Pharmacotherapeutic and pharmaco-economic value of docetaxel

for the treatment of prostate cancer

Dossier status: **Final dossier**
Date: 8 March 2011

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Abbreviations

ADT	Androgen Deprivation Therapy
BSC	Best Supportive Care
CI	Confidence Interval
CRPC	Castration-Resistant Prostate Carcinoma
CTC	Circulating Tumor Cells
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
EMEA	European Medicines Agency
ESMO	European Society for Medical Oncology
EVPI	Expected Value of Perfect Information
EVPIM	Expected Value of Perfect Implementation
FDA	United States Food and Drug Administration
HR	Hazard Ratio
ICER	Incremental Cost-Effectiveness Ratio
IKNL	Integraal Kankercentrum Nederland
LHRH	Luteinizing-Hormone-Releasing Hormone
LYG	Life-Years Gained
NCCN	National Comprehensive Cancer Network
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
ORR	Objective Response Rate
OS	Overall Survival
PFS	Progression Free Survival
PSA	Prostate Specific Antigen
QALY	Quality Adjusted Life Year
SPC	Summary of Product Characteristics
SRE	Skeletal Related Event
TNM	T primary tumor N regional lymph nodes M distant metastasis
TTP	Time To Progression
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organisation

Samenvatting

Nederlandse samenvatting

Inleiding
Prostaatcarcinoom is in Nederland de meest voorkomende vorm van kanker bij mannen. In 2008 was de incidentie 9559 nieuwe patiënten. De meeste patiënten hebben gelokaliseerde ziekte (Stadium I en II) en de prognose is dan zeer goed (5-jaars overleving bijna 100%, de meeste mensen overleven de ziekte). Indien prostaatcarcinoom is gemetastaseerd, is genezing niet meer mogelijk. De 5-jaarsoverleving van gemetastaseerd prostaatcarcinoom is 45%. Behandeling van gemetastaseerde ziekte bestaat uit hormonale therapie (het onderdrukken van testosteron, een belangrijke groeifactor voor prostaatcarcinoom). Meestal wordt de tumor progressief binnen twee jaar na het starten van hormonale therapie. Deze fase wordt castratie-resistent prostaatcarcinoom (CRPC) genoemd. De behandeling van CRPC is gericht op symptoombestrijding (radiotherapie, radionucleiden, bisfosfonaten, pijnstilling) en levensverlenging (hormonale therapie en chemotherapie).

Methoden
Om de farmacotherapeutische waarde van docetaxel en andere middelen voor CRPC vast te stellen onderzochten wij de klinische effectiviteit, kosten-effectiviteit en veiligheid van deze middelen in een literatuur onderzoek. Om het gebruik van deze middelen in de dagelijkse praktijk in Nederland te onderzoeken hebben wij medisch oncologen geïnterviewd en apothekers en patiënten betrokken. Ter illustratie evalueerden wij de behandelkeuzes in een academisch centrum. Tevens berekenden wij ter illustratie het werkelijke kostenbeslag van docetaxel in Nederland voor de indicatie prostaatcarcinoom.

Klinische effectiviteit
Er zijn verschillende behandelmogelijkheden voor patiënten met CRPC. De hormonale therapie wordt altijd voortgezet. In de jaren ’90 bestond de behandeling van symptomatisch CRPC uit mitoxantrone chemotherapie, dat geen overlevingswinst gaf maar wel de kwaliteit van leven verbeterde. In 2004 werd aangetoond dat docetaxel (in een 3-wekelijks schema, dosering 75 mg/m2 per infusie) de overleving significant verbeterde in vergelijking met mitoxantrone (mediane overlevingswinst 2.9 maanden) Docetaxel verbeterde ook de kwaliteit van leven, met een acceptabel bijwerkingenprofiel.

Alternatieve chemotherapie opties bestaan uit mitoxantrone of docetaxel in een wekelijks schema. Bij progressieve ziekte na een interval van minimaal drie maanden na succesvolle behandeling met docetaxel wordt docetaxel in de praktijk vaak opnieuw ingezet. Recent zijn er een aantal belangrijke en veelbelovende ontwikkelingen gaande: voor cabazitaxel, een nieuw middel uit de zelfde klasse als docetaxel, werd recent een overlevingsvoordeel aangetoond in vergelijking met mitoxantrone als tweedelijns behandeling na docetaxel voor CRPC patiënten. Behandeling met cabazitaxel gaf wel meer bijwerkingen. Van studies naar nieuwe hormonale behandelmogelijkheden in zowel eerste als tweede lijn worden binnenkort resultaten verwacht: de verwachting is dat abiraterone binnenkort een plaats zal krijgen in de behandeling van CRPC. Immunologische behandeling met autologe vaccinaties (Sipuleucel-T) is weliswaar erg kostbaar maar gaf wel een overlevingsvoordeel in minimaal symptomatische CRPC patiënten. Andere immunologische behandelingen worden momenteel onderzocht.

Richtlijnen
De Nederlandse richtlijn voor behandeling van prostaatcarcinoom is gedateerd (Oncoline, 2007). De plaats van docetaxel in de behandeling van CRPC in de Nederlandse, Europese (ESMO) en Amerikaanse (NCCN) richtlijn is niet verschillend. In de Amerikaanse richtlijn is het inzetten van Sipuleucel-T en cabazitaxel al opgenomen.

Kosten-effectiviteit
Er zijn meerdere kosten-effectiviteit evaluaties uitgevoerd. Mitoxantrone als eerste-lijns behandeling domineert prednison in een Canadese evaluatie uit 1998. Docetaxel is kosten-effectief bij een drempel van ongeveer €38,000 bij extrapolatie van de data van de NICE evaluatie uit 2007. De kosten van docetaxel zijn recent gedaald bij het beschikbaar komen van generieke preparaten. Er zijn geen evaluaties gepubliceerd over de kosten-effectiviteit van cabazitaxel en mitoxantrone als tweede-lijns behandeling. Er zijn ook geen evaluaties bekend betreffende de Nederlandse situatie.

Ervaring, gebruiksgemak en bijwerkingen
Er is ruime ervaring met docetaxel. Docetaxel wordt meestal 3-wekelijks toegediend in dagbehandeling op de polikliniek. De belangrijkste bijwerkingen zijn neutropenie en neuropathie. De behandeling met docetaxel wordt meestal goed verdragen. Er worden 10 kuren toegediend, tenzij eerder progressieve ziekte wordt aangetoond of er limiterende bijwerkingen zijn. Leeftijd is op zichzelf geen contra-indicatie voor chemotherapie. Bij het selecteren van de groep patiënten die baat heeft van chemotherapie is meewegen van de co-morbiditeit van belang.

Dagelijkse praktijk
In de dagelijkse praktijk worden mannen met prostaatcarcinoom aanvankelijk door de uroloog behandeld. Er lijkt op basis van onze interviews een relevant percentage van patiënten door urologen te worden behandeld met tweede-lijns hormonale therapie (estramustine) alvorens verwijzing naar de medisch oncoloog plaatsvindt. Tevens wordt een deel van de patiënten door urologen niet verwezen omdat zij deze patiënten ongeschikt achten voor chemotherapie. Het is onbekend hoe groot deze groep is en wat de gevolgen hiervan zijn. Docetaxel in 3-wekelijks schema is de eerste keus behandeling van CRPC. Er is geen consensus over tweede-lijns behandeling. In sommige klinieken wordt mitoxantrone voorgeschreven, in andere niet. Behandeling in studieverband is dan het alternatief. Docetaxel in wekelijks schema wordt niet in alle klinieken ingezet. Geriatrische consultatie wordt in enkele ziekenhuizen gebruikt om patiënten die geschikt zijn voor chemotherapie beter te selecteren.

Input van patiënten
Voor patiënten is er een keuze in behandelmogelijkheden (wel of geen behandeling, chemotherapie of hormonale of immunologische behandeling, behandeling in studieverband of niet, etc). Volledige en objectieve informatieverstrekking is daarom belangrijk in de begeleiding van patiënten.

