



PETTERI HERVONEN

Chemotherapy for Castration Resistant
Metastatic Prostate Cancer



ACADEMIC DISSERTATION

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ACADEMIC DISSERTATION

University of Tampere, School of Medicine
Tampere University Hospital, Department of Oncology
Finland

Supervised by

Professor Pirkko Kellokumpu-Lehtinen
University of Tampere
Finland

Reviewed by

Professor Inkeri Elomaa
University of Helsinki
Finland
Professor Kimmo Taari
University of Helsinki
Finland

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Abstract

Prostate cancer is the most common malignancy in males in Western Europe, with 4495 new cases and 882 deaths in Finland in 2011. The mean age at the time of diagnosis in Finland is 71 years.

The diagnosis of prostate cancer is based on histopathological examination of prostate tissue obtained by transrectal ultrasound-guided multiple core needle biopsies.

While the disease is often slow and indolent in nature, it may present in an aggressive form associated with rapid progression and younger age of onset.

Chemical or surgical castration has been the cornerstone of metastatic prostate cancer therapy for decades. However, the condition becomes resistant to hormonal therapy and is progressive despite castration levels of testosterone, being thus currently referred to as castration-resistant prostate cancer (CRPC). The term used in the literature previously was hormone-refractory prostate cancer (HRPC).

Most patients with metastatic CRPC present with osseous sclerotic metastasis. Visceral disease was previously considered uncommon and has been associated with neuroendocrine phenotypes and poor outcome.

Many chemotherapeutic agents have been studied in CRPC, with modest benefit.

The present purpose was therefore to investigate the efficacy and tolerability of chemotherapy in patients with CRPC. Specific aims were to evaluate the palliative efficacy and potential toxicity of ifosfamide chemotherapy (I), the pharmacokinetics of docetaxel combined with ifosfamide (II), the safety and efficacy of docetaxel-ifosfamide combination therapy (III) and the safety of biweekly dosing with docetaxel compared to the standard three-weekly regimen (IV).

The study population comprised of 229 patients with castration-resistant metastatic prostate cancer included in the prospective phase I-III trials.

In study I 30 patients were randomized to receive a total of six chemotherapy cycles of ifosfamide on two alternative infusion schedules. The treatment was well tolerated with no severe grade 3-4 toxicities observed in either of the treatment arms. Antitumor response was reported as PSA response in 30 % of the patients.

In Study II ifosfamide was combined with docetaxel in a sequential manner, the sequence of chemotherapy agents being reversed in the second cycle. All 10 patients involved received identical treatment. The purpose of this phase I study was to evaluate the antitumor activity, potential toxicity and pharmacokinetics of docetaxel combined with ifosfamide.

The clearance of docetaxel was not modified by co-administration of ifosfamide.

In study III a total of 31 patients received 40-60 mg/m² docetaxel followed by ifosfamide 3.0 g/m² with mesna for a maximal duration of six chemotherapy cycles. This was a non-randomized phase I dose escalation study which was continued as a phase II study. We conclude that there is no significant additional benefit in adding ifosfamide for patients who tolerate standard docetaxel chemotherapy.

In study IV patients were centrally randomized to receive 75 mg/m² docetaxel every three weeks or 50 mg/m² docetaxel every two weeks with an identical cumulative dose of docetaxel. The study reported the pre-planned safety analysis of the first 158 patients.

The treatment duration, the number of patients receiving the study drug for at least six months and the number of serious adverse events favoured the investigational biweekly treatment arm.

Throughout the study our aim was to develop a better tolerated and efficacious treatment for CRPC.

Tiivistelmä

Eturauhassyöpä on miesten yleisin pahanlaatuinen sairaus Suomessa, vuonna 2011 todettiin 4495 uutta tapausta. Sairastuneiden keski-ikä on 71 vuotta.

Diagnoosi perustuu eturauhaskoepalan histopatologiseen tutkimukseen. Sairaus on usein hidaskulkuinen ja oireeton, mutta taudinkulku on vaihteleva ja usein nuoremmilla potilailla esiintyy aggressiivisempaa tautimuotoa.

Kemiallinen ja kirurginen kastratio on pitkään ollut levinneen eturauhassyövän hoidon kulmakivi. Kastratio-resistentillä eturauhassyövällä (CRPC) tarkoitetaan ajan myötä hormonihoidolle reagoimattomaksi muuttunutta sairautta.

Useimmilla levinnyttä eturauhassyöpää sairastavista potilaista esiintyy luustoetäpesäkkeitä, sen sijaan sisäelin- ja viskeraalimetastasointi on harvinaisempaa ja liittyy huonompaan ennusteeseen.

Tutkimuksen tarkoitus oli tutkia solunsalpaajahoidon turvallisuutta ja tehoa CRPC:n hoidossa tavoitteena kehittää paremmin siedetty ja tehokkaampi hoitomuoto. Tarkempina tavoitteina oli arvioida ifosfamidi –hoidon palliativista tehoa ja potentiaalista toksisuutta (I), dosetakselin farmakokinetiikkaa yhdistettynä ifosfamidiin (II), dosetakseli-ifosfamidi –yhdistelmähoidon tehoa ja turvallisuutta (III) sekä dosetakseli –hoidon uuden annostelutavan turvallisuutta verrattuna standardi annostelutapaan.

Tutkimuksessa hoidettiin 229 levinnyttä kastratio-resistenttiä eturauhassyöpää sairastavaa potilasta osatöissä I-IV.

Tutkimuksessa I potilaat satunnaistettiin saamaan joko 24 tunnin ifosfamidi – infuusio tai 4 vrk:n ifosfamidi –infuusio kolmen viikon välein. 30 potilaan aineistossa molemmat tutkimushaarat osoittautuivat turvallisiksi ja hoitovaste saavutettiin 30 % potilaista.

Tutkimuksessa II ifosfamidi yhdistettiin dosetakselihoitoon lääkaineiden farmakokinetiikan ja yhdistelmähoidon potentiaalisen toksisuuden tutkimiseksi 10 potilaan hoidossa. Ifosfamidi ei vaikuttanut dosetakselin puhdistumaan.

Tutkimuksessa III dosetakselin ja ifosfamidin yhdistelmähoido annettiin 31 potilaalle annoseskalaatiotutkimuksessa, jota jatkettiin faasi II tutkimuksen muodossa yhdistelmähoidon tehon ja turvallisuuden arvioimiseksi. Ifosfamidin lisäämisen standardi dosetakselihoitoon ei todettu tuovan merkittävää lisähyötyä.

Tutkimuksessa IV potilaat satunnaistettiin saamaan joko 75 mg/m² dosetakselia kolme viikon välein tai 50 mg/m² dosetakselia kahden viikon välein identtisellä kumulatiivisella annoksella. 158 potilaan turvallisuus analyysi osoitti, että kahden viikon välein annosteltava dosetakselihoito oli paremmin siedetty.

Tutkimuksen tavoitteena on ollut turvallinen ja tehokas solunsalpaajahoito. Tutkimustulokset ovat vaikuttaneet hoitokäytäntöihin ja edesauttaneet yksilöllisemmän hoidonvalinnan kehittymistä levinnyttä kastroatio-resistenttiä eturauhassyöpää sairastavien potilaiden hoidossa.

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I. Hervonen P, Lehtinen T, Tammela TL, Kellokumpu-Lehtinen P. A randomised dose-finding phase II study on ifosfamide in metastatic hormone-refractory prostate cancer (HRPC). *J Exp Clin Cancer Res* 2002 Jun;21(2):177-80.

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Abbreviations

ADT Androgen deprivation therapy

ALK Alkaline phosphatase

CI Confidence interval

CRPC Castration-resistant prostate cancer

3-D CRT 3-Dimensional conformal radiotherapy

EBRT External beam radiation therapy

Gy Gray

HRPC Hormone-resistant prostate cancer

IMRT Intensity-modulated radiotherapy

KPS Karnofsky performance score

LD Lactate dehydrogenase

LHRH Luteinizing hormone-releasing hormone

MAB Maximal androgen blockade

PIN Prostatic intraepithelial neoplasia

PLND Pelvic lymph node dissection

PSA Prostate-specific antigen

RP Radical prostatectomy

SWOG South-western oncology group

1 Introduction

The prostate gland is located in the pelvic area of the abdomen between the urinary bladder and the rectum, is small in size and weighs only about 20 grams. The prostate is in part responsible for the production of the seminal fluid. In prostate cancer, mutation of the glandular cells, mediated by male hormones, leads to adenocarcinoma. (Griffiths 1889, Walker 1906, Waltz et al. 2007)

Prostatic intraepithelial neoplasia (PIN) is characterized by normal glandular structure with adenocarcinoma cells present. Invasive cancer may develop over time as the cancer cells multiply and invade surrounding tissues or metastasize via blood vessels or the lymphatic system. (Epstein and Herawi 2006, Schoenfield et al. 2007, Bonkhoff et al. 2013)

Multifocal high-grade PIN is shown to predict cancer more accurately than unifocal high-grade PIN in prostate biopsy material studies. The probability of detecting cancer cells is higher in the close vicinity of high-grade PIN, but a large number of cancers are also encountered in various other biopsy samples. (Clouston and Bolton 2012, Merrimen et al. 2013, Chornokur et al. 2013)

Prostate cancer is the most common malignancy in males in Western Europe and in Finland, with 4495 new cases in Finland in 2011. (Engholm et al. 2013, www.cancerregistry.fi) It is a common cause of death in males, with more than 882 deaths in 2011. The age-adjusted incidence of the disease in Finland is 85.6/100 000 and is rising due to population demographics and widespread prostate-specific antigen (PSA) testing. The mean age at time of diagnosis in Finland is 71 years. The percentage of patients alive 5 years after diagnosis is today 86.5% in Finland. (Engholm et al. 2013)

There are over 41 000 men alive in Finland with a prostate cancer diagnosis. (Engholm et al. 2013) The cause of the condition remains largely unknown despite of intensive basic research. Genetic alterations have recently been described, but it is probable that only 5-10 % of cases are hereditary. There are known risk factors such as age, race and hormonal factors, but there are also conflicting results on the effect of genetic factors and dietary factors such as dietary fats, dairy and calcium intake, multi-vitamin use and folic acid supplementation in the development of prostate cancer. On the other hand, lycopene and selenium might protect against prostate cancer. (Armstrong and Doll 1975, Rose and Connolly 1992, Whittemore et al. 1995, Bairati et al. 1998, Kristal et al. 2010, Gao et al. 2005, Lawson et al. 2007, Pienta 1997)

The risk of prostate cancer varies by race and the incidence is higher in the African-American (200/100000) population as compared to the Asian population in the United States (80/100000) and among other European ethnicities. (Ellis and Nyborg 1992, Ross et al. 1992, Roddam et al. 2008, Miller et al. 2013, Harras et al. 1996) In the year 2008, 910 000 new prostate cancer cases were recorded accounting for about 14% of all malignancies worldwide in that year. Over 70% of cases are detected in the more developed countries. Testosterone is converted into dihydrotestosterone which is the most active androgen in the prostate gland. The natural level of testosterone is reduced with age while the risk of prostate cancer increases with age. (Atan et al. 2013, Isaacs et al. 1992) The effect on prostate cancer of surgical or chemical castration can be considered the most powerful proof of the key role of testosterone in the prostate cancer development. The role of genetic variation in androgen biosynthesis and metabolism, including the potential role of the androgen receptor in the risk of prostate cancer, is currently under extensive investigation. (Wu and Gu 1991, Ross et al. 1998, Rajender et al. 2007, Carter et al. 1991) Prognostic factors could assist in evaluating the course of the disease at an early stage and thus optimize the use of curative and adjuvant

treatments in the future. (Ruijter et al.1999, Haas and Sakr 1997, Armstrong et al. 2007)

The diagnosis of prostate cancer is based on histopathological examination of prostate tissue obtained by transrectal ultrasound-guided multiple core needle biopsies. Pathological staging is based on the Gleason scoring system (Epstein et al. 2005) and grading of cancer morphology. The Whitmore-Jewett system, which stages prostate cancer as A, B, C or D, is no longer commonly used. (Catalona et al. 1989) Clinical staging includes measurement of plasma prostate specific antigen (PSA) and additional diagnostic examinations like alkaline phosphatase and bone scan. (Thompson et al. 2004, Barry 2001) Additional markers of biological aggressiveness including p53 mutations are under investigation in numerous studies. Several reports indicate that p53 overexpression is a predictive factor for poor prognosis and disease recurrence. (Thomas et al. 1993, Shurbaji et al. 1995, Bauer et al. 1995)

Prostate cancer growth is dependent on testosterone metabolism, and it was shown as far back as 1942 that androgen ablation therapy by orchiectomy is an effective treatment in controlling disease progression in the androgen-dependent stage of the disease. (Huggins 1942)

Prostate cancer growth and its development into a clinically significant disease is a long and often slow process and varies widely individually. It has been postulated based on tissue samples obtained from autopsies that prostate cancer cells are present in a very high proportion of males over the age of 70. (Sakr et al. 1996, Powell et al. 2010, Stamatiou et al. 2006)

While the disease is often slow and indolent in nature, it also may present in an aggressive form associated with rapid progression and younger age of onset. In this latter subgroup the cancer is characterized by a higher pathological grade and Gleason score and a lower rate and shorter duration of response to initial hormonal therapy. (Partin et al. 1997)

Prostate cancer which has become resistant to hormonal therapy and is progressive despite castration levels of testosterone is currently referred to as castration-resistant prostate cancer (CRPC). The earlier term used in the literature was hormone-refractory prostate cancer (HRPC).

Most patients with metastatic CRPC present with osseous metastasis. The reason for this proclivity to bone metastasis is unclear. Widespread disease typically presents with multiple osseous metastases and pathological compression fractures of the spine, causing pain and neurological complications and risk of paralysis. (Kemp 1999)

Visceral disease was previously considered uncommon and has been associated with neuroendocrine phenotypes and poor outcome. (Pouessel et al. 2007, Pond et al. 2014, Chi et al. 2013, Lorient et al. 2013, Kelly et al. 2012, Riisnaes et al. 2013) New data suggest that metastatic prostate cancer commonly involves the viscera, particularly in the advanced stages of disease. A high incidence of visceral disease has been observed in 49% of patients in computer tomography examination (CT) performed within 3 months of death. (Pezaro et al. 2013)

2 Review

2.1 Prognostic and predictive factors

The development of widespread prostate-specific antigen (PSA) testing during the last 20 years has resulted in the early diagnosis of prostate cancer in men with asymptomatic, clinically localized disease (5 NCCN guideline 2.2013). The extent of the disease, the pathological Gleason score and PSA level at diagnosis are

effectively utilized in the stratification of patients into different categories of risk. (Schmid et al. 2013, Armstrong et al. 2010). The initial treatment decision is also greatly influenced by estimated life expectancy, co-morbidities, toxicity of therapy, expected quality of life during treatment and also to a growing extent patient preference. (Orom et al. 2013)

While it is possible to estimate the life expectancy for different groups of patients, it is more difficult on an individual level. Life expectancy adjusted for individual patients can be estimated based on various nomograms combined with physician's estimate of patients' overall health.

