjective in nature. In addition, it is not possible to determine whether the advantages of palliative chemotherapy are worth their costs, unless we know about the patients´ personal values in regard to the relevance of the QoL changes. However, most QoL questionnaires do not take into account patients´ personal preferences. In most clinical trials, the data are analyzed to show whether there is a difference in the mean changes of scores from baseline between the arms of the trial. While small numerical differences in mean scores derived from QoL assessments may give statistically significant results when large samples of subjects are involved, the clinical interpretation of the meaning of these changes remains challenging. There are two approaches to defining clinical significance, anchor-based (comparing QoL scores to other criteria) and distribution-based (calculating an individual patient or group effect size) (Wyrwich & Wolinsky. 2000). Osoba et al. (1998) correlated the results from patients completing the EORTC QLQ C-30 on repeated occasions and rating their perception of change since the previous assessment (Osoba *et al.* 1998). When the functional scale scores changed by 5–10 points on a 0-100 scale, the patients described their change as ´a little´ better/worse. A change of 10–20 points correlated with a ´moderate´ change and a change greater than 20 points was ´very much´ better/worse. One strategy to interpret the results is to use one of the above-mentioned changes as a cut-off point to determine the number of patients whose scores have changed more than the cut-off point, hence the proportion of patients who improved after the intervention. This result may be more easily interpreted than mean change scores (Osoba *et al.* 2005, Osoba. 2007b). In any case, it is important to note that the differences in the interpretation of clinical significance in QoL depend on the perspective of the observer (e.g. patient, clinician, policy setter) (Frost *et al.* 2002). Clinical significance is a subjective endpoint and, by definition, QoL goes beyond standard clinical end points. Thus, there might be important QoL findings without direct correlation with a clinical parameter. Therefore, one has to carefully assess whether this result is a statistical or real phenomenon that should be reassessed in future trials (Movsas. 2003).

6.4. Treatment costs

In the present study, the additional treatment costs related to toxicity accounted for 20 %. Most additional treatment costs were due to treatment of adverse effects, especially neutropenic infections. Of these additional treatment costs, 60 % consisted of hospital-stay costs due to management of treatment toxicity. Lathia *et al.* (2010) have reported high treatment costs of febrile neutropenia, also mainly due to hospitalization (Lathia *et al.* 2010). It has been estimated that the total mean direct medical costs per febrile

neutropenia episode is Can$ 6,324 +/- 4,783 in 2007 (€ 4,688 +/- 3,545) (Lathia *et al.* 2010). At the time this study was done, a Canadian team suggested that therapies entailing less than € 12,000 per life year gained should immediately be added to the therapeutic arsenal; between € 12,000 and € 60,000 they can be recommended, while therapies at a cost higher than € 60,000 should not be adopted (Calhoun *et al.* 2001). Our schedule falls into the recommended therapy even with additional treatment costs, but indirect costs were not taken into account in the present study, as they are not included in Calhoun's recommendations either. We agree with Calhoun *et al*. (2001) that cost studies should optimally include both direct and indirect treatment costs of adverse events. In their study with gynecological cancers, the level of indirect costs was 34–86 % (Calhoun *et al.* 2001). We estimated an increase of 20 % in only direct costs over a six-month treatment. All but three patients were given long-term sick leave over the treatment period. Our patients were selected with specific inclusion/exclusion criteria. Therefore, in clinical practice with unselected patients, the treatment may cause even more adverse events and additional costs.

6.5. Bone markers

The current, widespread clinical practice to detect bone metastases in addition to symptoms is to measure serum tALP even though the specificity and sensitivity of bone markers in detection of bone metastases is still rather low. Although tALP is an indicator of osteoblast activity, it is widely used also in conditions such as BC, where increased osteoclast activity and osteolysis dominate. To improve specificity, monoclonal antibodies to the bone specific isoform of alkaline phosphatase (BAP) have been developed (Fohr *et al.* 2003). The paradox in using bone-formation markers such as tALP or BAP for the diagnosis or follow-up of osteolytic bone metastases is further stressed by the fact that increased bone resorption at the site of developing bone metastases is not, unlike in healthy bone, coupled to increased bone formation (Meijer *et al.* 1998). Therefore, in theory, markers of bone resorption might be more sensitive than tALP in the diagnosis of BC bone metastases.

TRACP 5b is specifically derived from osteoclasts, but its serum levels are affected by changes in both pathological and physiological bone turnover. Elevation of TRACP 5b during follow-up most probably indicates bone metastases, but it can also indicate physiological bone turnover due to postmenopausal osteoporosis (Halleen *et al.* 2001). ICTP is specific for pathological collagen degradation, but it is not bone-specific. Our hypothesis was that the combined elevation of TRACP 5b and ICTP should be a clear indication of bone metastases.

The findings in the present study indicate that the bone-resorption markers TRACP 5b and ICTP are equally sensitive and specific in skeletal metastatic BC as compared with tALP. The fact that the tested serum markers of bone resorption did not outperform tALP may be because some patients in this study had already been treated with bisphosphonates and/

or aromatase inhibitors, which influence bone-marker levels. Typically, when osteolytic lesions respond to treatment, the physiological coupling between bone resorption and formation is partly restored, and serum concentrations of bone formation mirror the events of bone resorption again (Meijer *et al.* 1998). The analyses were therefore also performed without these patients. Thus, the present study did not answer the question of bone markers´ sensitivity to detect bone markers, but rather the correlation of bone markers to existing skeletal metastasis.