Werkelijk kostenbeslag en generieke producten
In 2010 kwamen generieke preparaten van docetaxel beschikbaar. De prijs van docetaxel (80mg vial) bedraagt thans €705-€737. Een illustratieve berekening van het werkelijk kostenbeslag van docetaxel voor prostaatcarcinoom in Nederland is door ons uitgevoerd op basis van alleen de geneesmiddelkosten zonder BTW. De totale kosten voor docetaxel in de eerste-lijns palliatieve behandeling bedragen €6,682,200 (variatie in sensitiviteits analyse €2,863,800 tot €12,887,100).

Lacunes

- Evaluatie klinische en kosten-effectiviteit van behandeling in de tweede lijn met docetaxel na eerdere respons op docetaxel versus cabazitaxel
- Evaluatie van de sequentie van (nieuwe) beschikbare behandelingen in 1e en 2e lijn
- Evaluatie van kosten-effectiviteit van nieuwe behandelmogelijkheden en docetaxel in de Nederlandse situatie
- Evaluatie van interventies om doelmatigheid te vergroten, zoals geriatrische evaluatie.
- Evaluatie van adherentie aan richtlijnen, met name ook door urologen, en verwijspatronen naar medisch oncologen
- Evaluatie van patiënt tevredenheid omtrent informatievoorziening en begeleiding bij het maken van behandelkeuzes

Summary

Research question

1. To evaluate the pharmacotherapeutic value of docetaxel and other anticancer agents for the treatment of prostate cancer, in terms of effectiveness, cost-effectiveness, adverse effects, safety and clinical implications.
2. To evaluate the use of docetaxel and other anticancer agents in Dutch clinical practice.

Methods

Systematic review of literature concerning effectiveness
Systematic review of treatment protocols and guidelines
Systematic review of literature concerning cost-effectiveness
Structured interviews with clinical experts
Illustration of daily practice in one academic centre
Illustrative economic evaluation concerning direct costs of docetaxel in prostate cancer

Results and conclusion

Although prostate cancer is the second most common cause of cancer in men, the majority of patients will never develop metastatic disease. Approximately 10,000 patients are diagnosed with prostate cancer in the Netherlands each year. In 2008, 18.5% of prostate cancer patients were staged in stage IV and those patients will eventually develop castration-resistant prostate carcinoma (CRPC). Chemotherapy is indicated in metastatic CRPC only.

Clinical effectiveness
Evidence of clinical research implicates that docetaxel (regimen: 3-weekly 75 mg/m2) is currently the most effective agent in symptomatic CRPC, with significant improvement of survival (median survival benefit 2.9 months) and quality of life. Docetaxel has an acceptable toxicity profile when compared with mitoxantrone. Second-line chemotherapy with mitoxantrone is applied but only indirect evidence for the effectiveness is available. Recently, cabazitaxel was reported to significantly prolong survival over mitoxantrone in second-line therapy, but more toxicity was reported in the cabazitaxel-group. Sipuleucel-T (an autologous dendritic cell vaccine) has been reported to improve overall survival in asymptomatic or minimally symptomatic CRPC patients. Evaluation of novel hormonal (including abiraterone) and immunological therapies is ongoing.

Guidelines
The European (ESMO) and American (NCCN) guidelines have been updated recently and docetaxel is standard first-line therapy. In the NCCN guideline Sipuleucel-T is considered as first-line therapy in asymptomatic or minimally symptomatic CRPC patients. No consensus exists on second-line treatment. In the NCCN guideline mitoxantrone and cabazitaxel are considered appropriate second-line treatment options. In the ESMO guideline second-line treatment is not mentioned. The Dutch (Oncoline) guideline has been published in 2007 and is considered to be outdated.

Cost-effectiveness
Docetaxel is cost-effective when the willingness to pay is approximately €38,000 per QALY. These data are extrapolated from a NICE evaluation in the UK in 2007. Since

generic preparations have become available recently, it is expected that the costs of docetaxel will decrease. Mitoxantrone is both effective and cost-effective in palliation of symptomatic CRPC patients as first-line therapy. However, clinical effectiveness is inferior to docetaxel. No economic evaluations on cabazitaxel and second-line treatment in CRPC are currently available.

Experience, ease of use and toxicity
Experience with docetaxel is extensive. Docetaxel is used in cycles of 75 mg/m2 intravenously once every three weeks. Docetaxel is administered in the outpatient clinic. Docetaxel in a 3-weekly schedule is generally well tolerated. The most important dose-limiting side-effects are neutropenia and neuropathy. Docetaxel is generally discontinued after 10 cycles, or disease-progression, or dose-limiting toxicity. Age is not an absolute contra-indication. Clinical performance and comorbidity are the main parameters for selection of patients.

Daily practice
In daily practice, prostate cancer patients generally start treatment by an urologist and are referred to a medical oncologist in the course of the disease. Docetaxel for CRPC is widely used by medical oncologists, both as first-line treatment and as second-line rechallenge, when patients responded to docetaxel and at least 3 months interval. Some urologists delay the onset of therapy with docetaxel by prescribing estramustine, which impairs the delivery of optimal first-line chemotherapy to CRPC. Patterns of referral to medical oncologists differ in hospitals. The effect of withholding referral to patients is not known.

Cost-assessment
Generic preparations of docetaxel have become available in 2010. Direct costs of docetaxel (80 mg vial) are currently €705 to €737 in the Netherlands.
An illustrative calculation of annual direct costs of docetaxel for prostate cancer in the Netherlands was conducted (based on direct drugs costs only and no VAT included). The total costs of docetaxel for first-line palliative treatment in CRPC are €6,682,200 (range in sensitivity analyses €2,863,800 to €12,887,100).

Unexplored areas
Novel treatment strategies, including cabazitaxel and novel hormonal and immunological therapies, are likely to change treatment protocols and improve outcome in the near future. Robust cost-effectiveness evaluations are needed to optimally incorporate these treatment options into clinical practice. Adequate selection of patients for chemotherapy treatment in CRPC is challenging. Development and incorporation of tools for medical oncologists, including geriatric assessment, may improve this selection. Future research should also be directed at direct comparison of treatment options and evaluation of the optimal sequence of treatment options in CRPC. Evaluation of adherence to guidelines and referral patterns to medical oncologists is needed. Evaluation of patient's satisfaction and counselling in treatment choices are needed.

1. Introduction

1.1 Type of disease/disorder

Diagnosis
Prostate cancer is malignant transformation of the prostate gland. The prostate function is to produce fluid in semen en hence is only present in men. The primary risk factors for prostate cancer are increasing age and a positive family history. Most patients are asymptomatic at the moment of diagnosis. The diagnosis is suspected based on elevated PSA levels and abnormal digital rectal examination. The diagnosis is confirmed by positive histology on prostate biopsies. More than 95% of prostate tumors are adenocarcinoma. Prostate cancer can be graded according differentiation of the tumor. Well differentiated tumors have a low Gleason score (5-6) and produce PSA, while undifferentiated tumors (8-10) can produce low PSA levels which do not correspond with the extent of the disease. A high Gleason score is associated with poor prognosis (1;2). The prognostic Halabi-nomogram collects readily available clinical information (such as primary tumor Gleason score, performance status, PSA, lactate dehydrogenase, alkaline phosphatase, hemoglobin, and presence of visceral metastases) and divides patients into quartiles of risk with good discriminatory ability for median overall survival in men with CRPC (3).