Various nomograms are also utilized in the treatment decision-making process when selecting the most suitable treatment option from among active surveillance, radical prostatectomy, neurovascular bundle preservation, radical prostatectomy with or without pelvic lymph node dissection (PLND), brachytherapy or external beam radiation therapy (EBRT). (Table 1)

Some models are used to predict metastasis and some to predict cancer-specific death, these models being however, often less than totally accurate. Additionally, independent prognostic factors such as PSA doubling time as a measure of risk of death, molecular markers and radiological evaluations of the prostate are being studied for clinical use. (Heidenreich et al. 2014a) Optimal treatment requires validated risk group stratification and risk assessment combined with clinical staging. (Heidenreich et al. 2014b)

Table 1: Nomograms and accounted variables in different stages of prostate cancer

Author(s)	Stage of disease	Variables
Kattan MW et al. 1998	Pre-treatment, local	Clinical stage, Gleason, PSA
Smaletz O et al. 2002	Hormone-refractory	Age, Karnofsky status (KPS), Albumin, Hemoglobin, PSA, Lactate dehydrogenase (LDH), Alkaline phosphatase (AP)
Stephenson AJ et al. 2005	Salvage radiation	PSA post prostatectomy, Gleason score, seminal vesicle invasion, radical prostatectomy, extra-capsular invasion, PSA doubling time, neo-adjuvant therapy

Pre-treatment nomograms are utilized in the treatment decision-making process. A 10-year nomogram was developed to provide prognostic information related to the long-term treatment effect of modern conformal external beam radiotherapy. (Kattan et al. 1998)

Many of the nomograms used to date take into account traditional prognostic variables associated with disease extent and risk of disease dissemination. It is expected that the predictive accuracy of a nomogram could be significantly enhanced with the availability of more reliable molecular markers and functional imaging information which could hopefully better discriminate between patients who have micrometastatic disease at their diagnosis from those with localized disease only (Kattan et al. 1998). Ultimately, nomograms will have the greatest utility for decision-making strategies for patients when they begin to incorporate functional outcome endpoints other than tumor control. Several reports have indicated that functional outcomes (e.g., urinary continence, erectile and bladder and bowel function) all play a significant role in how patients decide on particular treatment interventions. (Kattan et al. 1998)

2.2 Treatment of early prostate cancer

2.2.1 Active surveillance

Prognostic information as to the effect of different treatment modalities on the possibility of a curative result in prostate cancer is based on three basic elements: 1) extent of disease as characterized by the TNM classification, 2) pathological numerical grading of cancer cells via the Gleason grade or score and 3) PSA levels measured in plasma samples. Prostate cancer patients can be divided into three risk groups: low, intermediate and high risk, based on these three parameters.

Nomograms are utilized to assess the risk of biochemical relapse or PSA recurrence, metastasis and even death from prostate cancer.

Active surveillance or watchful waiting is considered for low-risk cancer patients with a short life expectancy. The strategy of monitoring the course of the disease with the expectation of intervening if the cancer progresses includes advantages such as avoiding side-effects of unnecessary treatments and retaining the quality of life. There is also the potential risk of missing the opportunity of cure as the cancer progresses or metastasizes during surveillance. (Klotz 2013) The decision on active surveillance should be based on clinical research and individual patient and disease characteristics and patient preference, with predetermined trigger points for intervention based on eventual PSA, histological or clinical progression.

In the Scandinavian Prostate Cancer Group prospective trial (SPCG-4) radical prostatectomy compared with watchful waiting was reported to reduce the rate of death from prostate cancer. Estimated 15-year results on 695 men with early prostate cancer randomly assigned to watchful waiting or radical prostatectomy showed that radical prostatectomy was associated with a reduction in the rate of death from prostate cancer. Men with extracapsular tumor growth were shown to benefit from adjuvant local or systemic treatment. (Bill-Axelsson et al. 2011 and 2014) However, there is only one prospective randomized trial in the PSA era comparing surgery with observation. (Wilt et al. 2012) Although 731 patients were included, there was no difference in prostate cancer-specific mortality between the surgery and observation groups after a median follow-up of 10 years. (Wilt et al. 2012)

2.2.2. Prostatectomy

Prostatectomy is currently considered one of the standard treatment options for men with localized organ-confined prostate cancer with no regional lymph node

involvement. Radical prostatectomy (RP) is performed as open surgery or laparoscopically with or without robotic assistance. The alternative treatment options for localized disease are intensity-modulated external radiotherapy or brachytherapy. There are very limited data available comparing the efficacy and long-term safety of these treatment modalities and the decision should always be based on careful assessment of individual patient characteristics, co-morbidities, tumor risk factors and patient preference. (Merino et al. 2013, Chung 2013)

Patients with locally advanced disease presenting with multiple regional lymph node metastases carry an increased risk of death from the disease, whereas those with single lymph node involvement could still be considered candidates for RP and adjuvant hormonal treatment and have a more favorable prognosis and better local disease control. (Cheng et al. 2013) A postoperative nomogram for prostate cancer recurrence after radical prostatectomy (RP) has been independently validated as accurate and discriminating. (Stephenson et al. 2005)

The risk of the recurrence of prostate cancer after definite therapy with curative intent is largely dependent on three variables: Pre-treatment PSA and pre-treatment PSA velocity, Gleason score and positive or negative surgical margin after RP. (Table 2)

Table 2: Risk of recurrence according to PSA level, Gleason score and surgical margins after radical prostatectomy

Risk of recurrence (%) at 5 years for pT2 prostate cancer at different PSA levels before surgery, Gleason scores and a positive surgical margin in the radical prostatectomy specimen.

	PSA 5 ng/ml	PSA 10 ng/ml	PSA 20 ng/ml
Gleason 7	26	36	43
Gleason 8-10	42	55	63

Risk of recurrence (%) at 5 years for pT3 prostate cancer at different PSA-levels before surgery, Gleason scores and negative or positive surgical margin in the radical prostatectomy specimen.

	PSA 5 ng/ml	PSA 10 ng/ml	PSA 20 ng/ml
Gleason score 7 + neg margin	21	30	35
Gleason score 7 + positive margin	54	67	75
Gleason 8-10 + negative margin	34	46	54
Gleason score 8-10 + positive margin	74	86	91

A PSA velocity greater than 2.0 µg/l per year is associated with a 10-fold increase in prostate cancer-specific mortality despite surgery. (Anscher 2005)

2.2.3 Radiation therapy

Modern external beam radiation therapy (EBRT) offers a similar progression-free survival result compared to radical prostatectomy in low-risk patients with clinically localized prostate cancer. (Kupelian 2004, Potosky 2004, D'Amico 1998, Chou et al. 2011) Localized prostate cancer is categorized into low-risk, intermediate-risk and high-risk groups according to extent of disease, Gleason score, PSA level and percentage of tumor in biopsy material (Table 3).

Table 3: Risk categorization of local prostate cancer

Low-risk
T1a-T2a, Gleason score max 6 and PSA <10 µg/l, PSA doubling time >3 years and <20 % of tumor in biopsy material
Intermediate risk
T2b or Gleason score 7 (3+4) or PSA 10-20 µg/l or PSA doubling time 1-3 years or 20-40 % of tumor in biopsy material
High Risk
T2c or Gleason score 7 (4+3) or >7 or PSA >20 µg/l or PSA velocity >2 µg/l/year or PSA doubling time < 1 year or >40 % of tumor in biopsy material

Improved 3-dimensional conformal radiation (3-D-CRT) techniques integrate computer tomography images in the treatment position shaping the high radiation volume precisely to allow higher cumulative doses delivered with lower risk of late effects. Intensity-modulated (IMRT) and image-guided radiation therapy (IGRT) is the preferred technique with a reduced risk of gastrointestinal toxicities compared with 3-D-CRT. (Thompson et al. 2013, Sheets et al. 2012)

Randomized trials with novel techniques have reported improved biochemical outcomes associated with dose escalation without increased toxicity. (Heemsbergen et al. 2013, Zaorsky et al. 2013) The radiation dose in these studies has risen from the conventional 70 Gy up to 81 Gy for intermediate- to high-risk patients and to 75.6-79.2 for low-risk cancers. (Michalski et al. 2013, Pollack et al. 2013)

In addition to high-quality radiation techniques it is vital to identify patients who will benefit from inclusion of pelvic lymph node irradiation and neoadjuvant/concomitant/adjuvant androgen deprivation therapy (ADT) according to risk stratification into low-, intermediate- and high-risk groups.

Compared to surgical therapy there are several advantages in radiation therapy, for example avoidance of bleeding and transfusion-related effects and the risk associated with anesthesia. (Wilt et al. 2008) Combined with ADT, radiation increases overall survival in locally advanced prostate cancer with margins of the prostate included in the treatment volume. ADT increases the risk of erectile dysfunction. (Ahmadi and Daneshmand 2013, Widmark et al. 2009)

The long treatment duration of 8 to 9 weeks with daily irradiation fractions can be considered a clear disadvantage in EBRT. Temporary symptoms of bladder or bowel dysfunction during and after treatment are common in up to 50% of patients. Radiation proctitis is rare and the risk of erectile dysfunction increases over time.

A meta-analysis of 35 radiation treatment studies involving 11 835 patients reported late-occurring urinary tract side-effects as follows: grade II 17 % and

grade III or over 3 %. Late-occurring rectal side-effects were observed as follows: grade II 15 % and grade III or over 2 %. Toxicity was evaluated according to RTOG/EORTC Late Radiation Morbidity Scoring Criteria. (Ohri et al. 2012) Proton therapy utilizes proton beams as an alternative radiation source. Proton therapy can theoretically be used to treat deeply located tumors with less damage to surrounding tissues, but is not recommended for routine use due to lack of evidence. (Zaorsky et al. 2013)

2.2.4. Hormonal treatment

For locally advanced disease, adjuvant hormonal treatment for up to 2-3 years should be considered to improve disease-specific and overall survival (Kubes et al. 2013). Hormone therapy combined with either prostatectomy or radiotherapy is associated with significant clinical benefits in patients with local or locally advanced prostate cancer. Significant local control may be achieved when hormonal therapy is given prior to prostatectomy or radiotherapy. When given adjuvant to these primary therapies, hormone therapy not only provides a method for local control but there is also evidence for a significant survival advantage.(Kumar et al. 2006) However, hormone therapy is associated with significant side-effects such as hot flushes and gynecomastia, as well as cost implications.

Surgical or chemical castration has been the cornerstone of metastatic prostate cancer therapy for decades. The most commonly used agents include luteinizing hormone-releasing hormone (LH-RH) the agonists triptorelin, leuprorelin, buserelin and goserelin, and antagonists such as degarelix acetate which inhibit the function of the pituitary gland and the gonads and the secretion of gonadotropins and sex steroids. (Heidenreich et al. 2014b) Dutasteride, which is used for treatment of benign prostate hyperplasia has been shown to reduce the risk of incident prostate cancer. (Andriole et al. 2010)

Anti-androgens, or androgen antagonists, are used in combination with LH-RH agonists to prevent androgen-expressed effects on prostate cancer by altering the androgen pathway by blocking the androgen receptors. Anti-androgens such as bicalutamide and other drugs such as cyproterone acetate competitively bind to the androgen-receptor sites on the cancer cell surface, and also affect androgen production. (Alva and Hussain 2014)

The combination of LH-RH agonists and anti-androgens is referred to as maximal androgen blockade (MAB) treatment. The most common side-effects of hormonal therapy include fatigue, hot flushes, feminization, impotence and anemia. LHRH-agonist treatment is usually maintained through different stages of the disease continuum and combined with chemotherapy, thus increasing the risk of long-term side-effects such as anemia and osteoporosis. (Sountoulides and Rountos 2013)

The majority of patients (up to 85% to 90%) with locally advanced or metastatic prostate cancer respond initially to maximal hormonal blockade treatment, but over time most develop castration-resistant disease with progression in spite of castrating levels of testosterone. The duration of hormonal treatment varies greatly, but the median time to disease progression into CRPC is 2 to 3 years.

2.3 Chemotherapy of prostate cancer

2.3.1 Chemotherapy in high-risk or locally advanced prostate cancer

For high-risk patients with local disease undergoing surgery, local control of the disease is a key target of therapy. Combined neoadjuvant chemotherapy and hormonal therapy before prostatectomy has been tested in several studies. (McKay et al. 2013) Androgen blockade in combination with ketoconazole and doxorubicin alternating with estramustine and vinblastine proved a feasible treatment according to one trial, although the primary goal of 20% of pT0 stage was not reached. Other studies using neoadjuvant estramustine and etoposide have also been conducted. In the SWOG 9921 trial the patients underwent radical prostatectomy and combined androgen blockade or prostatectomy and combined androgen blockade plus mitoxantrone and prednisone. The study was closed to further accrual after 983 patients due to three cases of acute leukemia. (Flaig et al. 2008) More studies are warranted and there is at present no standard neoadjuvant chemotherapy.

Radiotherapy in combination with AD therapy is considered a standard treatment for elderly patients with localized intermediate- or high-risk prostate cancer. For even more optimal results, several randomized trials of adjuvant docetaxel treatment have been conducted or are currently open for recruitment. (Kellokumpu-Lehtinen et al. 2013a) While the benefits of neoadjuvant and adjuvant hormonal treatment in locally advanced PC have been demonstrated, the efficacy of adjuvant docetaxel remains to be explored. A pre-planned safety analysis of 100 patients in the SPCG-13 randomized trial evaluating the efficacy of six cycles of docetaxel as adjuvant treatment for intermediate- or high-risk prostate cancer after radical radiotherapy showed higher frequency of neutropenia than on previous studies in patients with metastatic disease. (Kellokumpu-Lehtinen et al.

2013a) However, the toxicity was manageable and there were no docetaxel-related deaths in the whole trial.

According to Eastham and colleagues, estramustine has a limited effect as a single agent in hormone refractory prostate cancer but may act synergistically with some cytotoxic agents, docetaxel being apparently the most promising. (Eastham et al. 2003) In the SWOG 90203 trial, patients with high-risk localized disease were treated either with radical prostatectomy alone or with estramustine and docetaxel before radical prostatectomy. (Eastham et al. 2003)

Phase I-II trials with docetaxel and estramustine have been conducted, with evidence of synergistic activity. (Petrylak et al. 1999 and 2004)

In a neoadjuvant phase II trial, six cycles of weekly docetaxel 40 mg/m² were given to 29 patients with locally advanced prostate cancer, followed by radical prostatectomy. The reduction in PSA levels after chemotherapy was statistically significant (12.00 ± 1.86 ng/ml versus 8.42 ± 1.63 µg/l, $P < 0.03$), 79% of patients showing a reduction in PSA level compared to 24% who had at least a 50% increase. (Dreicer et al. 2004)

There are several ongoing randomized trials comparing docetaxel adjuvant treatment to surveillance after radical prostatectomy or radical radiotherapy. (Kellokumpu-Lehtinen et al. 2013b, clinicaltrials.gov) The short-term results of these clinical trials are expected within 5 years.