The use of composite markers, consisting of two or more markers of a given biological phenomenon or disease, *e.g.* BC, may result in a better diagnostic performance than the use of any of the markers alone (Li *et al.* 2002). Of the various marker combinations tested in this study, the AUC value was higher for the combination of TRACP 5b and ICTP than for any of the markers alone, but the difference did not reach statistical significance. However, due to the small number of the patients, especially of those who were not treated with bisphosphonates and/or aromatase inhibitors, it is difficult to estimate the benefit of the combination.

Probably due to the osteoblastic nature of skeletal metastases in prostate cancer, tALP had greater sensitivity and specificity than TRACP 5b in PC patients. As PSA is derived from prostatic cells and reflect the tumor cell burden rather than skeletal metastases, its sensitivity and specificity were the lowest in detecting bone metastases. As in the treatment of BC, hormonal therapy in the treatment of PC can change bone metabolism with the result of increased bone resorption (Daniell *et al.* 2000, Shahinian *et al.* 2005). TRACP 5b levels apparently increased with increasing months of androgen-deprivation therapy, reflecting increased bone resorption and turnover due to castration. Thus, TRACP 5b should be further studied in terms of improving the clinical arsenal to follow the skeletal health of PC patients.

Although promising, the use of bone markers in a clinical setting is not routine at present. On their own, they have not been shown to be sensitive and specific enough for detection of bone metastases. One of their promising roles seems to be in monitoring response to treatment and disease progression (Blomqvist *et al.* 1996, Lipton *et al.* 2008). Interestingly, according to Wu *et al.* (2010) TRACP 5b activity and its interval change after treatment also had a prognostic role in the survival of BC patients (Wu *et al.* 2010). Further prospective studies are necessary to confirm these results. In addition, new horizons in the treatment of metastatic bone disease include personalized treatment by using bone markers to guide the frequency of bisphosphonate administration and bone-targeting agents such as denosumab (human monoclonal antibody to RANKL) (Neville-Webbe & Coleman. 2010, Roodman & Dougall. 2008, Saad & Lipton. 2010).

The main limitation of the bone-marker studies were the relatively small sample sizes and the fact that these were cross-sectional studies including a heterogenous group of patients, some of whom had received bisphosphonates for bone metastases.

7. SUMMARY AND CONCLUSIONS

Our phase II study shows that the combination of epirubicin and docetaxel is effective and reasonably safe first-line chemotherapy in MBC, even though it is quite toxic. Today, anthracycline- and/or taxane-based regimens are preferred in first- and second-line treatment of MBC, mostly sequentially. Combination therapy is, however, still used in symptomatic patients and/or in rapidly progressive situations (Beslija *et al.* 2007). Due to the high frequency of myelotoxicity and neutropenic infections, prophylactic colony stimulating factors are recommended. In addition, epirubicin and docetaxel are increasingly used in adjuvant and neoadjuvant settings. It is becoming increasingly common for patients to be pretreated with either an anthracycline or a taxane, or both, at the time of diagnosis of metastatic disease (Bedard *et al.* 2010, De Laurentiis *et al.* 2008, Joensuu *et al.* 2009). Extensive anthracycline use is restricted by the cumulative risk of cardiotoxicity, while broader use of taxanes is limited by cumulative neurotoxicity.

MBC is often responsive to therapy, though MBC remains still largely incurable. Advances in the treatment of BC over recent decades have been significant; a wide array of options exists in the metastatic treatment setting. In addition to efficacy, the toxicity of the treatment should be taken into consideration when choosing the treatment. Toxicity not only increases the treatment cost, but also impairs the QoL of the patients.

The studies with bone metastasis markers indicate that the detection and follow-up of bone metastasis is a complicated issue. Markers of bone metabolisms have increasingly been studied; however, currently the sensitivity and specificity are not high enough for clinical routine use.

The data from the present thesis lead to the following conclusions:

I The combination of epirubicin and docetaxel is effective first-line chemotherapy in metastatic breast cancer, especially for patients with good performance status, but requires individual dose adjustment to avoid neutropenic infections, and/or use of growth factors to maintain a feasible dose level in individual patients. The response is not significantly jeopardized by the individual dose modification.

II The treatment of metastatic breast cancer with the combination of epirubicin and docetaxel entails additional use of health resources due to neutropenic infections. Treatment of infections adds significant costs to the treatment.

III First-line chemotherapy in metastatic breast cancer with epirubicin and docetaxel does not cause acute clinical cardiac adverse effects during treatment.

IV The combination of TRACP 5b and ICTP shows potential in detecting bone metastases in metastatic breast cancer. Serum TRACP 5b and ICTP are at least equally sensitive and specific markers of bone metastases as tALP in breast cancer patients.

V TRACP5b is less specific and sensitive than tALP as a marker of skeletal changes in PC.

VI Despite the adverse effects of the combination of epirubicin and docetaxel, the global quality of life is not significantly compromised during the treatment. Variation occurs in some domains of QoL.

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