Staging and management

Staging groups	TNM staging	Gleason score	Incidence in the Netherlands 2003-2007 (%) (4)	5-year survival in the Netherlands 2003-2007 (%) (4)
I	T1aN0M0	Gleason 2-4	1,4%	100%
II	T1aN0M0 T1b-2N0M0	Gleason >4 Any G	64,1%	99%
III	T3N0M0	Any G	15,5%	94%
IV	T4N0M0 Any T N1M0 Any T any N M1	Any G	18,5%	45%

Table 1 Staging in prostate cancer (5)

The extent of prostate cancer is classified into four stages (see Table 1). The majority of patients is diagnosed with early, localized disease (Stage I and II) and has a very good prognosis. Treatment consists of local therapy (surgery or radiotherapy) and most patients survive the disease. Since prostate cancer is driven by dihydrotestosterone, deprivation of testosterone to castration level is an active treatment option. Androgen deprivation therapy can be accomplished using LHRH-agonists or –antagonists (medical castration) or bilateral orchidectomy (surgical castration). Additional androgen deprivation can be reached with anti-androgen therapy, estrogens or steroids. Adjuvant hormone therapy is only applied after local radiotherapy in high risk groups. At Stage III the tumor is locally advanced. Treatment options are surgery (in selected patients only, T3a), radiotherapy, hormone therapy or combination therapy. Adjuvant hormone therapy after radiotherapy is beneficial in high risk groups.
A minority of patients present with metastatic disease (Stage IV) at diagnosis, and a further 20% of patients with localized disease will develop metastatic disease (6). These patients can not be cured and the treatment is palliative. First line treatment consists of hormone therapy (bilateral orchidectomy, LHRH-agonists or –antagonists, anti-androgens). In metastatic disease, the median response to hormone therapy is

approximately two years. When the disease is progressive despite a castration level of circulating androgens, this condition is called castration-resistant prostate cancer (CRPC).
After development of CRPC, survival with best supportive care is not expected to exceed 12 months. Hormone therapy is continued or may be replaced by second line hormone therapy (e.g. corticosteroids, estrogens, ketoconazole). Palliative analgesics, external beam radiation therapy, bisphosphonates (e.g. zoledronic acid) and radionucleides (e.g. samarium-153, strontium-90) are used to palliate skeletal events (pain, fractures or spinal cord compression). Chemotherapy is considered for symptomatic disease (1;2).There is a tendency to start chemotherapy earlier.

1.2 Dutch epidemiological data

Prostate cancer is the most common cause of cancer in men, except for non-melanoma skin cancer (7). The absolute annual incidence of prostate cancer in the Netherlands in 2008 is 9559 new patients, and the crude annual incidence is 117.5/100,000 (4). The crude annual incidence of prostate cancer in the European Union is 78.9/100,000 men (8). No exact figures of the Dutch national prevalence are currently available. However, the regional 10-years prevalence (1993-2004) in the IKNL Amsterdam region is 454/100,000 men (4). The absolute mortality caused by prostate cancer in the Netherlands in 2008 is 2421 deaths. Dutch prostate cancer mortality rates in 2008 are 25.2/100,000 (4), as compared to 39.6/100,000 in Europe (8). Incidence rates increase with higher age. In age group 35-39 years, the incidence is 0.5/100,000 men. This gradually increases to 725.3/100,000 men in age group 75-79 years. In men older than 80 years the incidence decreases (4).

Incidence rates increase with increasing age. In age group 35-39 years, the incidence is 0.5/100,000 men. This rate gradually increases to 725.3/100,000 men in age group 75-79 years. In men older than 80 years the incidence rate decreases (4). Screening and early detection have an important influence on the incidence of prostate cancer.

1.2.2 Burden of disease

Individual burden of disease
Local treatment of early stage prostate cancer may cause sexual dysfunction, infertility and incontinence. Radiotherapy may also cause radiation-induced enteropathy. Androgen suppression may cause gynaecomastia, osteoporosis and fractures, obesity and increased risk for cardiovascular disease and diabetes. The symptoms of CRPC may be related to local symptoms of compression of the urethra, metastases and adverse effects of treatment. Bone metastases of prostate cancer may cause pain, pathological fractures and spinal cord compression. Other specific problems are psychological problems, depression, anxiety and social stress (5).

Societal burden of disease
Since increasing age is the primary risk factor and the population is increased ageing, incidence rates are expected to increase (9). Early detection and treatment of prostate cancer that do not threaten life expectancy results in unnecessary side effects, which impair quality of life and health care expenses (5). In the UK, prostate cancer was responsible for almost 40,000 hospital episodes in 2003-4 (10). To our knowledge, no Dutch data on hospital episodes are available.

1.3 Registered indication of the drug

In the Netherlands, docetaxel (Taxotere, Sanofi Aventis; generic docetaxel), mitoxantrone (generic mitoxantrone) and estramustine (Estracyt, Pfizer) are licensed for the treatment of CRPC.

Docetaxel is licensed for the treatment of metastasized CRPC in combination with prednisone or prednisolone. The registration date of docetaxel (Taxotere, Sanofi Aventis) for breast cancer was in 1995, and for prostate cancer in 2004.

Mechanism of action
Docetaxel is a member of a class of drugs known as taxanes, derived from precursor extracted from the needles of the European yew tree, *Taxus baccata*. It is an inhibitor of tubulin depolymerization, causing inhibition of cell division and subsequently leading to cell death.

Dosing
Docetaxel is administered as a one-hour intravenous infusion once every three weeks, in the recommended dose of 75 mg/m2 during 10 cycles. This allows treatment in the out-patient clinic. Prednisone or prednisolone (prednisone is a prodrug of prednisolone and is considered equivalent to prednisolone) tablets are administered continuously, at 10 mg per day. Alternatively, 5 weekly docetaxel infusions of 30 mg/m2 in 6 weeks during 5 cycles can be considered because of a lower hematological toxicity profile.

Side-effects
Adverse events are common. Neutropenia is the main toxicity (grade 3 and 4 more than 30%), but is reversible. Febrile neutropenia is uncommon (3%). Neutropenia is significantly less when using the weekly regimen. Non-hematological adverse events occurring in more than 5% of patients include alopecia, nail changes, fluid retention, nausea, diarrhoea, stomatitis/pharyngitis, taste disturbance, vomiting, sensory neuropathy, anorexia, tearing, myalgia and fatigue. Prophylactic steroids (usually dexamethasone) are administered to prevent fluid retention and hypersensitivity reactions. Mild to moderate peripheral neurotoxicity occurs in 40% of patients. (Summary of Product Characteristics, (11))

Mitoxantrone is licensed in the Netherlands for the treatment of pain in metastasized CRPC in combination with prednisone.

Mechanism of action
Mitoxantrone is an anthracenedione derivative, related to the anthracyclines, and acts as a type II topoisomerase inhibitor.

Dosing
The recommended dose is 12mg/m2 intravenously every three weeks. Prednisone tablets are administered continuously, at 10 mg per day. This allows treatment in the outpatient clinic.

Side-effects
Neutropenia is very common (grade 3 up to 45%), as are mild to moderate nausea and vomiting. Dose-related cardiotoxicity is reported so regular cardiac monitoring is warranted in high-risk patients (11).

Estramustine is a derivative of estradiol-17-beta and has been used to treat advanced prostate cancer for approximately three decades. It was originally developed by combining oestrogen with the alkylating agent, non-nitrogen mustard. However, its mechanism of action does not appear to be by DNA alkylation, and experimental data suggest that estramustine disrupts cytoplasmic microtubules by binding to the

associated proteins and inhibiting the assembly of nuclear matrix. It is available in 140mg capsules. Standard starting dosage is 4-6 capsules a day in divided doses with later adjustment according to response and gastrointestinal tolerance. The most common adverse reactions include gynaecomastia and impotence, nausea/vomiting and fluid retention/oedema. The most serious reactions are thromboembolism, ischemic heart disease, congestive heart failure and, rarely and angioneurotic oedema. (11). Estramustine is not routinely administered by medical oncologists in the Netherlands.

Cabazitaxel has been approved by the FDA for second line treatment of metastasized CRPC recently (2010), and approval by the EMEA is pending. Cabazitaxel is currently available for patients in the Netherlands in a restrictive compassionate use program.