2.3.2 Chemotherapy in advanced prostate cancer

Many chemotherapeutic agents have been studied in CRPC with modest benefit. In one small Finnish study, estramustine phosphate was as effective as low-dose adriamycin in the treatment of advanced CRPC. (Elomaa et al. 1991)

Mitoxantrone, an anthracenedione anti-neoplastic agent, has shown a palliative effect when compared to prednisone in two randomized studies and was approved

for symptomatic metastatic CRPC in 1996. No effect on the overall survival of patients has been demonstrated. A combination of mitoxantrone and prednisone can be considered an option for patients with symptomatic disease for whom docetaxel therapy is not suitable (Table 4).

Table 4. Randomized chemotherapy trials in CRPC

Author	Regimen	pts	PSA response(%)	OS (mo)
Tannock et al. 1996 (M = Mitoxantrone, P = Prednisone)	M+P vs P	161	33 vs 22	NR
Hudes et al. 1999 (V = Vinblastine, E = Estramustine)	V + E vs V	193	25 vs 3	11,9 vs 9,2
Kantoff et al. 1999	M + H vs M	242	19 vs 14	13,3 vs 12,6
Berry et al. 2001 (Pa = Paclitaxel)	Pa + E vs Pa	166	48 vs 25	NR
Oudard et al. 2002 (D = Docetaxel)	D (*) + E vs M	130	77 vs 65 vs 21	18,6 vs 18 vs 11
Abratt et al. 2003 (A = aminoglutetimide, H = Hydrocortisone)	V + A + H vs A + H	414	30 vs 19	14,7 vs 15,2
Eisenberger et al. 2004	D (*) + P vs M + P	1006	45 vs 45 vs 32	18,9 vs 17,3 vs 16,4
Petrylak et al. 2004	D + E vs M + P	666	50 vs 27 18 vs 16	

(*Docetaxel given in two dosing schedules)

Carboplatin is a platinum-based anti-neoplastic agent used mainly in the treatment of lung and head-and-neck cancers and seminoma. It has been evaluated for use in CRCP and has shown some efficacy as a palliative salvage treatment option for late

stage CRCP. (Kentepozidis et al. 2012) In addition, satraplatin has shown only modest antitumor activity in CRPC. (Figg et al. 2013, Vaishampayan et al. 2014)

2.3.3 Docetaxel chemotherapy

The TAX 327 study was a phase III, non-blinded, multinational, multicenter randomized study in which 1006 patients with progressive metastatic CRPC were randomized to receive docetaxel 75 mg/m² every 3 weeks or docetaxel 30 mg/m² weekly or mitoxantrone 12 mg/m² every three weeks (Tannock et al 2004). In addition, all patients received prednisone 5 mg twice daily. The primary endpoint of the study was overall survival (OS), secondary endpoints being pain, PSA levels and quality of life. The hazard ratio for death was in the three-weekly docetaxel group compared to the mitoxantrone group 0.76 (p=0.009) and in the weekly docetaxel group 0.91 (p=0.39). The median survival was 16.5 months in the mitoxantrone group, 18.9 months in the every-three-weeks docetaxel group (p=0.009) and 17.4 months in the weekly docetaxel group (p=0.36).

Among these three groups, 32%, 45% and 48% had an at least 50% decrease in serum PSA level (p<0.001). 22%, 35% and 31% had predefined reductions in pain and 13%, 22% (p<0.009) and 23% (p<0.005) improvements in the quality of life. Adverse events such as grade III/IV neutropenia, fatigue, nail changes, sensory neuropathy and infection were more frequent in the docetaxel group, while the incidence of cardiac events was higher in the mitoxantrone group.

In the SWOG9916 trial 770 patients with advanced CRPC were randomized to receive 280 mg of estramustine three times daily on days 1-5 and 60 mg/m² of docetaxel on day 2 given every three weeks, or 12 mg/m² of mitoxantrone on day 1 and 5 mg of prednisone twice daily given every three weeks. The overall survival was 17.5 months in the docetaxel group compared to 15.6 months in the mitoxantrone group (p=0.02). The corresponding hazard ratio for death was 0.80. PSA declines of at least 50% occurred in 50% and 27% of patients (p<0.001).

Grade III/IV neutropenic fevers ($p=0.01$), nausea and vomiting ($p<0.001$) and cardiovascular events ($p=0.001$) were more common in the docetaxel than in the mitoxantrone group. Pain relief was similar in both groups.

Docetaxel is the standard chemotherapeutic agent for the first-line chemotherapy of metastatic CRPC combined with prednisone based on a registration study TAX327. (Tannock et al. 2004)

Docetaxel has been shown to alleviate symptoms and in the TAX 327 study demonstrated an overall survival benefit of 2.3 months compared to mitoxantrone.

2.3.4 Cabazitaxel chemotherapy

In recent years docetaxel has been utilized in an earlier stage of the disease in the treatment of patients with only minimal or even no symptoms, resulting in an improvement in performance status in cases considered for subsequent therapies such as cabazitaxel and abiraterone.

The most commonly used chemotherapeutic agents docetaxel, cabazitaxel and mitoxantrone have individual safety profiles and different dose-limiting toxicities, as presented in Table 5. Two registration studies conducted had a similar mitoxantrone comparator arm and the results for mitoxantrone in both are quite similar.

Table 5: Safety of docetaxel, cabazitaxel and mitoxantrone in the TAX 327 and Tropic studies

Adverse Event	Docetaxel (Tannock et al. 2004)	Cabazitaxel (de Bono et al 2010) per cent	Mitoxantrone (Tannock et al 2004)
Gr 3 or 4 neutropenia	32	82	22/1
Febrile neutropenia	3	8	2/1.3
Fatigue	53	37	35/28
Grade 3 or 4	5	5	5/3
Diarrea		47	11
Nausea, vomiting	42	57	38/33
Sensory neuropathy	30		

Cabazitaxel is a tubulin-binding taxane with demonstrated preclinical activity in taxane-resistant tumor models. A randomized phase III trial involving 755 patients with disease progression during or after prior docetaxel treatment compared cabazitaxel 25mg/m² with mitoxantrone 12 mg/m², both in combination with prednisone and administered every three weeks in a second-line treatment setting. The primary endpoint was overall survival and secondary endpoints progression-free survival, PSA response, objective tumor response, pain response and time to tumor progression. Patients were stratified according to performance status and those who had previously had mitoxantrone therapy or substantial radiotherapy to bone were excluded. (de Bono et al. 2010)

Patients receiving cabazitaxel had a longer overall survival of 15.1 months compared to 12.7 months in the mitoxantrone treatment arm.

There was notable hematologic toxicity associated with cabazitaxel treatment, 82% of patients presenting with grade 3 or 4 neutropenia, 8% febrile neutropenia and 5% resulting in death. Prophylactic neutrophil growth factor support is recommended for older patients and patients with bone marrow function impaired due to prior radiotherapy. Cabazitaxel should be considered a clinical treatment option for patients with good performance status who have received prior docetaxel when alternative treatment options such as abiraterone are not available.

2.4 Novel therapies

Randomized studies of first-line chemotherapy for metastatic CRPC with overall survival as primary endpoint have yielded comparable figures with 3-6 months survival benefit compared to mitoxantrone or placebo. Studies with new-androgen signaling targeted therapies such as abiraterone and immunotherapy with sipuleucel-T are included in Table 6. There are a number of notable differences in baseline patient characteristics in the studies, thus preventing direct comparison of different results and therapies.

Table 6: Summary of overall survival in the phase III studies in CRPC

Authors	Regimen	n of patients	OS mo
Chemotherapy-naïve, first-line treatment			
Tannock et al. 2004	D + P vs M + P	772	18.9 vs 16.5
Ryan et al. 2013 (Abi = Abiraterone, PI = Placebo)	Abi + P vs PI	1088	35.3 vs 30.1
Kantoff et al. 2010 (S-T = Sipuleucel-T)	S-T vs PI	512	25.8 vs 21.7
Post-docetaxel, second-line treatment			
De Bono et al. (C = Cabazitaxel)	C + P vs M+P	755	15.1 vs 12.7
Fizazi et al. 2013	Abi + P vs PI +P	1195	15.8 vs 11.2
Scher et al. 2012	Enzalutamide vs PI	1199	18.4 vs 13.6
Parker et al. 2013	Radium-233 vs PI	921	14.9 vs 11.3

2.4.1 Sipuleucel-T therapy

Sipuleucel-T is an autologous immunotherapy approved by the U.S. Food and Drug Administration for the treatment of asymptomatic or minimally symptomatic metastatic CRPC. (Kantoff et al. 2010) The approach employs ex vivo immune-cell activated antigen-presenting cells collected from peripheral blood. Immune response is mediated by fusion of prostatic acid phosphatase and granulocyte-macrophage colony-stimulating factor. Three randomized controlled studies have been published comparing sipuleucel-T to placebo for CRPC. Median overall survival has ranged from 19.0 mo to 25.9 mo for the sipuleucel-T treatment arms in the three studies involving 65-341 patients compared to an overall survival of 15.7mo to 21.7 mo for the placebo arms covering 33 to 171 patients, respectively. Time to disease progression was somewhat surprisingly not increased with the immunotherapy and PSA response rates for a PSA level reduction of <50 % did not differ statistically between the treatment arms in the three studies.

The findings are comparable to those in other studies showing a delayed onset of antitumor activity associated with immunotherapy.

Sipuleucel-T therapy is considered safe and well tolerated based on the three randomized studies. There was no statistical difference in rates of adverse events and serious (grade 3-5) adverse events between the immunotherapy and placebo arms.

The basic mode of action by which sipuleucel-T immunotherapy mediated antitumor activity occurs is not fully understood. Immune-monitoring and the identification of plasma biomarkers and critical analysis of current clinical endpoints such as disease-free or progression-free survival are needed.

2.4.2 Radium-233 dichloride therapy

Radium-233 dichloride (radium-233) is a bone-seeking calcium mimetic which selectively binds to osteoblastic or sclerotic metastases in bone. The therapeutic antitumor effects are mediated by radiation consisting in high-energy alpha particles followed by DNA damage. The radiation effect is strong and localized, with a range of less than 100 μm , thus causing only minimal toxicity to nearby organs and especially the bone marrow. (McDevitt et al. 1998, Kerr 2002, Li et al. 2004, Parker et al. 2013)

Radium-233 has been studied in a randomized multicenter, placebo-controlled double-blind setting in patients with metastatic CRPC to demonstrate antitumor effect, clinical efficacy and safety. Patients with two or more bone metastases and no visceral metastases were randomized to receive 6 intravenous injections of radium-233 or placebo every 4 weeks. Other inclusion criteria were: symptomatic disease, castration level of serum testosterone while on maximal androgen blockade treatment, and evidence of increasing PSA values, good performance status and adequate hematological, renal and liver function.

Patients were stratified according to previous docetaxel and bisphosphonate treatment.

Radium-233 was found to be effective, with an overall survival benefit of 3.6 months in the treatment group compared to placebo (14.9 mo vs 11.3 mo). Secondary endpoints such as time to first symptomatic skeletal event and time to PSA progression also favored the radium-233 treatment arm.

The safety analysis revealed a favorable safety profile of radium-233 compared to placebo, with consistent results in all safety endpoints and an improvement in quality of life according to the FACT-P total score in the radium-233 group.

2.4.3 Abiraterone therapy

Abiraterone is a potent inhibitor of CYP17 alfa-hydroxylase, an enzyme which induces adrenal and gonadal synthesis of androgens. (Potter et al.1995, Barrie et al. 1994) In the COU-AA-301 trial abiraterone was studied in a large, randomized placebo-controlled trial of 1195 men with metastatic CRPC progressing after or during docetaxel treatment as second-line therapy. The primary endpoint of the study was overall survival and the study was un-blinded after a planned interim analysis meeting on predefined efficacy limits.

There was a 4.6 month survival advantage for the abiraterone arm in the second and final preplanned interim analysis (15.8 mo vs 11.2 mo) (Scher et al. 2011) Secondary endpoints, time to progression, PSA response and radiological progression-free survival showed a statistically significant benefit for abiraterone, with notably low toxicity. Abiraterone acetate was investigated in 1088 chemotherapy-naïve patients in a double-blind randomized study called COU-AA-302. Patients were randomized to receive abiraterone acetate (1000 mg) plus prednisone (5 mg twice daily) or placebo plus prednisone. Radiographic progression-free survival and overall survival were the main end points in the study. A planned interim analysis was made after 43% of the expected deaths had occurred and the study was unblinded. The median radiographic progression-free survival was 16.5 months with abiraterone-prednisone and 8.3 months with prednisone alone (hazard ratio for abiraterone-prednisone vs. prednisone alone, 0.53; 95% confidence interval (CI), 0.45 to 0.62; $P < 0.001$). Abiraterone-prednisone treatment was also superior compared to prednisone alone in four different end points: Time to initiation of cytotoxic chemotherapy, opiate use for cancer-related pain, prostate-specific antigen progression, and decline in performance status. There were some side-effects which occurred more frequently with abiraterone-

prednisolone, for example Grade 3 or 4 mineralocorticoid-related adverse events and abnormalities on liver function testing. (Ryan et al 2013)

2.4.4 Enzalutamide therapy

Enzalutamide inhibits prostate cancer growth via the androgen-receptor-signaling pathway. It has shown activity in prostate cancer models with overexpression of the androgen receptor, which is believed to be the main driver of hormone-refractory prostate cancer.

Enzalutamide inhibits nuclear translocation of the androgen receptor and binding of DNA inducing anti-tumoral effects in animal models. It has a greater affinity for the androgen receptor than other anti-androgen agents. (Guerrero et al. 2013)

On the basis of the antitumor activity shown in phase I-II studies, an international, phase III, randomized, double-blind, placebo-controlled study was conducted. Men with prostate cancer previously treated with one or two chemotherapy regimens were enrolled.

Other inclusion criteria were castration level of testosterone, previous treatment with docetaxel and progressive disease with increasing PSA or radiographically confirmed progression.

Enzalutamide was given in a dose of 160 mg orally once daily.

Overall survival was chosen as the primary endpoint of the study and the measures response and progression were analyzed as secondary endpoints.

The study was called AFFIRM and enrolled 1199 patients, of whom 800 received enzalutamide and 399 placebo. The primary endpoint of overall survival was 18.4 months in the enzalutamide group compared to 13.6 months in the placebo group. The estimated reduction in the risk of death was 37 % with using enzalutamide as compared with placebo at the prespecified interim analysis, resulting in the discontinuation of the study and unblinding. (Scher et al. 2012)

2.5 Other palliative treatments in CRPC

In addition to the previously described cancer-specific treatments such as hormone therapy, chemotherapy and vaccines, more specifically bone-targeted therapies are used in CRPC. Palliative external radiotherapy in single or multiple fractions or half-body radiation is still effective in palliation of pain or prevention of fractures. Bisphosphonates slow down osteoclast activity and might relieve pain and lower high calcium levels. Clodronate has shown inadequate in one Finnish study. (Kylmä et al.1997) Zoledronic acid is approved in the treatment of metastatic CRPC due to efficacy shown in a phase III study. (Saad et al. 2002) The drug reduced the incidence of skeletal-related events (SRE) and increased the delay to first SRE. (Saad et al. 2002) Aminobisphosphonates are associated with some side-effects, including flu-like symptoms and bone or joint pain. Caution should be observed when treating patients with poor kidney function. One rare serious side-effect of bisphosphonates and also denosumab is osteonecrosis of the jaw. (Hinchey et al. 2013, Qi et al. 2013)

Denosumab is a humanized monoclonal antibody which affects a mediator of tumor cell-induced osteolysis called RANK-L. Denosumab binds to RANK-L and inhibits osteoclast function.(Rajpar and Fizazi 2013) Denosumab was compared to zoledronic acid in a phase III study and increased the time to first SRE from 17.1 to 20.7 months. (Fizazi et al. 2011) The drug is given as an injection under the skin every 4 weeks. Men given this drug are urged to take a supplement containing calcium and vitamin D to prevent problems with low calcium levels. Common side-effects of denosumab treatment include nausea, diarrhea, and feeling weak or tired.

Corticosteroid drugs (such as prednisone and dexamethasone) can help relieve bone pain in CRPC and form part of the docetaxel treatment schedule to reduce allergic side-effects. (Tannock et al. 2004, de Bono et al. 2010)

3 Purpose of the study

The purpose of the present study was to investigate the efficacy and tolerability of chemotherapy in patients with castration-resistant metastatic prostate cancer.

Specific aims were to study;

1. the palliative efficacy and potential toxicity of ifosfamide chemotherapy (I)
2. the pharmacokinetics of docetaxel combined with ifosfamide (II)
3. the safety and efficacy of docetaxel-ifosfamide combination therapy (III)
4. the safety of the new biweekly dosing of docetaxel compared to the standard three-weekly regimen (IV)

4 Patients and methods

The study population consisted of 229 patients with castration resistant metastatic prostate cancer included in the prospective phase I-III trials. Patients in studies I-III were treated in 2001-2002 and those in study IV from March 2004 to May 2009 at Tampere University Hospital. The first three studies (I-III) included only patients from the Department of Oncology, Tampere University Hospital. The fourth (IV) was a multicenter prospective randomized trial and included patients from Finland, Sweden and Ireland (clinicaltrials.com NCT00255606). The principal investigator and the randomization center of this phase III trial were at the Department of Oncology, Tampere University Hospital, Finland. A summary of patients in the different studies is shown in Table 7.

Table 7. Patients and methods

Study	Patients	Phase of trial	Treatment	Endpoint
I	30	II	Ifosfamide	Safety, PSA response
II	10	I-II	Ifosfamide-Docetaxel	Pharmacokinetics
III	31	II	Ifosfamide-Docetaxel	PFS, OS, safety, dose escalation
IV	158	III	Bi-weekly Docetaxel vs Standard docetaxel	PFS, Safety, OS, QoL

OS = overall survival, PFS = progression-free survival, QoL = quality of life

4.1 Main patient inclusion and exclusion criteria

The study population consisted of 229 patients with castration-resistant metastatic prostate cancer. The main inclusion criteria were the following: Age over 18 years, histologically proven metastatic prostate cancer, a rising PSA during complete androgen ablation treatment with castration level testosterone, performance status 0-2 in studies I-III according to ECOG (Eastern Cooperative Oncology Group) and <2 in study IV according to WHO/ECOG, and written informed consent. In Studies I and II the maximum age of the patients was 75 years and a life expectancy of 3 months was required. In the randomized phase III trial (IV) no upper age limit was set.

The main exclusion criteria were: Unstable heart disease, severe renal or hepatic failure, compromised bone marrow function and any previous malignancy.

The mean age of the patients was 64 (range 49-74) in Study I and 70 (range 58-82) and 69 (range 45-87) years in studies III and IV, respectively. The median PSA values at baseline were 214 µg/l (range 28-1270 Study I), 476 µg/l (range 37-2491) Study II, 300 µg/l (range 2-1577 Study III) and 104 µg/l (range 11-1490 Study IV). All patients presented with metastatic disease, the main site of metastasis being bone in 72% (Study IV) to 97% (Study III) of patients.

4.2 Treatments

Chemotherapy was administered mainly as first-line treatment; a minority of patients had received prior estramustine phosphatase treatment (19% in Study II and 43% in study I).

In study I 30 patients were randomized to receive a total of six chemotherapy cycles of ifosfamide in two alternative infusion schedules consisting of ifosfamide 5g/m² with mesna 5 g/m² by a short 24-hour infusion or ifosfamide 1.5 g/m² with mesna 0.3 g/m² by long continuous infusion on days 1-4, every three weeks.

In Study II ifosfamide was combined with docetaxel in a sequential manner and the sequence of chemotherapy agents was reversed in the second cycle of therapy. Docetaxel was administered at a low dose of 40 mg/m² in a 1-hour infusion and ifosfamide at a dose of 3000 mg/m² in a 24-hour infusion. All ten patients involved received identical treatment.

In study III 31 patients received 40-60 mg/m² docetaxel followed by ifosfamide 3.0 g/m² with mesna for a maximal duration of six chemotherapy cycles. This was a non-randomized phase I dose escalation study which was continued as a phase II study.

In study IV patients were centrally randomized to receive docetaxel 75 mg/m² every three weeks or docetaxel 50 mg/m² every two weeks with an identical cumulative dose of docetaxel. All patients received the standard dexamethasone 7,5 mg pre-treatment 12 hours before docetaxel infusion. The study reported the pre-planned safety analysis of the first 158 cases.

PSA responses in studies I, II and III were assessed and reported using recommendations from the prostate antigen working group for eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer (Bubley et al. 1999). These guidelines show an association of PSA lowering of >50%, constituting a partial response (PR), with prolonged survival.

In study IV tumor response was assessed according to the Response Evaluation Criteria in Solid Tumours (RECIST) (www.eortc.be/recist) every 12 weeks using computed tomography for lesions determined to be measurable at baseline. Toxicities were evaluated according to National Cancer Institute –Common

Terminology Criteria of Adverse Events (NCI-CTCAE) statistical analysis software, version 3.0. (<http://ctep.cancer.gov>)

4.3 Ethical statement

All studies were approved by the ethics committee of Tampere University Hospital. Study IV was registered at ClinicalTrials.gov with the study identifier NCT00255606. All studies were conducted in accordance with the Declaration of Helsinki and Finnish patients' rights laws. All patients gave written informed consent. Study I was supported in part by Aventis Pharma, Finland and Study IV was supported in part by Sanofi.

4.4 Statistical analysis

In Study IV a pre-planned interim analysis of 158 patients was made. The toxicity and tolerability of the treatment arms were analysed based on a reduction in the frequency of grade 3-4 side-effects from 40% to 20% using $\alpha=0.05$ and $\beta=0.20$. The results of this analysis are published separately from the final efficacy analysis.

5 Results

Study I: A Randomized dose-finding phase II study on ifosfamide in metastatic hormone-refractory prostate cancer (HRCP).

Patients with CRPC were treated with ifosfamide chemotherapy to investigate the palliative efficacy and potential toxicity of the agent in this phase II randomized study.

Thirty consecutive patients with a median age of 64 (range 49-74) years were randomized to receive ifosfamide 5 mg/m² with mesna 5g/m² by a long 24-hour infusion on day 1 (Group B) or a shorter 3-hour infusion of ifosfamide 1.5g/m² with mesna 0.3g/m² on days 1-4 (Group A) every three weeks until progression of disease or a total of six chemotherapy cycles. (Table 8)

Table 8 Patient characteristics. Study I patient population

	All patients	Group A	Group B
TNM			
T2-T3	7/30 (23%)	4 pts	3 pts
T4	23/30 (77%)	11 pts	12 pts
Age	64 (49-74)	64.1 yrs	63.6 yrs
Time from Dg to Ifosfamide treatment			
< 6 months	3/30 (10%)		
6-12 months	8/30 (27%)		
>12 months	11/30 (36%)		
>24 months	8/30 (27%)		
Prior therapy			
Orchiectomy	12/30 (40%)		
LHRH	12/30 (40%)		
MAB	22/30 (73%)		
Estramustine	13/30 (43%)		

The maximum of six cycles was given only to 17 (57 %) patients, 8 patients in group A and 9 patients in group B. Two patients received no treatment at all and 3 received only one treatment cycle due to rapidly progressing disease, but all 30 patients were included in the final analysis.

The treatment was well tolerated with no severe grade 3-4 toxicities observed in either of the treatment arms. Three patients presented with grade 2 leukocytopenia during treatment; one in the group A and one in the group B. Three patients had minor symptoms, resulting in 10-15 % dose-reductions.

Antitumor response was reported as PSA responses in 30 % of patients with 3 % of patients showing PSA normalization and 27 % partial response and 10 % evincing disease/PSA stabilization as measured by PSA. The antitumor effect of ifosfamide was mainly observed during chemotherapy cycles 3-6, which suggests a gradually developing response to chemotherapy. There were no statistically significant differences between the treatment arms in antitumor effect or toxicity. The mean time to disease progression was 2.4 months for all patients and 8.5 months for those responding to the treatment. The median overall survival was 13.6 months (range 2-52 months).

Study II: Docetaxel-ifosfamide combination chemotherapy in patients with metastatic hormone-refractory prostate cancer: a phase I pharmacokinetic study.

The purpose of the study was to evaluate the antitumor activity, potential toxicity and pharmacokinetics of docetaxel combined with ifosfamide in patients with CRPC. Ten patients were treated with docetaxel 40 mg/m² in a 1-hour infusion followed by ifosfamide 3000 mg/m² in a 24-hour infusion every three weeks. The order of administration was reversed in the second cycle to study the optimal

sequence of administration of these two agents. During the first and second chemotherapy cycles pharmacokinetic blood samples were collected from all patients for docetaxel analysis, six sample times being planned in the protocol: before initiation of docetaxel infusion, before completion of infusion and at 15 min, 90 min, 5h and 19 h after the end of infusion. Plasma docetaxel concentrations were measured by liquid chromatography/mass spectrometer in the Drug Metabolism and Pharmacokinetic Department of Aventis pharma, Antony, France.

With regard to toxicity, no grade 4 toxicities were recorded and grade 3 leukopenia resulted in dose-reductions in 6 cycles (13.3 %). The median treatment duration was 4.6 cycles. Antitumor activity was assessed by PSA response and 44.4 % of patients showed complete or partial PSA responses.

The pharmacokinetic parameters and antitumor effects of both chemotherapeutic agents were investigated in a small cohort of study subjects. As no conclusions could be drawn as to the antitumor effect or the differences in treatment schedules, the study was continued as a phase II extended study of 30 patients. Plasma half-lives and the AUC of docetaxel can be studied with more reliability. The maximal plasma concentration was similar in all patients (range 1.338-1.812) and AUC varied from 848 to 1.227. The clearance rate varied from 17.2 to 25.1, with a mean of 19.9. All parameters could be presented in six out of nine patients. The pharmacokinetic parameters for cycle one in four cases were not reported by reason of inconsistent time-concentration data (two patients) and inconsistent documentation of start and close times of infusion (two patients). Pharmacokinetic data in the second cycle could be analysed for all nine patients. The clearance of docetaxel was not modified by the co-administration of ifosfamide.

Study III: No additional benefit of adding ifosfamide to docetaxel in castration-resistant metastatic prostate cancer.

Docetaxel and ifosfamide differ in respect of mechanisms of antitumor action and toxicity profiles. The pharmacokinetic interactions of ifosfamide and docetaxel had previously been studied and this study was a phase I dose-escalation study which was continued as a phase II combination study in the treatment of CRPC.

A minority of patients receiving docetaxel chemotherapy do not respond initially or become resistant to docetaxel after transient response. (Tannock et al. 2004) It is therefore vital to develop well tolerated combination chemotherapy, as in many other cancer types, for these CRPC patients. .

The objective PSA response rate in this study population was 32 % in 11/31 patients. The overall median survival was 14.1 months. The results are comparable to those of other phase II chemotherapy regimens (Goodin et al. 2005, Ryan et al. 2007), but inferior to more intensive single-agent docetaxel chemotherapy, and it is therefore our conclusion that no significant additional benefit is gained in adding ifosfamide for patients who tolerate standard docetaxel chemotherapy.

Study IV: Bi-weekly docetaxel is better tolerated than conventional three-weekly dosing for advanced hormone-refractory prostate cancer.

The standard dose of 75 mg/m² of docetaxel every three weeks is often associated with considerable transient bone-marrow toxicity, mainly neutropenia, leading to infections and hospitalizations. Our hypothesis in this study was that 50 mg/ m² every two weeks in a lower single total dose, but similar weekly dose intensity (weekly dose 25 mg/m²), could be better tolerated due to reduced peak drug concentrations.

This pre-planned interim safety analysis of 158 patients consisted in an interim hematological toxicity analysis performed when patients had participated in the trial for at least 3 months. The statistical analysis was based on a reduction in the frequency of grade 3-4 side-effects from 40 % to 20 % using $\alpha=0.05$ and $\beta=0.20$. Seventy-nine patients were required in each arm for a total of 158 patients.

The treatment duration, the number of patients receiving the study drug for at least six months and the number of serious adverse events favoured the investigational biweekly treatment arm.

There were differences between the arms in Grade 3-4 adverse events. The most prominent toxicities such as neutropenia, infection with/without neutropenia and leukopenia are presented in Table 9.

Table 9. Grade 3-4 adverse events.

Grade 3-4 adverse event	Biweekly treatment arm % of cycle given	Triweekly treatment arm % of cycle given
Neutropenia	14 %	20%
Infection w/wo neutropenia	3 %	8 %
Leukopenia	3 %	8 %

Most common (<10 % of cycles) grade 1-2 non-hematological side-effects such as fatigue, alopecia, nail changes and anorexia were evenly distributed.

The final comparison of the efficacy of the treatment arms is an important additional study objective, as the biweekly docetaxel treatment offers an option to administer docetaxel chemotherapy to our patients.

6 Discussion

When this study was initiated in the pre-docetaxel era, our aim was to study a fairly high dose of ifosfamide. Ifosfamide is an alkylating isomeric cyclophosphamide analogue with antitumor effect in a variety of solid tumors including breast cancer and sarcoma. (Sorio et al. 2003, Walczak et al. 2013) Only studies involving a small number of CRPC patients had been published previously, with only modest benefit and low response rates of 7-11 %. (Williamson et al. 1996) The first patient population had fairly advanced disease, but median survival and response rate were nonetheless relatively good. To increase effectiveness docetaxel was added. Again there was palliative gain and the pharmacokinetics of docetaxel was not affected by the addition of ifosfamide. However, CRPC differs from many other cancers (e.g. breast, testicular, lymphomas) in that none of the combinations tested in clinical studies has increased the response rate or survival. The strength of our studies was the unselected patient population treated with the same principles, but numbers of patients in the first studies were low, as over ten years ago the general condition of CRPC patients coming to the oncology unit was poor and patients received mostly palliative treatment.

The patient population in study III were poor prognosis patients, since the majority evinced only a short-lasting response to prior hormonal therapy, presented with a symptomatic disease requiring analgesic medication and palliative radiation therapy for bone pain and had a very high median baseline PSA level of 300 (range 3-1577) $\mu\text{g/l}$ compared to those in the TAX 327 (median 108-114 $\mu\text{g/ml}$) (Tannock et al. 2004) and SWOG trials (median 84-90 $\mu\text{g/ml}$). (Petrylak 2005) Our patients thus represented the real-life patient population at oncology units, presenting with more advanced disease and a need for palliative measures to alleviate symptoms prior to and during chemotherapy treatment.