Mechanism of action
Like the taxanes docetaxel and paclitaxel, cabazitaxel acts by targeting tubulin, the protein component of microtubules, to stabilize microtubules and prevent progression of mitosis in the cell cycle.

Dosing
The recommended dose is 25 mg/m² intravenously over one hour every three weeks. Prednisone tablets are administered continuously, at 10 mg per day. This allows treatment in the outpatient clinic.

Side-effects
The most common (≥ 10%) grade 1-4 adverse reactions in cabazitaxel-treated patients were neutropenia, anemia, leucopenia, thrombocytopenia, diarrhoea, fatigue, nausea, vomiting, constipation, asthenia, abdominal pain, hematuria, back pain, anorexia, peripheral neuropathy, pyrexia, dyspnea, dysgeusia, cough, arthralgia, and alopecia. The most common (≥ 5%) grade 3-4 adverse reactions in cabazitaxel-treated patients were neutropenia, leucopenia, anemia, febrile neutropenia, diarrhoea, fatigue, and asthenia (11).

1.4 Research question / objective

1. To evaluate the pharmacotherapeutic value of docetaxel and other anticancer agents for the treatment of prostate cancer, in terms of effectiveness, cost-effectiveness, adverse effects, safety and clinical implications.
2. To evaluate the use of docetaxel and other anticancer agents in Dutch clinical practice.

2. Methods

2.1 Methods literature search

A systematic literature search was performed in collaboration with a clinical librarian. The Dutch national guideline on prostate cancer, published in 2007 and accessible via www.oncoline.nl, was considered the basis of the literature (1). The search was therefore limited to articles published from 1st of January, 2005. A search of relevant databases (Medline, Embase and Cochrane) was performed and articles were included if published before the 4th of November, 2010. The search terms included prostatic neoplasms and docetaxel, and the search was limited to clinical trials, guidelines, meta-analyses or systematic reviews, published from 2005 (see appendix C for full literature search protocol). A total of 408 unique articles were screened for relevance, by evaluation of titles and abstracts. Full paper manuscripts of potentially relevant articles were obtained and assessed for inclusion. Inclusion criteria were studies on patients with prostate carcinoma and treatment with anticancer agents, phase III clinical trials, meta-analyses, systematic reviews, guidelines and English or Dutch language. Studies concerning non-adenocarcinoma prostate cancer were excluded. The list was expanded by related articles, such as relevant phase II articles, and relevant articles from the reference list of the Dutch national guideline.

The search for economic studies was not limited to date and added the search term cost and cost analysis, leading to a total of 58 unique articles screened for relevance. Inclusion criteria were cost-effectiveness analysis, cost-utility analysis and cost-minimization analysis.

Clinical guidelines from Oncoline (Dutch), ESMO (Europe) and NCCN (United States) were reviewed. Reports of the BOM-committee were obtained from the website www.nvmo.org.

Ongoing clinical trials on prostate cancer were searched on the Clinical Trials Registry of the U.S. National Library of Medicine (www.clinicaltrials.org, accessed December 2010).

2.2 Methods evaluation on daily practice

Medical oncologists were invited for a structured interview. When accepted, they received a list of the items addressed in the interview. These items were general characteristics of the hospital (region, hospital type and size, number of medical oncologists, number of oncology beds, number of new outpatient oncology contacts per annum, number of prostate cancer patients), treatment regimens used in treating prostate carcinoma, experiences in efficacy and toxicity, participation in study protocols, means of informing patients, means of counselling patients, and experiences with referral for second opinion in the Netherlands and abroad. Each medical oncologist was visited for an interview of approximately one hour. The interviews were recorded for processing only.

A representative of the Dutch patient association, SCP (Stichting Contactgroep Prostaatcarcinoom), was interviewed to obtain input from the patients.

Input from pharmacists was obtained by cooperation of a pharmacist in the project team. The input included, but was not limited to, data on generic products, the actual costs of anticancer agents in the Netherlands and illustrative data on anticancer agent use in daily practice.

3. Results

3.1 Review of guidelines (regarding CRPC)

The Dutch national guideline has been published in 2007 (1). In CRPC, hormone treatment should be continued. In symptomatic patients, second-line hormone treatment should be considered. In case of a limited number of bone metastases and symptoms, external beam radiation therapy is recommended. If multiple symptomatic bone metastases can not be controlled with analgesics and local radiotherapy, and chemotherapy is no option, systemic treatment with radionucleides (samarium-153, strontium-90) can be considered. Bisphosphonates are considered in symptomatic bone metastasis. Chemotherapy is an option in all patients with CRPC who are fit for chemotherapy and 3-weekly docetaxel 75 mg/m2 combined with prednisone 10 mg daily, is considered standard treatment. However, it is explicitly stated that the modest survival benefit (2 months) and modest chance of improvement of quality of life (22%) needs to be considered in the light of potential adverse events and costs.

The European (ESMO) guideline has been published in 2010 (2). Patients with CRPC should have continued androgen suppression. Patients with CRPC should receive second-line (anti-androgen) and third-line (corticosteroid) hormone therapy. Fourth-line hormonal therapy can be considered (estrogen or ketoconazole). 3-Weekly docetaxel 75 mg/m2 combined with prednisone 10 mg daily should be considered for symptomatic disease. Mitoxantrone can be considered if there is a contraindication to docetaxel. Docetaxel + estramustine is an effective regimen but appears to be more toxic. External beam radiotherapy should be offered to patients with painful bone metastases. Radionucleide therapy should be considered for patients with painful bone metastases. Intravenous bisphosphonates should be considered for patients with bone pain resistant to palliative radiotherapy and conventional analgesics.

The American (NCCN) guideline has been updated in 2010 (5). Treatment in clinical trials is especially encouraged. Androgen suppression is continued. In CRPC without metastases, second-line hormonal treatment (anti-androgen, adrenal enzyme inhibitor or estrogen therapy) is advised. In case of PSA relapse or non-visceral metastases, treatment with Sipuleucel-T is appropriate for asymptomatic or minimally symptomatic patients with a good clinical performance status (ECOG 0-1) and a life-expectancy of >6 months. In metastasized CRPC, 3-weekly docetaxel 75 mg/m2 combined with prednisone 10 mg daily is recommended. In patients with contra-indications other docetaxel regimens or mitoxantrone can be considered. Secondary hormone therapy is recommended. Palliative radiotherapy or radionucleides for symptomatic bone metastases are recommended. Bisphosphonates are recommended for patients with bone metastases. When progressive, patients are offered treatment in clinical trials, salvage therapy (second line chemotherapy with cabazitaxel or mitoxantrone) or best supportive care.

In The Netherlands, the BOM-committee (commissie BOM) evaluates new anticancer agents. Up to date, the BOM-committee has not given advice concerning chemotherapy or anticancer agents in prostate cancer.

3.2 Review of literature – clinical effectiveness

For an overview of phase III trials, see Tables 3 and 4. A Cochrane review concerning chemotherapy in CRPC was published in 2006 (12). Studies on estramustine (as single-agent or in a combination regimen), cyclophosphamide, 5-fluorouracil, doxorubicin and vinorelbin were included. None of these agents has proven to be beneficial in terms of survival, symptom palliation or improvement of quality of life compared to best supportive care. Trials on mitoxantrone and docetaxel have also been included in this Cochrane review, but will be discussed below.

In the 1990s, two randomized trials showed that mitoxantrone plus a corticosteroid (hydrocortisone or prednisone) in CRPC improved palliative endpoints (pain control), but not survival, as compared to a corticosteroid alone (13;14). Subsequently, a survival benefit of docetaxel in CRPC was demonstrated in the TAX-327 trial in 2004 (15;16). Docetaxel 75mg/m2 given every three weeks plus daily prednisone significantly prolonged survival compared to mitoxantrone plus prednisone (median survival 18.9 versus 16.5 months, p=0.009). In this trial, an alternative docetaxel regimen (docetaxel 30mg/m2 given weekly plus daily prednisone) did not significantly improve survival (median survival 17.4 months, p=0.36). This survival benefit was despite crossover of one quarter of patients after progression (17). Importantly, the median age was 68 years and 20% of patients were over 75 years of age (15). Serious adverse events were seen in 26% of the docetaxel 3-weekly group, as compared to 20% in the mitoxantrone group and 29% in the docetaxel weekly group. Grade 3 or 4 neutropenia was significantly higher in the docetaxel 3-weekly group (32% versus 2% in the docetaxel weekly group and 22% in the mitoxantrone group, p<0.05), however febrile neutropenia was rare. In the docetaxel groups, sensory neuropathy was significantly more common (30% and 24% versus 7%, p<0.0015).