Docetaxel is administered as an intravenous infusion of 75 gm/m² every three weeks with prednisone 10 mg daily orally. An alternative treatment schedule with biweekly treatments of 50 mg/m² every two weeks with prednisone 10 mg daily has been studied with promising findings of lower toxicity and longer time to treatment failure. (Kellokumpu-Lehtinen et al. 2013)

The most common side-effects of docetaxel chemotherapy are leukocytopenia, nausea, alopecia, fatigue and peripheral neuropathy. Most side-effects are mild and reversible over time, but treatment-related infections must be carefully monitored and treated with caution to avoid any additional morbidity. Due to the cumulative toxicity associated with prolonged chemotherapy, new alternative dosing schedules have become common practice. Intermittent chemotherapy with drug-free periods of several months has been studied and re-treatment with the same modality may be an option for some patients who have had a prior clinical benefit and have recovered from prior drug-related toxicity.

Throughout the study our aim was to develop a better tolerated and efficacious treatment for CRPC and the multinational PROSTY trial therefore was planned before the docetaxel registration trials (Tannock et al. 2004, Petrylak et al.2004) were published. According to the results docetaxel given every second week was better tolerated (study number IV) and more efficacious.

In the PROSTY study 361 patients were randomly assigned to receive docetaxel every 2 or 3 weeks The 2-weekly administration was associated with significantly longer time to treatment failure than was 3-weekly administration (5.6 months, 95 % CI 5.0-6.2 vs 4.9 months, 4.5-5.4; hazard ratio 1.3, 95 % CI 1.1-1.6, p=0.014). Grade 3-4 adverse events occurred more frequently in the 3-weekly than in the 2-weekly administration group, including neutropenia (93 [53 %] vs 61 [36 %]), leukopenia (51 [29 %] vs 22 [13 %]), and febrile neutropenia (25 [14 %] vs six [4 %]). Neutropenic infections were reported more frequently in patients who received docetaxel every 3 weeks (43 [24 %] vs 11 [6 %], p=0.002).The authors conclude that the administration of docetaxel every 2 weeks is well tolerated in

patients with castration-resistant advanced prostate cancer and could be a useful option when 3-weekly single-dose administration is unlikely to be tolerated. (Kellokumpu-Lehtinen et al. 2013a)

Many novel agents with different mechanisms of action have been combined with docetaxel chemotherapy to gain better control of the disease and improve the quality of life of patients with CRPC.

Cabozantinib is a multikinase targeting agent which has shown promising activity in phase I and II studies and is currently being studied in a phase III setting with much anticipated results.

Studies with anti-angiogenic agents such as bevacizumab in combination with docetaxel have failed to show superiority when compared to docetaxel alone. Other angiogenesis inhibitors such as lenalidomide, VEGF TRAP aflibercept and VEGF receptor inhibitors have been investigated in randomized phase III and II studies combined with docetaxel chemotherapy. (Nabhan et al. 2014, Tannock et al. 2013) None of these has proved superior to the standard single docetaxel chemotherapy alone.

Clinical phase III trial results indicate that prostate cancers may be driven only in part by angiogenesis. (Small et al. 2012) Small molecule targeted agents such as the tyrosine-kinase inhibitor sunitinib have also failed to improve the antitumor effects of standard single agent docetaxel chemotherapy and, despite a PFS benefit, no overall survival benefit has been reported in the post-chemotherapy setting with sunitinib. (Michaelson et al. 2014)

The endothelin receptor antagonist zibotentan was studied in a large, randomized phase III study of CRPC patients with bone metastasis. Median overall survival was 24.5 months compared to 22.5 months for the placebo control arm, a difference not statistically significant. (hazard ratio 0.87; $p=0.240$) (Nelson et al. 2012)

The addition of calcitriol to docetaxel proved to be more harmful to patients and the trial in question was discontinued prematurely due to a higher number of deaths in the calcitriol than the control (prednisone) arm. (Scher et al. 2011)

GVAX immunotherapy in patients receiving docetaxel has been studied in two phase III trials, both of which were terminated early due to a low chance of meeting the predefined primary endpoint of overall survival and due to an imbalance in the number of deaths (67 in the GVAX+docetaxel group versus 47 in the docetaxel + prednisone group). (Higano et al. 2008)

Metastatic prostate cancer is an incurable disease, which presents in a continuum of different types of disease progression patterns and affects patients in notably different ways. Chemotherapy for CRPC is palliative in nature and the aim of treatment varies from long-term disease-free survival gain to palliation of symptoms of rapidly progressing disease and maintaining performance status. It is therefore vitally important to study different options for chemotherapy treatments and combinations of agents with antitumor effect against CRPC.

Docetaxel chemotherapy remains the standard of care in first line treatment of CRPC with optional dosing schedules. New hormonal agents and bone-targeted agents are an addition to the treatment options and combination studies with docetaxel address the question of the optimal combination and sequence of administration.

7 Summary and Conclusions

The purpose of the studies reported here was to improve the treatment of CRPC patients. The aim in Study I was to assess the safety of ifosfamide as a single-agent chemotherapy option. The results showed that ifosfamide was a well-tolerated treatment and has antitumor efficacy. These conclusions led to a phase II study with a taxane-based combination chemotherapy regimen; docetaxel + ifosfamide.

In Study II we thus investigated the pharmacokinetic parameters of ifosfamide and docetaxel in sequential dosing in the treatment of CRPC. Due to the limited number of study subjects, no conclusions as to the antitumor effects or differences in the two treatment schedules can be drawn. However, the plasma half-lives and AUC of docetaxel could be measured in a sufficiently large number of serum samples. As a conclusion, the sequence of administration of ifosfamide and docetaxel did not influence the pharmacokinetics of the latter.

In Study III docetaxel-ifosfamide combination chemotherapy was further studied in a phase I dose-escalation study which was continued as a phase II combination study. Study subjects mainly presenting with an aggressive form of the disease characterized by short duration of response to primary hormonal manipulation and the presence of symptomatic metastatic disease and a high median level of PSA at study baseline represent the real-life patient population. In spite of this, the response to the treatment was fairly good, with a 32 % PSA response rate and a median survival of 14.1 months. This result is comparable to those with other chemotherapy regimens used earlier in CRPC, but it proved no better than the single-agent docetaxel chemotherapy and our conclusion was therefore that there is no additional benefit in adding ifosfamide to docetaxel in this patient population. The standard dosing for docetaxel chemotherapy is 75 mg/m² every three weeks.

Our hypothesis in Study IV was that a biweekly dosing schedule with a dose of 50 mg/m² every two weeks could result in increased tolerability without reducing the intensity and the antitumor effect of the treatment. We reported the pre-

planned interim safety analysis results on 158 patients and the conclusion was that the treatment duration, the number of patients on the study drug at six months and the number of serious adverse events favored the biweekly treatment arm. Biweekly docetaxel treatment offers a safe option in the administration of chemotherapy to patients with CRPC.

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A Randomised Dose-Finding Phase II Study on Ifosfamide in Metastatic Hormone-Refractory Prostate Cancer (HRPC)

P. Hervonen, T. Lehtinen, T.L. Tammela, P. Kellokumpu-Lehtinen

Depts. of Oncology and Urology, Tampere University Hospital and Medical School, University of Tampere, Finland

The palliative efficacy and toxicity of single-ifosfamide chemotherapy were investigated in patients with progressive metastatic hormone-refractory prostate cancer (HRPC).

Thirty patients were randomised to receive ifosfamide by a 24-hour infusion on day 1 or a 3-hour infusion on days 1-4 at three week intervals until renewed disease progression or a total of six chemotherapy cycles. Response was analyzed according to the guidelines of the Prostate-Specific Antigen Working Group (1999).

All 30 patients were included in the final analysis. 1 (3%) PSA normalization, 8 (27%) partial responses, 3 (10%) stable diseases and 18 (60%) progressive diseases. The mean time to progression was 2.4 months, (range 0 -17) months and the median survival time was 13.6+ months, (range 2 -52). The treatment was well tolerated. No severe gr III-IV hematotoxicities were observed.

In conclusion ifosfamide is effective and well tolerated as a single-agent in the treatment of HRPC. Further studies including ifosfamide in combination chemotherapy of HRPC are in progress.

Key Words: Hormone-resistant, Palliation, Single-agent chemotherapy

Prostate cancer is the most commonly diagnosed malignancy among males in Western countries and is increasing rapidly in Finland with an age-adjusted incidence of >72/100 000 in the year 1997 (1). Although the increasing number of new cancers are organ-confined, advanced tumours are still common. Androgen withdrawal therapy has been a standard treatment for patients with an advanced disease. Although maximal androgen blockade (MAB) was expected to improve treatment results, its clinical efficacy has not been shown to be superior to conventional castration (2,3).

Almost all patients with metastatic disease eventually develop androgen-independent cancer (4,5). In several studies the median overall survival time was only 8-12 months in duration for patients with bone metastases (3,6). Previous usage of chemotherapy for HRPC has been of only modest benefit in slowing disease progression and increasing overall survival time as well as minimal effect on the quality of life. Due to the lack of consensus on response criteria it has been difficult to compare results of previous studies. The alledged association

of PSA decrease of over 50% from baseline value with prolonged survival has led to the development of guidelines for PSA response criteria in clinical trials (4). However these guidelines are yet to be validated.

Previous phase II evaluations of ifosfamide monotherapy in metastatic prostate cancer have demonstrated low response rates of 7-11% (7,8). However, these studies were performed on a small number of patients and a major part of the target accrual goal was never achieved (8).

Recently various agents and combinations of chemotherapy have been shown to have a promising activity against HRPC (9,6,10,11). Combined treatment with mitoxantrone and corticosteroids have been more successful than corticosteroids alone with only modest toxicity (6) with no difference in overall survival. For most patients responding to treatment both an improvement in health-related quality of life and a decrease in PSA levels was observed (12). Palliative effect with low toxicity can be considered the most important goal of treatment based on results of a single-agent chemothera-

py of HRPC patients.

The combination of docetaxel, estramustine and low dose hydrocortisone has been proven to be efficacious and well tolerated with >50% PSA responses in 66% of the patients and an overall survival time of 27 months. Substantial responses of more than 40% PSA value reduction and a more than 50% reduction in patients with measurable disease were seen in 17 out of 35 (49%) patients in a recent study (10). The benefit of chemotherapy with mitoxantrone and navelbine has been investigated with PSA responses in 44% of evaluated patients (11).

Ifosfamide is an alkylating agent that has shown a positive effect against a variety of solid tumours including breast cancer (13) and sarcoma (14,15). Ifosfamide can be administered intravenously as a bolus or short infusion or as a continuous long infusion over 1-4 days. Conventional single agent doses in earlier schedules range between 5g/m² and 10g/m².

The object of this study was to compare toxicity, PSA progression and overall survival of patients randomised to receive single-ifosfamide chemotherapy either as a 24-hour infusion or as a 3-hour infusion on days 1-4.

Materials and Methods

The trial was an open, randomised study to which patients with hormone-refractory histologically proven metastatic prostate cancer were eligible if they had a life expectancy of more than 3 months, were younger than 76

years and gave informed consent. Exclusion criteria were: heart infarction within 6 months, unstable angina pectoris, severe renal or hepatic failure (alat >1.5 x normal, asat >1.5 x normal) and any history of previous malignancy except skin carcinoma. The local ethics committee approved the protocol.

Patients were randomised to receive either ifosfamide 5 g/m² with mesna 5g/m² by 24-hour infusion/ day 1 or ifosfamide 1.5 g/m² with mesna 0.3 g/m² on days 1-4 by short infusion at three week intervals until a total of six chemotherapy cycles or until renewed disease progression.

A total of 30 consecutive patients, with a median age of 64 years (range 49-74) were randomised, 2 patients did not receive treatment at all and 3 patients received only one treatment due to rapid disease progression, development of renal failure and poor overall condition. All 30 patients were included in the final analysis (Table I). All patients were treated in an inpatient setting during infusions. The analysis of treatment effect and response as measured by PSA included 17 patients in the 1-4 day treatment group (arm A) and 13 patients in the 24-hour treatment group (arm B). PSA responses were analysed in the same accredited laboratory prior to treatment and each chemotherapy cycle according to the guidelines of the Prostate-Specific Antigen Working Group (1999) (4). Creatinine-clearance analyses were done prior to each treatment cycle resulting in dose reductions for two patients.

Results

All except one patient had bone metastases at the beginning of ifosfamide treatment. There were no significant differences between the two treatment arms in baseline patient characteristics (Table I). A median PSA value of the treatment arms at baseline were in Arm A 202 µg/l, in arm B 229 µg/l and for all patients 214 µg/l, range 28-1270. The maximum of six chemotherapy cycles were given to 17 patients (57%), 8 patients in the 1-4 treatment group (arm A) and 9 in the 24-hour treatment group (arm B).

As a whole the treatment was well tolerated. No grade IV hematotoxicity was observed and only 3 patients presented grade II leucocytopenia during treatment. No septic infections occurred. One patient developed angina pectoris symptoms requiring a 10% dose-reduction of chemotherapy. Deterioration of kidney function was observed in two patients resulting in dose-reductions of 15%.

Transient grade II disorientation was observed during

Table I - Patient characteristics

	All patients	Group A	Group B
TNM			
T ₂₋₃ N _x M ₁	7/30 pts (23%)	4 pts	3 pts
T ₄ N _x M ₁	23/30 pts (77%)	11 pts	12 pts
Age	63.9 yrs (49-74)	64.1 yrs	63.6 yrs
Time from Dg to ifosfamide treatment			
< 6 months	3/30 pts (10%)		
6-12 months	8/30 pts (27%)		
>12 months	11/30 pts (36%)		
>24 months	8/30 pts (27%)		
Mean time	22.9 months (5-80)		
Prior therapy		Primary / Secondary treatment	
Orchiectomy	12/30 pts (40%)	12/30 pts	
LHRH	12/30 pts (40%)	12/30 pts	
MAB	22/30 pts (73%)		22/30
Estramustine	13/30 pts (43%)		13/30

2 treatment cycles of one patient in the 24-hour infusion group. There was one (3%) patient with PSA normalization, 8 (27%) patients with PR and 3 (10%) patients with disease stabilization during the treatment cycles. The effect of ifosfamide treatment on PSA values was mainly observed during treatment cycles 3-6. The overall median survival was 13.6 months (2-52 months) with 4 patients alive at the time of analysis.

The overall median progression free survival was 2.4 months as compared to a median progression free survival of 8.5 months for patients responding to treatment (CR, PR or SD).

Discussion

The results of this study showed a 30% PSA response rate including 3% PSA normalization and 27% partial PSA responses. 10% of the patients had a stable disease and 18 patients (60%) progressed during the treatment. The mean time to PSA progression was 8.5 months for responding patients, range 1-17 months. Median survival time was 13.6 months with 5 patients alive 2 years after beginning of the ifosfamide treatment.

As the treatment schedule consisted of a maximum of six chemotherapy cycles administered every 3 weeks, the overall duration of chemotherapy was 4-5 months respectively, which can be considered a reasonable duration of palliative treatment. In addition, the toxicity profile of single-ifosfamide treatment was favourable which becomes an important aspect of palliative treatment of patients with compromised performance status.

Based on PSA value analyses, it seems evident that PSA response develops gradually during ifosfamide treatment and lasts longer for patients receiving the maximum of 6 chemotherapy cycles. Although additional treatment cycles might lengthen the duration of PSA response, toxicity of treatment and quality of life could become limiting factors. The overall benefit of more than six treatment cycles of combined chemotherapies has not been shown in randomized trials. The possible advantageous effect of a longer duration of ifosfamide treatment in patients with complete PSA responses and sufficient performance status after six treatment cycles calls for further investigation.

An earlier study reported either a CR, PR or SD PSA response in 64% of patients receiving hydrocortisone and mitoxantrone combination therapy and a median survival time of 12.3 months. However, no significant improvement in survival was shown as compared to hydrocortisone treatment alone (6).

Our study showed that single-ifosfamide treatment

was equally well tolerated with longer median survival time and simplified treatment schedule.

Preliminary results of docetaxel monotherapy in the treatment of hormone-refractory prostate cancer are encouraging with a median overall survival time of 27 months and a 66% PSA response rate. These results suggest durable activity for docetaxel as a single-agent therapy (10).

A phase II trial of single-docetaxel in HRPC confirmed the substantial single-agent activity of docetaxel with PSA response of more than 50% reduction in 38% of patients (7/21) (9). Paclitaxel in combination with estramustine has been shown to induce PSA value reduction of more than 50% in 63% of patients. However, significant toxicity was observed as neutropenia, which might limit the use of the combination (16).

Half of our patients had received estramustine for progression before ifosfamide treatment and thus had a very advanced disease. In spite of that the results of the present study are more encouraging than previous results with this chemotherapeutic agent (7,8) and our previous results (17).

The results of this study indicate that ifosfamide as a single-agent is an active and well-tolerated treatment option of HRPC. Further studies including ifosfamide in combination with docetaxel are ongoing and needed as treatment of hormone refractory prostate cancer evolves.

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Petteri Hervonen M.D.
Department of Oncology
Tampere University Hospital
P.O.B. 2000
FIN -33521 Tampere, Finland
Tel.: +358-3-247 3456; Fax: +358-3-247 3001,
E-mail: petteri.hervonen@pshp.fi

DOCETAXEL-IFOSFAMIDE COMBINATION CHEMOTHERAPY IN PATIENTS WITH METASTATIC HORMONE-REFRACTORY PROSTATE CANCER: A PHASE I PHARMACOKINETIC STUDY

HERVONEN P.¹, JEKUNEN A.,² LEFEBVRE P.,³ KELLOKUMPU-LEHTINEN P.¹

1) Department of Oncology, Tampere University Hospital, Tampere, Finland.

2) Aventis Pharma, Espoo, Finland.

3) Aventis Pharma, Paris, France.

Summary: *This phase I study was designed to evaluate the activity, toxicity and pharmacokinetics of docetaxel combined with ifosfamide in the treatment of hormone-refractory prostate cancer. Ten patients received a median of 4.6 treatment cycles. Docetaxel was administered at a dose of 40 mg/m² in a 1-hour infusion followed by ifosfamide 3,000 mg/m² in a 24-hour infusion every 3 weeks. The optimal sequence of chemotherapeutic agents was investigated by reversing the order of administration in the second cycle and by collecting a total of six pharmacokinetic blood samples per cycle from all patients during the first and second cycles. The sequence of administration did not influence the pharmacokinetics of docetaxel. Prostate-specific antigen (PSA) responses were observed in four out of nine patients, with a PSA response rate of 44.4 % (complete response + partial response). The treatment was well tolerated. No grade IV toxicities were recorded and grade III leucopenia resulted in dose-reductions in 6 cycles (13.3%). The pharmacokinetic parameters of docetaxel were similar in both sequences. Our recommendation for further phase II studies is ifosfamide followed by low-dose docetaxel. Further phase II efficacy studies are warranted.*

Introduction

Ifosfamide is an alkylating isomeric analogue of cyclophosphamide that shows activity against a vari-

ety of solid tumor types, including non-small cell lung cancer, testicular cancer, breast cancer and sarcoma. The optimal dosage and sequencing of ifosfamide in combination chemotherapy has been a principal question in numerous phase I studies. The single-agent dose range in earlier studies was 5-10 g/m² (1-3). Docetaxel is a semisynthetic taxoid that enhances microtubule assembly and inhibits the depolymerization of tubulin, leading to accumulation of microtubule bundles in the cell and causing mitotic

Address for correspondence: P. Hervonen, Department of Oncology, Tampere University Hospital, P.O.B. 2000, FIN-33521 Tampere, Finland.

Tel: +358 3 247 3456 Fax: +358 3 247 3001

E-mail: petteri.hervonen@pshp.fi

arrest in the M phase of the cell division cycle. The major dose-limiting toxic effect of docetaxel is neutropenia, which is usually dose-dependent, noncumulative and of short duration. Other prominent detrimental effects reported include febrile neutropenia, skin and nail toxicities, fluid retention, hypersensitivity reactions, mucositis and alopecia. Docetaxel exhibits significant activity in breast cancer, ovarian cancer and non-small cell lung cancer and has been evaluated in phase III studies in several other tumor types (2). There are reports of docetaxel and ifosfamide combinations in uroepithelial cancer (4) and in non-small cell lung cancer (2). No data are available on the pharmacokinetics between low-dose docetaxel and ifosfamide in prostate cancer. The therapy requirements for advanced prostate cancer patients are unique by reason of the low tolerance of adverse effects introduced by medium or high-dose chemotherapies. Prostate cancer patients are elderly and usually exhibit many symptoms and poor overall performance status. Low-dose chemotherapy with a tolerable adverse effect profile should also suffice to control prostate cancer, which has a slow natural course. In the present study we used a special method of administration of chemotherapeutic drugs to the same patients to study intra- and interindividual pharmacokinetics of this combination therapy.

Materials and methods

The pharmacokinetics of docetaxel (Taxotere[®], Aventis Pharma, Dagenham, Rainham Road, South Dagenham, Essex, UK) given in combination with ifosfamide (Holoxan[®], Asta Medica Ag, Frankfurt am Main, Germany) was assessed in ten chemotherapy-naïve patients with metastatic hormone-refractory prostate cancer. The protocol was approved by the local Ethical Committee of Tampere University Hospital and all patients gave written informed consent.

The inclusion criteria were histologically proven metastatic prostate cancer, a life expectancy of more than 3 months and age < 76 years. Exclusion criteria were cardiac infarction within the previous 6 months, unstable angina pectoris, severe renal or hepatic failure and a history of previous malignancy except skin carcinoma. The trial was a nonrandomized phase I study.

During the first cycle, docetaxel 40 mg/m² was given in a 1-h intravenous infusion, immediately followed by ifosfamide 3,000 mg/m² in a 24-h infusion, repeated every 3 weeks with reversed dose sequence in cycle 2 (ifosfamide immediately followed by docetaxel infusion). Standard premedication for docetaxel was used.

The pharmacokinetics of docetaxel were studied in ten patients during the first treatment cycle and in nine patients during the second treatment cycle. For docetaxel analysis, six sampling times were planned in the protocol: before initiation of docetaxel infusion (5 min) and before completion of infusion (15 min, 90 min, 5 h and 19 h after the end of infusion). The limited blood sampling strategy design (optimal sampling times) was based on population parameter estimates obtained from phase I data (1). In cycle 2, blood samples were taken up to 5 h after the end of infusion.

Plasma docetaxel concentrations were measured by liquid chromatography/mass spectrometer/mass spectrometer (with a limit of quantitation of 1 ng/ml) in the Drug Metabolism and Pharmacokinetic Department of Aventis Pharma, Antony, France.

The method includes a single-step liquid-solid extraction using 96-well Empore C18 extraction disk plates and subsequent reversed phase high-performance liquid chromatography separation using a Hypersil BDS C-18 column and a mobile phase consisting of acetonitrile, water and formic acid. Quantitation was achieved on an Applied Biosystem API3000 mass spectrometer using turboionspray and multiple reaction monitoring in positive ion mode for docetaxel and the internal standard.

Pharmacokinetic parameters were calculated by a Bayesian estimation using time-concentration data for each patient and the previously defined population model as prior information (5). A three-compartmental structural model with first-order elimination was used. Individual pharmacokinetic analysis was performed using the NONMEM program (6). The analysis focused on docetaxel plasma clearance and the area under the curve parameters, as they are well estimated using the Bayesian approach (7) and constitute good predictors of clinical outcome (8). Clearance was estimated with the NONMEM program and the area under the curve (AUC) was calculated as $AUC = \text{dose}/\text{clearance}$.

Plasma time-concentration data were available for ten patients during the first treatment cycle and for nine patients during the second. As the beginning and end of infusion of this second cycle were not well documented, a 1-h infusion was assumed as described in the protocol. Time-concentration data on patients 2, 3, 6 and 10 on cycle 1 were inconsistent and no

pharmacokinetic analysis was performed with these data to evaluate pharmacokinetics.

Results

The individual pharmacokinetic parameters when docetaxel was administered prior to ifosfamide are presented in Table I. All parameters could be presented in six patients. The maximal plasma concentration was similar in all patients (range: 1,338-1,812) and AUC varied from 848 to 1,227. The clearance rate (CL) varied from 17.2 to 25.1, with a mean of 19.9.

Table I illustrates the individual pharmacokinetic parameters in the cycle consisting of docetaxel 40 mg/m² 1 h infusion + ifosfamide 3,000mg/m² 24 h infusion.

Figure 1 shows a typical pharmacokinetic profile. The pharmacokinetic parameters of patients 2 and 3 were not reported because the time-concentration data were inconsistent; the docetaxel plasma con-

Table I Individual pharmacokinetic parameters in cycle 1: Docetaxel 40 mg/m² 1-h infusion + ifosfamide 3,000 mg/m² 24-h infusion

Patient	CL (l/h)	C _{max}	CL (l/h/m ²)	AUC (ng/ml.h)	BSA
1	33.3	1,769	18.0	1,200	1.85
4	41.6	1,514	21.7	962	1.92
5	47.2	1,338	25.1	848	1.88
7	37.0	1,437	20.1	1,082	1.84
8	32.6	1,812	17.5	1,227	1.86
9	34.3	1,720	17.2	1,168	1.99
Mean	37.6	1,598	19.9	1,081	
SD	5.7	195	3.0	149	
CV%	15	12	15	14	
Median	35.6	1,617	19.1	1,125	
Minimum	32.6	1,338	17.2	848	
Maximum	47.2	1,812	25.1	1,227	
Number	6	6	6	6	

CL = clearance; AUC = area under the curve; BSA = body surface area; CV% = coefficient of variance.

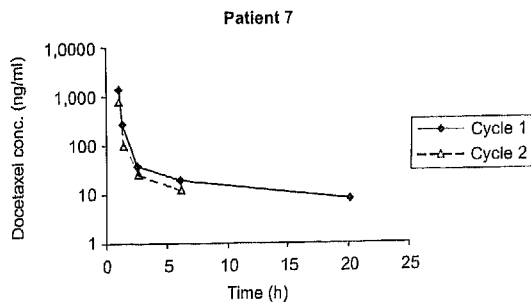


Fig. 1 A typical pharmacokinetic profile: Patient 7.

centration 15 min after the end of infusion was higher than plasma levels after the end of infusion. Documentation of the start and close of infusion was inconsistent for patients 6 and 10 and the values of the pharmacokinetic parameters of these two patients are also not reported. Pharmacokinetic data in

the second cycle could be analyzed in all nine patients (Table II). Individual CL values for both cycles are presented in Figure 2. Toxicity and responses were evaluated according to the World Health Organization's criteria (9) and quality of life and symptoms of disease were recorded at each cycle. Prostate-specific antigen (PSA) responses were observed in four out of nine patients (44%). One patient showed complete response, three showed partial responses, one had stable disease and four had progressive disease. The PSA response rate was 44.4% (complete response + partial response). The pretreatment PSA values varied greatly (range: 37-2,491); baseline mean PSA was 476.

The treatment was well tolerated, as no grade IV toxicities occurred and grade III leukocytopenia resulted in dose reductions in only 6 out of 45 cycles (13.3%) administered.

Table II Cycle 2: Ifosfamide 3,000 mg/m² 24-h infusion + docetaxel 40 mg/m² 1-h infusion

Patient	CL (l/h)	C _{max}	CL (l/h/m ²)	AUC (ng/ml.h)	BSA
1	29.4	1,985	15.9	1,362	1.85
2	54.0	1,070	29.7	741	1.82
3	41.5	1,552	20.3	965	2.04
4	36.8	1,677	19.2	1,086	1.92
6	46.3	1,250	25.3	863	1.83
7	41.9	1,397	22.8	954	1.84
8	48.8	1,098	26.3	819	1.86
9	38.7	1,388	19.5	1,033	1.99
10	38.4	1,772	18.5	1,040	2.08
Mean	41.8	1,465	21.9	985	
SD	7.2	309	4.4	181	
CV%	17	21	20	18	
Median	41.5	1,397	20.3	965	
Minimum	29.4	1,070	15.9	741	
Maximum	54.0	1,985	29.7	1,362	
Number	9	9	9	9	

CL = clearance; AUC = area under the curve; BSA = body surface area; CV% = coefficient of variance.

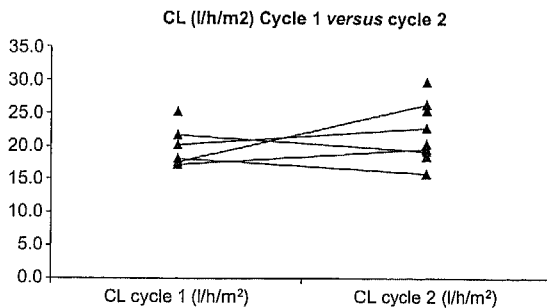


Fig. 2 Individual clearance values in cycles 1 and 2. CL = clearance.

Other toxicities included transient renal dysfunction requiring dose reduction in one cycle and transient disorientation after the first cycle of treatment (docetaxel-ifosfamide) experienced by three patients.

Discussion

In this pharmacokinetic phase I study a combination of docetaxel 40 mg/m² and ifosfamide 3,000 mg/m² was studied. The pharmacokinetic parameters of both chemotherapeutic agents were evaluated in a limited number of patients, thus limiting the conclusions concerning the anticancer effect of the combination. However, conclusions can be drawn on plasma half-lives and the AUC of docetaxel coadministered with ifosfamide.

Intra- and interindividual pharmacokinetic parameters were studied by reversing the order of administration of the chemotherapeutic drugs in the same patient.

These estimates are close to previous data concerning docetaxel as single agent in a large population of patients (20.9 ± 6.7 l/h/m², $n = 640$) (8). The results are in agreement with previously published results. When docetaxel was administered to patients

with advanced solid tumors at a higher dose (85 mg/m²) in a 1-h infusion immediately followed by ifosfamide in a 24-h infusion (5 g/m²), no pharmacokinetic interaction between docetaxel and ifosfamide was evidenced (10). In the present study, the clearance of docetaxel was not modified by the coadministration of ifosfamide, even though docetaxel is metabolized by CYP3A4 (11) and ifosfamide is metabolized by CYP3A and CYP2B (12).