A similar survival benefit for docetaxel-based chemotherapy has been seen in a second trial that compared docetaxel plus estramustine with mitoxantrone plus hydrocortisone in treating CRPC (18). However, serious adverse events were more common in the intervention arm (especially grade 3 and 4 cardiovascular events 47% versus 22%, p=0.001). Therefore, the docetaxel + prednisone combination is preferred over docetaxel + estramustine because of the increased risk of thromboembolic events associated with estramustine (18).

Several chemotherapy agents in combination with docetaxel have been investigated (including vinorelbine, capecitabine, thalidomide, carboplatin, epirubicin, calcitriol, oblimersen, custirsen) (19). Although there have been hopeful results in phase I and II studies, so far none have demonstrated superiority to docetaxel alone in phase III trials.

Epothilones (Ixabepilone) are macrolide antibiotics which stabilize microtubules by binding near the taxane-binding site. Ixabepilone has been shown to be active in CRPC in phase II trials although neurotoxicity has limited the clinical development of this drug (20). Ixabepilone is not available in the Netherlands at this moment.

Recently cabazitaxel, a novel taxane drug, has been compared to mitoxantrone as second line treatment in the TROPIC-study (20). Treatment with cabazitaxel was shown to improve overall survival in docetaxel-resistant CRPC (median survival 15.1 versus 12.7 months, p<0.0001). However, toxicity was increased in the cabazitaxel arm: diarrhoea (all grades) 47% *vs* 10%, neutropenia (grade 3/4) 82% *vs* 58%, febrile neutropenia 8% *vs* 1% and toxic deaths 5% *vs* 2%. This warrants the balancing of benefit against adverse effects and proactive management of side effects.

Satraplatin, an orally bioavailable platinum compound, has been evaluated in the phase

III SPARC-trial as second-line treatment in CRPC patients, with progression after docetaxel, mitoxantrone or other chemotherapy treatment (21). Treatment with satraplatin resulted in significant improvement in the time to disease progression and time to pain progression (hazard ratio (HR) = 0.64; 95% confidence interval (CI) 0.51–0.79; p<0.001), but no OS advantage (HR = 0.98; 95% CI 0.84–1.15; p=0.80) was observed. At this moment, satraplatin has not been licensed by the FDA and is not available in the Netherlands.

Publication	Patients	Intervention/ Comparator	PFS/TTP (months)	OS (months)	PSA decline >50% (%)
1st line					
Tannock (13) 1996	161 men mCRPC	M+P *vs* P	4.9 2.1	10 10 (n.s.)	33 22
Kantoff (14) 1999	242 men mCRPC	M+H *vs* H	3.7 2.3 (p=0.0254)	12.3 12.6 (n.s.)	38 22 (p=0.008)
Berry (22) 2002	120 men CRPC asymptomatic	M+P *vs* P	8.1 4.1 (p=0.017)	23 19 (n.s.)	48 24 (p=0.007)
Ernst (23) 2003	227 men mCRPC	M+P+Clo *vs* M+P	5.0 4.0 (n.s.)	10.8 11.5 (n.s.)	29.7 28.6 (n.s.)
Tannock (15) 2004	1006 men mCRPC	D75+P *vs* D30+P *vs* M+P		18.7 17.4 (n.s.) 16.5 (p=0.009)	45 48 (n.s.) 32 (p<0.001)
Petrylak (18) 2004	770 men mCRPC	D60-70+E *vs* M+P	6.3 3.2 (p<0.001)	17.5 15.6 (p=0.02)	50 27 (p<0.001)
Kelly (24) 2010 (abstract)	1050 men mCRPC	D75+P+Bev *vs* D75+P	9.9 7.5 (p<0.0001)	22.6 21.5 (n.s.)	57.9 69.5 (p=0.0002)
Kantoff (25) 2010	512 men mCRPC, Gleason<8 asymptomatic	Sipuleucel-T *vs* placebo	3.7 3.6 (n.s.)	25.8 21.7 (p=0.03)	2.6 1.3

Table 3 Published phase III trials on CRPC, first line therapy

M = mitoxantrone; P = prednisone; H = hydrocortisone; Clo = clodronate; D60-75 = docetaxel 60-75 mg/m2 every three weeks; D30 = docetaxel 30 mg/m2 every week; Bev = bevacizumab; n.s. = not significant

Publication	Patients	Intervention/ Comparator	PFS/TTP (months)	OS (months)	PSA decline >50% (%)
2nd line					
Sternberg (21) 2009	950 men mCRPC Post-chemotherapy	S+P *vs* P	2.6 2.3 (n.s.)	14.2 14.3 (n.s.)	
De Bono (20) 2010	775 men mCRPC Post-docetaxel	C+P *vs* M+P	2.8 1.4 (p<0.0001)	15.1 12.7 (p<0.0001)	39.2 17.8 (p=0.0002)

Table 4 Published phase III trials on CRPC, second line therapy

S = satraplatin; P = prednisone; C = cabazitaxel; M = mitoxantrone; n.s. = not significant

Immune therapy

Because of immunogenicity of prostate cancer, different approaches to induce an anti-tumour immune response are being investigated.

GVAX is an allogenic cellular vaccine, consisting of two inactive prostate cell lysates, modified to secrete GM-CSF. Based on promising phase II results, two phase III studies in metastasized CRPC have been initiated. However, VITAL-1 (GVAX *vs* docetaxel) and VITAL-2 (GVAX + docetaxel *vs* docetaxel) both have been terminated prematurely because of insufficient benefit in the results (26).

Sipuleucel-T is an autologous dendritic cell vaccine, primed with a recombinant fusion protein of a tumor-specific antigen. The first phase III trial in asymptomatic CRPC failed to meet the primary end point of progression-free survival (11.7 weeks for sipuleucel-T versus 10.0 weeks for placebo). However, based on exploratory analysis, median survival was longer in the Sipuleucel-T group (27). In the larger IMPACT-trial in minimally symptomatic or asymptomatic CRPC, patients on the vaccine arm experienced an extended median OS of 4.1 months compared with the placebo arm (25.8 versus 21.7; HR = 0.759; p=0.017) (25). These data have led to the FDA approving sipuleucel-T for the treatment of CRPC. However, when critically overviewing the results, the median overall survival of the placebo arm was less than expected (overall survival in asymptomatic patients is expected to be around 24 months). It is speculated that the "placebo" treatment consisting of leukaphoresis may have had a negative impact on survival. Another concern is the high cost of the Sipuleucel-T treatment: the manufacturer has set the cost of a 1-month course of sipuleucel-T at $93,000.
Targeted therapy in immune therapy has been beneficial in metastatic melanoma, when treatment with monoclonal antibody ipilimumab has been shown to improve overall survival (28). Ipilimumab works by blocking cytotoxic T-lymphocyte antigen-4 (CTLA-4), a critical negative regulator of the antitumor T-cell response. Phase III trials investigating ipilimumab in prostate cancer are ongoing (26).