The optimal order of administration of docetaxel and ifosfamide was studied in a defined prostate cancer population. The results were promising, showing low toxicity and good tolerance. Tolerability should be confirmed by prolonging the observation time to multiple treatment cycles. One of the end points of the phase II study should be to explore how many cycles of chemotherapy can be given without unacceptable toxicity or disease progression. We used a highly sensitive method in measuring docetaxel concentrations. The lowest detectable concentration for the method was defined as 1 ng/ml, far lower than the lowest detected plasma concentration, 4.35 ng/ml indicating that the method was sensitive enough to detect low-dose docetaxel plasma concentrations and possibly changes induced by ifosfamide.

No conclusions regarding the optimal order of administration can be drawn from this limited patient population which showed a low rate of toxicity. However, all central nervous system toxicities were manifested when ifosfamide was given before docetaxel. Central nervous system toxicity, presenting mainly as transient disorientation caused by ifosfamide, warrants further pharmacokinetic studies in ifosfamide-based chemotherapeutic combinations.

There are some reports on docetaxel and ifosfamide combinations in indications other than prostate cancer and a higher docetaxel dose (3). Twenty-two patients with advanced urothelial cancer were treated with 60 mg/m² docetaxel given over 1 h and 2.5 g/m² ifosfamide given over 24 h every 3 weeks with intravenous 500 mg mesna. Treatment was well

tolerated. The major toxic effect was grade 3 and 4 leucopenia in 17% and 4% of the cycles respectively.

Another study reported 34 patients with histologically confirmed solid tumors treated with docetaxel (a 1-h infusion) followed by ifosfamide in a 24-h infusion, or ifosfamide followed by docetaxel every 3 weeks (4). Docetaxel doses were high, ranging from 60 to 85 mg/m² and ifosfamide doses ranged from 2.5 to 5.0 g/m². Grade 3 and 4 granulocytopenia was observed in 89% of courses and was of short duration and related to the ifosfamide dose.

Nonhematological toxicities were mild to moderate and included alopecia, nausea, vomiting, mucositis, diarrhea, sensory neuropathy, skin and nail toxicity, hypersensitivity reactions and edema. Ifosfamide followed by docetaxel induced more gastrointestinal toxicity, but less febrile neutropenia. The dose-limiting toxicity for docetaxel followed by ifosfamide was neutropenic fever at a dose of 85 mg/m² docetaxel and 5 g/m² ifosfamide, while for ifosfamide followed by docetaxel it was neutropenic fever at a dose of 75 mg/m² docetaxel and 4 g/m² ifosfamide. Based on clinical side effect profiles, a dose of 75 mg/m² docetaxel combined with 5 g/m² ifosfamide was recommended for further studies. In a recent study, combining the two drugs at high doses did not change their respective plasma half-lives (10). The sequence of drug administration did not affect the clearance or the AUC of docetaxel.

The mean docetaxel clearance was 19.9 ± 3.0 l/h/m² when docetaxel was given immediately prior to ifosfamide infusion (cycle 1) and 21.9 ± 4.4 l/h/m² when given immediately thereafter (cycle 2). In this study, the pharmacokinetics of docetaxel were not influenced by the coadministration of ifosfamide, whatever the sequence of administration.

In an inpatient setting both sequences can be considered practical and easily adjustable to clinical practice. However, three patients showed transient disorientation after the first cycle of treatment with a

sequence of docetaxel followed by ifosfamide, which they did not exhibit in the reversed sequence cycle. Our recommendation for further phase II studies is a sequence of ifosfamide followed by low-dose docetaxel. As such a regimen is well tolerated and practical and as there is evidence of its antitumor activity, we have already initiated a phase II study.

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No Additional Benefit of Adding Ifosfamide to Docetaxel in Castration-resistant Metastatic Prostate Cancer

PETTERI HERVONEN, TAPIO TULIJOKI and PIRKKO KELLOKUMPU-LEHTINEN

Department of Oncology, Tampere University Hospital and Tampere University, Tampere, Finland

Abstract. *Background:* In the treatment of many types of cancer, combination chemotherapy has been shown to be better than single-agent chemotherapy. The aim of our phase I-II clinical trial was to assess the efficacy and toxicity of docetaxel-ifosfamide combination chemotherapy in patients with castration-resistant metastatic prostate cancer (CRPC). *Patients and Methods:* A total of 31 patients were enrolled to receive first-line chemotherapy consisting of 40-60 mg/m² docetaxel followed by 3.0 g/m² ifosfamide with mesna. All drugs were administered intravenously. The maximum duration of the chemotherapy was six cycles. The median age of the patients was 70 (range 58-82) years. Prostate specific antigen (PSA) responses were determined according to the PSA working group guidelines and all toxicities, time-to-progression and overall survival were determined according to the WHO criteria. *Results:* The objective PSA response rate was 32% in 11/31 patients. The mean PSA value at baseline was 300 (range 2.5-1577) µg/l. The overall median survival was 14.1 months; 15 patients were alive at a median follow-up time of 18 months. The observed side-effects were as expected, with grade 3-4 neutropenia developing in 38% of the cycles, whereas febrile neutropenia occurred in only 12% of the patients. The median number of administered cycles was 4.8. No acute hypersensitivity reactions were observed. Transient renal insufficiency developed in two patients, thus necessitating dose reductions. *Conclusion:* The combination of docetaxel and ifosfamide seems to be well-tolerated and has some activity in patients with CRPC. However, newer docetaxel-based combination chemotherapy regimens need to be further developed in order to provide more efficacious and well-tolerated treatment options for earlier phases of CRPC.

Correspondence to: Petteri Hervonen, Tampere University Hospital, Tampere, Finland. Tel: +358 331163456, Fax: +358 331163009, e-mail: petteri.hervonen@uta.fi

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Castration-resistant prostate cancer (CRPC) often presents with a clinical picture of multiple bone metastases, a deteriorating overall performance and a life expectancy of approximately 12 months (1, 2). This stage of the disease is frequently preceded by a transient but positive response to hormonal therapy. Taxane-based chemotherapy plays a key role in the treatment of CRPC (3, 4). The majority of patients who initially respond to chemotherapy become resistant and then enter a chemotherapy-resistant final stage.

Docetaxel is a semisynthetic taxoid that is widely indicated for use in the adjuvant and metastatic settings in the treatment of malignancies such as breast (5-7), lung (8-10) and ovarian cancer (11-13). A significant antineoplastic activity with an overall survival benefit with docetaxel-prednisone or docetaxel and estramustine, compared to mitoxantrone and prednisone in CRPC was demonstrated in two large randomized multicenter phase III studies (3, 4). As a result of these studies, docetaxel at 75 mg/m² is accepted as the drug of choice for the first-line, single-agent treatment of CRPC.

Docetaxel-based combinations with other chemotherapeutic agents such as vinorelbine, carboplatin and calcitriol have been studied, with promising results (14-16). The synergistic *in vivo* antineoplastic action of two or more chemotherapeutic agents administered at well-tolerated doses is essential for further improvement in results. Furthermore, the toxicity profiles of the combined drugs must be well-documented to avoid any unexpected additive or cumulative toxicities.

The major dose-limiting toxicity of docetaxel is dose-dependent and is typically transient neutropenia; other toxicities include alopecia, gastrointestinal symptoms, asthenia, hypersensitivity reactions, skin reactions, nail discoloration, sensory neuropathy and fluid retention (17-19). The docetaxel administration schedule is currently under intensive study to further reduce the level of toxicities without compromising its antineoplastic activity (20).

Ifosfamide is an alkylating agent with an antineoplastic effect against multiple solid tumor types, including non-small cell lung, testicular and breast cancer and sarcoma (21-23). The toxicity profile of ifosfamide involves mainly dose-dependent and transient urotoxicity, nephrotoxicity, neurotoxicity, myelosuppression, nausea and alopecia.

Standard single-agent doses range between 5 and 10 g/m², administered as a 24-hour infusion in most cases (25-27).

The majority of patients entering the castration-resistant stage of the prostate cancer face have a greatly limited life expectancy, and most experience a decrease in their quality of life due to fatigue, asthenia, anemia, cachexia, pain and bone-related events such as pathological fractures (1,2). The most important goal of treatment in CRPC remains palliation of symptomatic patients and postponement of the often inevitable decline in the quality of life. The majority of patients who are diagnosed with CRPC are elderly and often present with other chronic systemic diseases, such as diabetes mellitus; therefore, a better-tolerated, safer and more effective combination chemotherapy regimen is required.

Docetaxel and ifosfamide differ in their mechanisms of antineoplastic action and toxicity profiles; therefore, this phase I dose escalation study was continued as a phase II combination study in the treatment of CRPC. The pharmacokinetic interactions of docetaxel and ifosfamide have been previously studied. When docetaxel was administered to patients with advanced solid tumors at a higher dose (85 mg/m²) in a 1-h infusion immediately followed by ifosfamide in a 24-h infusion (5 g/m²), no pharmacokinetic interactions between docetaxel and ifosfamide were observed (8). Furthermore, the clearance of docetaxel was not modified by the co-administration of ifosfamide, even though docetaxel is metabolized by cytochrome 3A4 (CYP3A4) (28) and ifosfamide is metabolized by CYP3A and CYP2B (29). Because docetaxel is now widely accepted as a standard of care in this setting, it is clear that not all patients respond to treatment with docetaxel alone or stated otherwise, become resistant to chemotherapy. Thus, it becomes vital to develop suitable combination therapies and options for second-line palliative treatment for patients with favorable performance status.

Patients and Methods

This was a non-randomized, phase I-II study. Docetaxel-ifosfamide combination chemotherapy was administered to 31 eligible patients. The requirements for participation were CRPC with documented metastasis, a confirmed rising (PSA) in two separate measurements during androgen ablation (either with castration or with luteinizing hormone-releasing analogue), an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, and written informed consent.

Other inclusion criteria were the following: adequate renal function (serum creatinine <2 × normal) and adequate hepatic function (alanine aminotransferase <2 × normal) at baseline, no other serious illnesses and an estimated life expectancy of at least 6 months. Patients' characteristics such as previous treatment, sites of metastasis, significant co-morbidities and duration of response to hormonal treatment are presented in Table I.

Treatment schedule. Chemotherapy was administered in an in-patient setting due to the 24-h ifosfamide infusion. Adequate renal

Table I. Patients' characteristics.

Mean age at diagnosis, years	66.9 (range 55-80) years
Mean age at treatment, years	70.2 (range 58-82) years
Prior orchiectomy, n (%)	5 (16.1)
Prior LHRH treatment, n (%)	25 (83.3)
Prior anti-androgen treatment n, (%)	24 (77.4)
Median duration of anti-androgen treatment, months 34.6 (range 2-90)	
0 to 12 months, n (%)	11 (36%)
12 to 24 months, n (%)	4 (13%)
Longer than 24 months, n (%)	16 (51%)
Prior estramustine treatment, n (%)	6 (19%)
Prior radiation therapy of prostate, n (%)	3 (9%)
Prior palliative radiation therapy of bone, n (%)	16 (51%)
Analgesics: use of opiates at baseline, n (%)	6 (19%)
Use of other medication for pain relief, n (%)	21 (68%)
Bone metastasis, n (%)	30 (97%)
Other metastasis, n (%)	4 (13%)

function was determined by creatinine clearance measurements before every cycle. Docetaxel was administered as a 1-h infusion with routine premedication of oral dexamethasone. The treatment was repeated every three weeks for a maximum of six cycles.

Dose modifications. The starting dose of docetaxel was 40 mg/m² and was increased to 50 and 60 mg/m² after a minimum of three patients had tolerated the previous dose. In cases of any grade 3-4 hematological or non-hematological toxicities, the dose was reduced to the previous lower level. The ifosfamide dose was not modified to enable analysis of docetaxel-induced toxicity. Toxicities were evaluated according to the NCI Common Toxicity Criteria.

Criteria for response. PSA responses were based on the PSA Working Group guidelines. Complete response was defined as normalization of PSA; a partial response was defined as at least a 50% decrease from baseline; stable disease was defined as a decrease of less than 50% or an increase of less than 25%; and progression was defined as an increase of more than 25%. All responses were confirmed by a secondary measurement.

Statistical analysis. This was a non-randomized phase I-II dose-finding study. All patients who underwent at least one cycle of chemotherapy were included in the toxicity analyses, and all patients were included in the overall response rate and survival calculations. Overall survival was defined as the time between the first treatment and death; the time to progression was defined as the time between the first treatment and either PSA progression or another objective marker of progression of disease, the end of follow-up or the start of other antitumor treatment.

Results

Baseline patients' characteristics are presented in Table I. The patients had a median age of 67 years and a median performance status of 1 (ECOG scale). All patients exhibited progression of disease during androgen therapy, and all but

Table II. *Other phase II studies of docetaxel combination therapy.*

Author (ref)	Year	No of patients	Treatment	PSA response rate
Safarinejad <i>et al.</i> (32)	2005	42	D + EMP + SURAM	30.5%
Goodin <i>et al.</i> (14)	2005	40	D + VIN + filgrastin	27-39%
Ryan <i>et al.</i> (31)	2005	34	D + Exisulind	38%
Picus <i>et al.</i> (33)	2011	79	D + Bevacizumab + EMP	75%
Zurita <i>et al.</i> (34)	2009	25	D + Sunitinib + Prednisone	56%
Dahut <i>et al.</i> (35)	2004	75	D + Thalidomide	53%

VIN, Vinorelbine; EMP, estramustine phosphate; D, docetaxel; SURAM, suramin.

one had bone metastasis. The median baseline PSA level was 300 (range 2.5-1577) $\mu\text{g/l}$.

A total of 29 patients were treated per protocol. The median time from the start of primary hormonal therapy to castration-resistant disease was 34.6 (range 2-90) months.

The median number of combination chemotherapy cycles was 4.8 (range 1-6).

The most common hematological toxicity that resulted in dose reductions was grade 3-4 neutropenia in 9 (29%) patients and in 38% of the cycles, respectively. Febrile neutropenia occurred in only 4% of cycles. Transient renal insufficiency (grade 3) resulting in a 20% dose reduction of ifosfamide was observed in three cycles in two patients.

After the first cycle of chemotherapy, one patient was diagnosed with acute subdural hematoma that did not coincide with any trauma or thrombocytopenia; this situation necessitated the discontinuation of treatment. Another patient also underwent only one cycle of treatment due to their rapidly deteriorating overall condition and a subsequent need for palliative bone irradiation.

As regards to antitumor activity, ten patients (32%) exhibited a >50% decrease in PSA from the baseline level. The median time to PSA progression was 6.3 months.

The median survival for all patients was 14.1 months, and the median survival for PSA responders was 16.5 months; 15 patients were still alive after a median follow-up of 18 months.

Discussion

The treatment of CRPC has developed rapidly, and prior standard treatment regimens with demonstrated palliative benefit have been appropriately revised in the light of recent results from docetaxel-based chemotherapy trials (3, 4).

Although a higher percentage of patients now respond to novel treatment strategies and the often inevitable disease progression is postponed, there is still a growing need for a better-tolerated combination chemotherapy regimen that is suitable for older, more fragile patients with chronic comorbidities that limit the use of standard doses of docetaxel.

The increase in antitumor activity observed with more intensive chemotherapy appears to cause unacceptable toxicity and morbidity in these patients. The fatigue and neutropenia associated with docetaxel as well as the renal insufficiency associated with ifosfamide are dose-limiting and dose-dependent.

The results of this study are comparable to those of the other phase II chemotherapy studies in CRPC, presented in Table II (14, 30-35). The study treatment was well-tolerated and anti-tumor efficacy was notable. There was a low incidence of drug-associated toxicity leading to treatment discontinuation. The response to hormonal manipulations after the primary diagnosis was limited; disease in 49% of patients had progressed during the first 24 months and 36% had developed a castration-resistant stage of the disease within the first 12 months of hormonal treatment.

The patient population in this study was best characterized by a short response to hormonal therapy, symptomatic disease requiring analgesic medication and radiotherapy and a very high median baseline PSA level compared to the baseline PSA level of 108-114 $\mu\text{g/ml}$ in the TAX 327 study (3) and to the 84-90 $\mu\text{g/ml}$ level in the SWOG trial (4).

Patients in the TAX 327 study were required to have stable levels of pain for at least seven days before randomization, and 45% had pain at baseline. More than half 16/31 (51.6%) of our study population were treated with palliative radiation therapy for bone pain prior to study treatment; 19% had analgesic opioid treatment at baseline, and 68% experienced pain at baseline. These characteristics are typical of the patient population in normal clinical practice and underline the need for well-tolerated therapy. Novel combination therapies including sunitinib and bevacizumab, although well-tolerated, have not shown significant additional benefit. Compared to the patient population in the two largest randomized trials, our study patient population had more advanced disease. The treatment was well-tolerated and can be used in different types of combinations in the future, as our results are comparable to those of other phase II studies that investigated alternative chemotherapy agents.

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Biweekly Docetaxel Is Better Tolerated than Conventional Three-weekly Dosing for Advanced Hormone-refractory Prostate Cancer

PETTERI HERVONEN¹, HEIKKI JOENSUU², TIMO JOENSUU³, GINMAN CLAES⁴, MCDERMOTT RAY⁵, HARMENBERG ULRIKA⁶, NYANDOTO PAUL⁷, LUUKKAALA TIINA⁸, HEMMINKI AKSELI⁹, ZAITSEV IGOR¹⁰, HEIKKINEN MIRJA¹¹, NILSSON STEN¹², LUUKKAA MARJAANA¹³, LEHTINEN ILARI¹⁴ and KELLOKUMPU-LEHTINEN PIRKKO-LIISA¹⁵

^{1,15}Tampere University Hospital, Department of Oncology, Tampere, Finland;

²University of Helsinki, Department of Oncology, Helsinki, Finland;

^{3,9}Docrates Clinic, Helsinki, Finland;

⁴Karlstad Central Hospital, Department of Oncology, Karlstad, Sweden;

⁵McDermott Ray, Ireland Cooperative Oncology Research Group ICORG, Dublin, Ireland;

^{6,12}Karolinska University Hospital, Department of Oncology Stockholm, Sweden;

^{7,10}Päijät-Häme Central Hospital, Department of Oncology, Lahti, Finland;

^{8,14}University of Tampere, Tampere, Finland;

¹¹Oulu University Hospital, Department of Oncology, Oulu, Finland;

¹³Turku University Hospital, Department of Oncology, Turku, Finland

Abstract. *Background:* Docetaxel administered every three weeks is the standard treatment for advanced hormone-refractory prostate cancer (HRPC). However, biweekly administration might be better tolerated due to the reduced peak drug concentrations. Therefore, we compared biweekly to triweekly docetaxel as first- or second-line chemotherapy for advanced HRPC in this prospective randomized multicenter trial. *Patients and Methods:* In this study, 360 patients were randomly allocated to receive docetaxel 75 mg/m² i.v. d1 q3 weeks (tT) or 50 mg/m² i.v. d1 and d 14, q4 weeks (bT) from March 2004 to May 2009. Oral prednisolone (10 mg/day) was administered in both groups. The groups were well balanced according to the WHO performance status in terms of mean age (70 vs. 68, range 45-87 years) and median serum PSA level at the time of study entry (109 vs. 98 µg/l, range 11-1490 µg/l). The primary endpoint was time to treatment failure (TTF). *Clinical Trials.gov study identifier:* NCT00255606. *Results:* Ultimately, 158 patients (tT=79; bT=79) were included in this preplanned interim safety analysis; 567 and 487 cycles (equivalent to 1701 and 1948 weeks of treatment) were administered in the tT and bT

groups, respectively. The most common grade 3-4 adverse events (expressed as %/cycles) in tT /bT were neutropenia 20%/14%; infection with/without neutropenia 8%/3%; fatigue 3%/3%; febrile neutropenia 2%/1%; and bone pain 2%/1%. Serious adverse events occurred more frequently in the group tT (n=60, 10.6% of cycles) than in the group bT (n=29, 6.0%, p=0.012). One patient died due to coronary infarction, and another was diagnosed with acute lymphocytic leukemia (both in the bT group). Thirty patients (38%) in the bT group and 22 patients (28%) in the tT group were still receiving treatment at 6 months (p=0.176). *Conclusion:* Biweekly docetaxel was tolerated better than conventional triweekly with fewer serious adverse events and more patients were still on the therapy at 6 months. Biweekly docetaxel therapy might be considered as an option for elderly patients exhibiting a compromised general condition.

Prostate cancer is the most common type of cancer among men in Western countries. While there are many options for the treatment of localized prostate cancer, the optimal treatment of hormone-refractory prostate cancer (HRPC) warrants further investigation (1).

Docetaxel-based chemotherapy is considered the standard treatment for HRPC due to its ability to achieve progression-free survival and provide an overall survival benefit as well as a significant improvement in bone pain palliation and quality of life as compared to mitoxantrone plus prednisone in two randomized phase III studies (2, 3). Docetaxel-based

Correspondence to: Petteri Hervonen, Tampere University Hospital, Tampere, Finland. Tel: +358 331163456, Fax: +358 331163009, e-mail: petteri.hervonen@uta.fi

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Table I. *Patient characteristics.*

Baseline characteristics	Group bT: docetaxel 50 mg/m ²	Group tT: docetaxel 75 mg/m ²
Mean Age (years)	68 (46-84)	70 (44-86)
Mean PSA (ng/ml)	98 (11-1490)	109 (10-964)
WHO performance status		
0	25%	25%
1	65%	65%
Site of metastasis: Bone (n)	72	73
Liver metastasis (n)	6	6
Lung metastasis (n)	3	6
Lymph node metastasis (n)	26	26
Other metastasis (n)	6	4
Mean Alkaline phosphatase AFOS (range)	251 (42-1489)	263 (33-1487)

chemotherapy has been investigated in combination with estramustine phosphate, which resulted in only modest efficacy at the expense of increased gastrointestinal and thromboembolic complications (4). However, with this therapy, the median survival does not exceed 20 months, and treatment with docetaxel is associated with many toxicities, which should be taken into account when treating an elderly patient population. Patients with lower performance status and pain have been shown to have shorter survival when treated with docetaxel.

Docetaxel administration with a standard three-weekly schedule and dosing of 75 mg/m² is associated with grade 3 or 4 neutropenia in up to one third of patients. Other common adverse events include fatigue (53%), nausea and vomiting (42%) and diarrhea (32%)(5). The majority of patients with advanced prostate cancer are treated with long-term anti-androgen therapy and, typically, with maximal androgen blockade prior to chemotherapy, which often results in osteopenia, anemia, lowered performance status and fatigue at baseline. Treatment-related side-effects, comorbidities common in elderly patients and disease-related symptoms such as pain and fatigue play major roles in determining the optimal approach to palliative chemotherapy for HRPC for a given individual (6, 7).

The addition of antiangiogenic treatments such as bevacizumab or sunitinib to docetaxel chemotherapy has not proven beneficial (8-10). Recently, abiraterone and cabazitaxel were approved for the second-line treatment of docetaxel-resistant HRPC. Cabazitaxel seems to be beneficial and well-tolerated even after docetaxel treatment in a carefully selected study patient population. However, while grade >3 neutropenia occurred in 82% of patients, only 8% of patients exhibited febrile neutropenia. However, cabazitaxel-treated patients had a higher risk of death within 30 days of the last dose than those treated with mitoxantrone (11). Dose reduction was three times more common in cabazitaxel-treated patients.

Even today the optimal scheduling of an efficacious and safe first-line docetaxel-based chemotherapy regimen remains investigational. Better-tolerated treatments should be evaluated for the treatment of patients with advanced HRPC in common clinical practice (11, 12).

The purpose of the study was to develop an effective and well-tolerated treatment for this elderly patient population. We compared the safety and efficacy of a standard three-weekly schedule of docetaxel plus prednisone to an investigational arm of biweekly docetaxel plus prednisone as first-line chemotherapy of advanced HRPC. The preplanned interim safety results are reported here.

Materials and Methods

Patient selection. From March 2004 to May 2009, 360 patients with advanced HRPC were randomized to receive docetaxel-based chemotherapy in nine collaborating study centers in Finland, Sweden and Ireland; 158 patients were included in this preplanned interim safety analysis.

Eligible patients had confirmed adenocarcinoma of the prostate with metastasis and exhibited elevated serum PSA >10 µg/l during treatment with hormonal therapy, good performance status (<2 WHO), adequate renal and hepatic function and laboratory values including hemoglobin >11.0 g/dl, creatinine <1.5 times the upper limit and aminotransferase <2.5 times the upper limit. All patients had castrate levels of testosterone prior to treatment. The patient characteristics at baseline are presented in Table I.

All patients provided their written informed consent, and the study was approved by the Ethics Committee. The primary endpoint was the time to treatment failure (TTF), which was defined as the time interval from the date of randomization to the date of progression of the disease, unacceptable toxicity, the patient's refusal to continue treatment, or death.

The secondary endpoints were quality of life, response rates, safety and overall survival. Overall survival was calculated from the date of randomization to the date of death.

Patients were centrally randomly assigned to receive docetaxel at 75 mg/m² intravenously on day 1 every 3 weeks group or docetaxel 50 mg/m² intravenously on days 1 and 14 every 4 weeks group;

therefore, the cumulative dose (*i.e.*, 12 weeks) was identical. Continuous oral prednisolone (10 mg) daily and premedication with oral dexamethasone (7.5 mg twice daily for 3 days, starting 12 h before docetaxel, was also administered in both treatment groups. The prophylactic administration of G-CSF was not routinely performed.

All patients were evaluated for myelosuppression, renal and hepatic dysfunction and adverse events before the start of each treatment cycle and when clinically indicated. There was no predetermined maximal number of chemotherapy cycles. Each patient's medical history was recorded at baseline, and physical examinations and laboratory measurements were performed. Pretreatment evaluation of disease staging was performed using computed tomography and bone scanning.

Tumor response was assessed according to Response Evaluation Criteria In Solid Tumors (RECIST) every 12 weeks using computed tomography for lesions determined to be measurable at baseline, and the responses were confirmed within 4 weeks. Toxicities for every treatment cycle in both arms were evaluated according to the National Cancer Institute- Common Terminology Criteria of Adverse Events (NCI-CTCAE) statistical analysis software, version 3.0.

Interim hematological toxicity analysis was performed when 50 patients had participated in the trial for at least 3 months. The toxicity and tolerability of the two treatment arms were analyzed based on a reduction in the frequency of grade 3-4 side-effects from 40% to 20% using $\alpha=0.05$ and $\beta=0.20$. Seventy-nine patients were required in each arm for a total of 158 patients. The results of this pre-planned interim analysis are published separately from the final efficacy analysis.

Results

One hundred and fifty-eight patients were included in this preplanned safety analysis. The patient characteristics were well balanced between the treatment groups at baseline. The baseline PSA, age and type of metastasis are presented in Table I. The duration of the treatment is often associated with cumulative side effects. Seventy-nine patients in the tT group received a total of 567 cycles every three weeks, and 79 patients in the bT group received a total of 487 cycles every four weeks. Therefore, the overall length of treatment was 1701 and 1948 weeks, respectively, suggesting that therapy in the pT group was tolerated as least as well as in the tT group.

The most common ($\geq 10\%$ of cycles) grade 1-2 non-hematological adverse events were quite evenly distributed (biweekly *vs.* triweekly, expressed as % of the cycles): fatigue, 62/49; alopecia, 75/81; nail changes, 12/10; anorexia, 10/10; diarrhea, 13/12; stomatitis, 15/16; neuromotor, 29/19; tearing, 42/41; arthralgia, 14/14; bone pain, 33/31; myalgia, 13/15; and pain, 32/33.

There were significantly more patients receiving the study treatment for at least 6 months in the bT group (38%) than in the tT group (28). The most common grade 3-4 adverse events are presented in Table II. Serious adverse events were reported more frequently in the tT group (60 reports, 10.6 % of cycles) than in the bT group (29 reports, 6.0% cycles).

Table II. Grade 3-4 adverse events.

Grade 3-4 adverse events	bT Group % of cycle given	tT Group % of cycles given
Neutropenia	14	20
Infection with/without neutropenia	3	8
Leukopenia	3	8
Febrile neutropenia	1	2
Fatigue	3	3
Bone pain	1	2
Pain	2	1

One patient died of coronary infarction, and another patient was diagnosed with acute myelocytic leukemia after two cycles of treatment. Both patients were in the bT group.

Discussion

Docetaxel chemotherapy remains the standard treatment option for metastatic HRPC, although several new treatment options are currently being approved for the second-line treatment of docetaxel-resistant prostate cancer (13). Docetaxel chemotherapy is often associated with dose-limiting toxicity, mainly neutropenia, neuropathy and treatment-related fatigue, especially in elderly patients.

Biweekly docetaxel chemotherapy seems to be a well-tolerated and safe chemotherapy regimen for the treatment of HRPC. Grade 3-4 neutropenia occurred in only 14% of patients and was very rarely associated with an infection that required hospitalization. In the TAX 327 study (5), there was less febrile neutropenia than was observed in our tT group, which could be explained by the presence of more advanced disease in our study population, or by factors related to genetic variants in different populations.

In addition to the number of hospitalizations due to febrile neutropenia or infection, the patients in the biweekly arm reported fewer serious adverse events that extended the duration of treatment. The bT regimen could represent an option for the active treatment of elderly patients that present with co-morbidities and compromised performance status.

Historically, the combination of other agents with docetaxel has yielded disappointment, even in large randomized trials. Therefore, novel approaches to reverse drug resistance in castration-resistant prostate cancer should be explored (14, 15).

Conclusion

As patients present with different characteristics at the time of HRPC diagnosis, the treatment options and optimal chemotherapy regimen should be versatile and adapted to each

individual patient. The biweekly docetaxel chemotherapy regimen offers a safe and well-tolerated option for the administration of chemotherapy to our prostate-cancer patients. It will be important to study whether efficacy is sustained in the bT arm in comparison to the arm involving treatment with the standard tT regimen.

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