Targeted therapy
Several targeted therapy strategies are under investigation. Drugs targeting IGF-1R signalling, the PI3K/AKT/mTOR pathway and apoptosis (bcl-2) are being tested in phase I/II trials (26).
Targeted therapy against angiogenesis is promising in phase I/II trials, but the preliminary results of a phase III trial, in which bevacizumab (a monoclonal antibody targeting VEGF-A) was added to docetaxel, failed to show an improvement in overall survival (24). Aflibercept, a VEGF decoy receptor, is currently under investigation in a phase III trial (VENICE). Other anti-angiogenic agents under investigation are the oral compounds thalidomide and lenalidomide and multi-target tyrosine kinase inhibitors including sunitinib, sorafenib and dasatinib (19;20).
Targeted therapy against the bone-tumor interplay is directed at RANK-L (denosumab). Targeted therapy is also directed at endothelins (atrasentan en zibotentan). Clusterin-overexpression has been demonstrated in CRPC. Custirsen is an antisense oligonucleotide that blocks production of clusterin (19;20).

Hormonal therapy
Novel targets in hormonal therapy are promising, even in CRPC. Androgen receptor signalling is persistent active despite castrate level circulating androgens. New-generation specific peripheral anti-androgen MDV3100 is an oral compound, with promising results in a phase II trial (29). It is currently under investigation in a large phase III trial in chemotherapy-resistant CRPC. Abiraterone is an oral, selective, irreversible inhibitor of CYP17A1, a key enzyme essential for synthesis of androgen hormones and 10-30 times more potent than ketoconazole. Results of two phase III trials in both chemo-naïve and chemo-refractory CRPC are awaited. Orteronel (TAK-700) is another inhibitor of androgen hormone synthesis that is currently investigated in two large phase III trials (19;20).

An overview of current phase III trials is provided in Tables 5 and 6. An important Dutch trial that is not listed in the Clinical Trials Registry of the U.S. National Library of Medicine is the NEPRO-trial, a randomized phase II/III trial of docetaxel + risedronate (an oral bisphosphonate) versus docetaxel alone on CRPC. The trial is closed for accrual and results are awaited.

Trial nr.	Study start	Participants	Intervention/ comparator	Outcome
NCT00132301	2006 recruiting	636 men Adjuvant Poor prognosis (excl. N1 or M1)	D+P No intervention	1 PFS
NCT00796458	2005 recruiting	200 men Indication ADT	LHRH-A+D+P LHRH-A	1 PFS 2 OS 2 toxicity 2 QoL 2 cost analysis

Table 5 Ongoing phase III trials on adjuvant chemotherapy in prostate cancer (30)

D = docetaxel; P = prednisone; LHRH-A = Luteinizing-hormone-releasing hormone antagonist; QoL = Quality of life; ADT = androgen deprivation therapy

Table 6 (continued on next page)

Trial nr.	Study start	Participants	Intervention/ comparator	Outcome
Chemotherapy				
NCT00255606 PROSTY	2005 completed	360 men CRPC Chemo naïve	D+P 3-weekly *vs* D+P 2-weekly	1 TTF 2 QoL 2 toxicity 2 OS 2 reponse rate
NCT01224405	2010 closed for accrual	600 men CRPC Chemo naïve	D+P+LHRH-A *vs* D+P 2nd randomisation continuous vs intermittent treatment	1 OS 2 toxicity 2 PFS 2 QoL 2 Pain 2 cost analysis
NCT00436839	2007 recruiting	240 men CRPC Chemo naïve	D+P *vs* M+P	1 OS 2 ORR 2 TTP 2 QoL
Targeted therapy				
NCT00626548 ENTHUSE M0	2008 recruiting	1500 men CRPC Chemo naïve No metastasis	zibotentan + BSC *vs* BSC	1 OS 1 PFS
NCT00554229 ENTHUSE M1	2007 closed for accrual	848 men mCRPC Chemo naïve	zibotentan + BSC *vs* BSC	1 OS 2 PFS
NCT00617669 ENTHUSE-M1C	2008 closed for accrual	1445 men CRPC Chemo naive	D+P+zibotentan *vs* D+P+placebo	1 OS 2 PFS 2 toxicity 2 QoL
NCT00134056	2006 closed for accrual	930 men CRPC Chemo naive	D+P+atrasentan *vs* D+P+placebo	1 OS 1 PFS
NCT01188187 SYNERGY	2010 recruiting	800 men CRPC Chemo naive	D+P+custirsen *vs* D+P	1 OS 2 PFS 2 toxicity 2 PSA
NCT01083615	2010 recruiting	292 men CRPC Post-docetaxel	custirsen *vs* placebo	1 pain palliation
NCT00744497 CA180-227	2008 recruiting	1500 men CRPC Chemo naive	D+P+dasatinib *vs* D+P+placebo	1 OS 2 time to SRE 2 time to PSA progression 2 pain 2 toxicity

Trial nr.	Study start	Participants	Intervention/ comparator	Outcome
NCT00519285 VENICE	2007 closed for accrual	1200 men CRPC Chemo naive	D+P+aflibercept *vs* D+P+placebo	1 OS 2 PSA 2 pain 2 SRE
NCT00988208 CC-5013-PC-002	2009 recruiting	1015 men CRPC	D+P+lenalidomide *vs* D+P+placebo	1 OS 2 PFS
NCT00286091 SWOG-S0421	2006 closed for accrual	1435 men CRPC	denosumab *vs* placebo	1 time to first SRE
NCT00321620	2006 closed for accrual	1435 men CRPC	denosumab *vs* zoledronic acid	1 time to first SRE
Immune therapy				
NCT01057810 CA184-095	2010 recruiting	600 men CRPC Chemo naive	ipilimumab *vs* placebo	1 OS 2 PFS 2 toxicity 2 time to pain progression 2 time to systemic therapy
NCT00861614 CA184-043	2009 recruiting	800 men CRPC Post-docetaxel	ipilimumab *vs* placebo	1 OS 2 PFS 2 Pain response 2 toxicity
Hormone therapy				
NCT00887198 COU-AA-302	2009 closed for accrual	1000 men CRPC Chemo naive	abiraterone+P *vs* placebo+P	1 OS 1 PFS
NCT00638690 COU-AA-301	2008 closed for accrual	1158 men CRPC Post-docetaxel	abiraterone+P *vs* placebo+P	1 OS 2 PSA response
NCT01193257	2010 recruiting	1083 men CRPC Post-docetaxel	orteronel+P *vs* placebo+P	1 OS 2 PSA response 2 PFS 2 pain response
NCT01193244	2010 recruiting	1454 men CRPC Chemo naive	orteronel+P *vs* placebo+P	1 radiologic PFS 1 OS 2 PSA response 2 CTC counts 2 Time to pain progression
NCT01212991 PREVAIL	2010 recruiting	1680 men Chemo naive CRPC	MDV3100 *vs* placebo	1 OS 1 PFS 2 time to SRE 2 time to chemotherapy
NCT00974311 AFFIRM	2009 closed for accrual	… men CRPC Post-docetaxel	MDV3100 *vs* placebo	1 OS
Radionucleides				
NCT00699751 ALSYMPCA	2008 closed for accrual	900 men CRPC Multiple bone metastases	alpharadin (Radium-223) *vs* placebo	1 OS 2 toxicity 2 clinical benefit 2 time to disease specific events

Table 6 Ongoing phase III trials on CRPC (30)

D = docetaxel; P = prednisone; LHRH-A = Luteinizing-hormone-releasing hormone antagonist; M = mitoxantrone; TTF = time to treatment failure; BSC = Best supportive care; QoL = Quality of life; SRE = Skeletal related event

Quality of life
The impact of mitoxantone on QoL has been evaluated in two studies (13;14). In the study comparing mitoxantrone + prednisone with prednisone, three instruments were used to assess QoL, with a focus on prostate-specific symptoms, various QoL domains and a trial-specific questionnaire. In the mitoxantrone + prednisone group, a significant benefit compared to prednisone alone was reported for social functioning, pain and insomnia (31). In the study comparing mitoxantrone + hydrocortisone with hydrocortisone, five QoL-questionnaires were used with a focus on functional living, symptom distress, sexual and urologic functioning, problems in daily activities and impact of pain. There were no statistically significant differences between mitoxantrone + hydrocortisone versus hydrocortisone alone in a variety of QoL measures, including global QoL (14).

The impact of docetaxel on QoL has been evaluated with the FACT-P questionnaire (15). The percentage of patients who had an improvement in QoL (defined as an improvement of 16 points on a range from 0 to 156) was similar in the two docetaxel groups (22% in the group given docetaxel every three weeks and 23% in the group given weekly docetaxel) and significantly higher than that in the mitoxantrone group (13%; p=0.009 and p=0.005, respectively). The greatest benefit in the docetaxel groups was in the subscale representing prostate-specific concerns (including weight loss, appetite, pain, physical comfort, and bowel and genitourinary function). A reduction in pain was more frequent among patients receiving docetaxel every three weeks than among those treated with mitoxantrone (35% vs. 22%, p=0.01). In conclusion, docetaxel has superior palliative effects despite increased toxicity.

No results of QoL evaluation on the use of cabazitaxel have been published.

Study	Type of economic evaluation	Perspec-tive used	Time frame	Unit cost data	Source of effective-ness data	Source of resource use data	Comparator	Effectiveness (Mean survival)	Total costs	Cost-effectiveness results (ICER per LYG)	Remarks
Bloomfield (32) 1998	Cost-utility	Canada; Third party payer	Extrapolation to lifetime	Direct medical costs in 1996 CAN$ (plus conversion to US$), no discounting	CCI-NOV22 (13) QoL data (13)	Retrospective review of sample (n=114) trial patients (13)	M+P P	41.5 weeks (quality adjusted) 28.2 weeks	€ 20,074 (CAN$ 27,300) € 21,324 (CAN$ 29,000)	M+P dominates P ICER (upper 95% CI) CAN$ 19,700	Sensitivity analysis: (costs) Only variation inpatient days caused M+P to become more costly than P
Sanofi-Aventis (33) 2005	Cost-effectiveness	United Kingdom; NHS	Extrapolation to lifetime	Direct medical costs in UK £, no discounting	TAX 327 (15)	TAX 327 (15)	D75+P M+P	22.3 months (median 18.9 months) 18.7 months (median 16.5 months)	€ 18,549 (£ 15,767) € 11,425 (£ 9711)	€ 22,921 (£ 19,483) comparator	Sensitivity analysis: (survival) € 14,321 to 49,420 (£ 12,173 to 42,007) (ICER per LYG for D75+P based on median survival data € 35,623 (£ 30,280)
Collins (34) 2007	Cost-utility model	United Kingdom; NHS	lifetime	2003 UK£ Discount rate 3.5% per annum	TAX 327 (15) QoL data (35)	Sanofi-Aventis (33) Bloomfield (32)	D75+P M+P P D35+P	1.80 years QALY 0.96801 1.51 years QALY 0.81364 1.50 years QALY 0.81001 1.57 years QALY 0.84636	€ 18,686 (£ 15,883) € 12,746 (£ 10,834) € 13,208 (£ 11,227) € 30,904 (£ 26,268)	€ 38,478 / QALY (£ 32,706) comparator ICER dominated ICER dominated	Sensitivity analysis: (alternative discount rates, QoL estimates and impact side effects) € 32,964 to 39,174 (£ 28,019 to 33,298)
Sladkevicius (36) 2010	Cost-minimisation	Spain; hospital pharmacy	1 year period	2008 €	Similar profile assumed	Medline search Interviews pharmacists	Branded D Generic D	-	€ 970 / pt € 680 / pt	-	Annual cost saving in Spain: € 28.4 million (€ 17.1 - 42.8 million)

Table 7 cost-effectiveness chemotherapy in CRPC

1 € = 0.85 UK£ = 1.38 US$ = 1.36 CAN$ (currency rates February 2011, www.xe.com)

ICER = incremental cost effectiveness ratio; QALY = Quality-adjusted life-year; LYG = life-year gain; M = mitoxantrone; P = prednisone; D75 = docetaxel 75mg/m2 3-weekly; D35 = docetaxel 35mg/m2 weekly; QoL = Quality of life

3.3 Review of literature – cost-effectiveness

In Table 7 an overview of economic evaluations is provided.

In the United Kingdom, NICE has published the Guidance on docetaxel for the treatment of hormone-refractory metastatic prostate cancer in 2006 (10). They concluded that "docetaxel is recommended, within its licensed indications, as a treatment of men with hormone-refractory metastatic prostate cancer only if their Karnofsky performance score is 60% or more. It is recommended that treatment with docetaxel should be stopped at the completion of planned treatment of up to 10 cycles, or if severe adverse events occur, or in the presence of progression of disease as evidenced by clinical or laboratory criteria, or by imaging studies".

In 2007, an economic review has been published by Collins et al (34). The next two articles were discussed and evaluated in that review.

An economic evaluation of mitoxantrone in Canada has been published in 1998 (32). A cost-utility analysis was done from the perspective of a third-party payer. The clinical outcome data were derived from the CCI-NOV22 clinical trial (13). Costs were obtained from a local hospital and insurance company. Costs were expressed in 1996 Canadian dollars. Utility values were estimated based on patient-level data from the CCI-NOV22 trial. The baseline estimate of the cost-effectiveness indicated that the use of mitoxantrone + prednisone dominated prednisone, with an additional 13.3 quality adjusted weeks and a reduced cost of CAN$1,700. Mitoxantrone was consistently less expensive in whichever time period was used to compare costs. Cost-utility analysis showed that treatment with mitoxantrone is the preferred strategy with an upper 95% confidence interval for the incremental cost-utility ratio of CAN $19,700 per quality-adjusted life-year (QALY).

The sponsor submission of docetaxel by Sanofi-Aventis has been published in 2005 (33). The analysis was undertaken from an NHS perspective. A unique price year was not given. Outcome data (only the 3-weekly regimen) were derived from the TAX 327 clinical trial (15). The survival data were obtained by two methods: median survival from the Kaplan-Meier curve (difference between mitoxantrone and docetaxel 2.4 months) and mean survival based on extrapolation using parametric survival model and Weibull distribution (difference between mitoxantrone and docetaxel 3.73 months). The incremental costs per LYG for docetaxel were £30,280 based on median survival data, falling to £19,438 using mean survival data. In sensitivity analyses, the ICER ranged from £12,173-42,007 per LYG. No QoL adjustment has been made.

An economic model comparing different strategies has been developed by Collins et al (34). A probabilistic model using Monte Carlo simulation was developed from the perspective of the NHS with a lifetime time horizon. A 2003-2004 price base in UK ponds was used. In the first analysis, three strategies were considered (3-weekly docetaxel, mitoxantrone and best supportive care (prednisone alone)). In the second analysis, unlicensed strategies were considered (docetaxel weekly, docetaxel (35 and 70mg/m2) + estramustine with or without prednisone, and mitoxantrone + clodronate; all strategies combined with prednisone except stated otherwise). QoL utilities were derived from literature (37). Resource use and costs were based on the British National Formulary, the sponsor submission by Sanofi-Aventis (33) and the publication by Bloomfield (32). Best supportive care was dominated by mitoxantrone (i.e. BSC is more expensive and marginally less effective). The incremental cost-effectiveness ratio of docetaxel (3-weekly) compared with mitoxantrone was £32,706 per additional QALY. In the second analysis, all other strategies were dominated by docetaxel (3-weekly). The ICER associated with docetaxel (3-weekly) remained fairly robust to variations in

sensitivity analyses, ranging from £28,019 to £33,298 per QALY.

Based on the evaluation by Collins et al (34), a Bayesian decision-theoretic approach was used to develop an analytic framework to inform decision-making about resource allocation and establish the expected value of both perfect information (EVPI) and perfect implementation (EVPIM) (38). Given clinical practice in the UK in 2009, there appeared to be considerable scope for improving the efficiency of health-care provision. The EVPI (estimated to be over £13 million) indicates that acquiring further information (i.e., fund further research) could be cost-effective. The EVPIM (estimated to be over £4 million) suggests that investing in strategies to implement the treatment regimens being identified as optimal is potentially worthwhile. Given a cost-effectiveness threshold of £30,000 per QALY, the authors would recommend reimbursement of mitoxantrone and prednisone alongside commissioning of further research and investment in implementation efforts for improving the efficiency of health-care services delivery for CRPC patients (38).

The pharmacoeconomics of available treatment options for metastatic prostate cancer were evaluated in the United States in 2007 (39). Hormone-sensitive and locally advanced prostate cancer were also included in this review. Reviewed articles concerning androgen-independent prostate cancer (CRPC) in the evaluation included two articles regarding chemotherapy, one of which is discussed above (32). The other publication compared cost-effectiveness of four treatment options using a Markov model (40). The base case was a man with CRPC who had developed a painful solitary bone metastasis. The palliative treatment options were pain medication only, chemotherapy consisting of mitoxantrone and prednisone, single-fraction EBRT and multi-fraction EBRT. The costs were calculated from a payer's perspective, namely Medicare. Based on the incremental cost of $3,600 for chemotherapy over pain medication and less effectiveness of chemotherapy (4.93 *vs* 5.75 quality of life adjusted months, based on an estimated utility for the months spent during chemotherapy of 0.6)), chemotherapy was dominated by pain medication only. Single-fraction radiotherapy was the most cost-effective regimen for the base-case scenario. The data were robust in sensitivity analyses. However, the results should be interpreted with caution because of the effectiveness data of the chemotherapy were not specific for pain and the data for all treatments came from different trials.

A cost-minimization analysis from a hospital pharmacy's perspective on the net resource implications and budget impact of using generic docetaxel instead of branded docetaxel was published in Spain in 2010 (36). The indications included but were not limited to prostate cancer. Due to reduced acquisition costs of docetaxel (€970 compared to €680) and reduced reconstitution time by pharmacy technicians (because generic docetaxel and not branded docetaxel is a ready made-up solution) the cost-saving would be €28.4 million (based on 97,000 docetaxel infusions annually in Spain).

3.4 Daily practice in the Netherlands

Five medical oncologists were interviewed, representing 2 academic and 3 peripheral hospitals spread over the Netherlands. The total annual count of new patients with prostate carcinoma treated in these hospitals is 575 (range per hospital: 30-300 patients). One representative of the Dutch prostate cancer patient alliance was interviewed. This representative has 400 fellow-patient contacts in the Netherlands every year.

Prostate cancer patients generally start treatment by an urologist. Differences between hospitals exist in referral patterns to medical oncologists, once the disease develops resistance to castration. In some regions all patients are referred to oncologists once they are castration-resistant, whereas in other regions urologists treat their patients with second- or third-line hormonal therapies or estramustine (for example, 30% estramustine treatment prior to referral is estimated in some hospitals). A difference between academic and peripheral hospitals was noted in the interviews. In academic centers, a greater proportion of patients was estimated that are informed by urologists about chemotherapy and it is assumed that a significant subgroup of patients is not referred to the oncologist. This may lead to suboptimal information and withholding of choice to a patient.

Docetaxel (3-weekly regimen) is the standard first-line chemotherapy treatment in CRPC, and is offered to patients by all interviewed oncologists. Weekly docetaxel is rarely considered (and only in 2 out of 5 hospitals). Treatment with docetaxel is well tolerated. Hospital admission because of toxicity of docetaxel is rare. Dose-adjustments are infrequent. Rechallenge of docetaxel is considered if progression develops after a significant interval (3 months minimum). For second-line treatment mitoxantrone is considered in 3 out of 5 hospitals. Despite no robust evidence is available and treatment benefit is questionable for second-line treatment with mitoxantrone, arguments to consider mitoxantrone are experiences of response and clinical benefit, and no available alternatives. Two hospitals incorporated geriatric consultation before the start of chemotherapy in order to adequately select the subgroup of elderly patients that could benefit from chemotherapy. In all hospitals, patients are informed on the treatment by the medical oncologist and by a specialized nurse as well.

Dutch clinical guidance is outdated. It is not possible to estimate adherence to this guideline. Treatment protocols after progression on first-line therapy differ between hospitals and regions. An important reason for these differences may well be the limited options beyond standard first-line therapy.

Whenever possible, treatment in study trials is preferred, according to both oncologists and the patient's representative. It is estimated by the interviewed oncologists that this is offered to 40 to 70% of patients. However, the patient representative argues this estimate to be lower.

According to the representative of the Dutch prostate cancer patient alliance, approximately 3.5% of prostate cancer patients are members of the alliance. Quality of life should be emphasized when treating CRPC. The majority of patients does not question the advice given by the treating physician, reflected by a low estimate of 5% second opinions. Patients treated in peripheral hospitals are not actively encouraged to seek a second opinion. However, important regional differences in treatment advices or choices concerning surgery, radiotherapy and systemic therapy including chemotherapy are presumed. The concept of chemotherapy is still frightening to patients nowadays. If a physician informs a patient and emphasizes limited benefit (for example, in terms of only 2.9 months survival benefit), combined with a presumed frightening concept of

chemotherapy, the patient will probably not choose chemotherapy. This choice is probably based on subjective information. Alternatively, referral for treatment in clinical trials with hormonal or immunological treatments is an option. Therefore, objective information concerning treatment options is pivotal. The patient alliance plays an important role in offering objective information to patients by means of education in their magazine, fellow patient contacts and education on the internet. Optimally, a nurse practitioner could play a role as a case manager.

A group of patients is seeking a second opinion. No structured information is available of optional clinics where second opinions can be obtained. A subgroup of these patients will obtain a second opinion abroad, generally in Belgium or Germany, but even in the United States. The reasons for a second opinion include uncertainty about the advice, a patient's opinion of more sophisticated care abroad, or patient's preference for an alternative therapy. If patients want to have a second opinion abroad, guidance by the referring physician can prevent problems and disappointments of the patient. This accounts especially to non-validated and non-reimbursed treatments.

Illustration
Obtaining reliable absolute counts of prostate cancer patients and how they are treated is difficult and time consuming. Therefore, an illustration is provided of the results of one academic centre. In 2010, 168 patients were referred to the medical oncology department with the diagnosis prostatic adenocarcinoma. The preferred treatment strategy in this hospital for first-line treatment of CRPC is docetaxel 75mg/m2 3-weekly. When progression occurs, rechallenge of docetaxel after a minimum 3 months interval or second-line mitoxantrone 12mg/m2 3-weekly is considered. Cabazitaxel 25mg/m2 3-weekly is offered in a compassionate use programme for docetaxel-refractory disease. Clinical trials that are conducted are ipilimumab *vs* placebo for first-line therapy in asymptomatic patients (phase III) and for second-line therapy in docetaxel-refractory patients (phase III); docetaxel + lenalidomide *vs* docetaxel for first-line therapy (phase III); and docetaxel + carboplatin *vs* docetaxel for second-line therapy (phase II). In Table 8 a summary is given.

Of 168 patients, 63 patients (38%) were actually treated with chemotherapy. When treated with docetaxel 75mg/m2, dose reductions were necessary in 7 out of 47 patients (15%). The patients who were not treated with chemotherapy (62%) were heterogenic (treated hormonally, treated with experimental therapies without chemotherapy or treated elsewhere). An evaluation to determine which subgroup declined chemotherapy or was not offered chemotherapy was not performed.

Stage	Treatment strategy	Patients*
Stage IV	Docetaxel 75 mg/m2	47 patients
CRPC	Docetaxel 35 mg/m2	2 patients
168 pts	Mitoxantrone	25 patients
	Docetaxel+carboplatin	9 patients
	Cabazitaxel	10 patients
	Unknown / no chemotherapy	105 patients
Total		168 patients

Table 8 Illustration: Referred patients to medical oncologists in one hospital
* Total treatments is more than 168, because of patients receiving more lines of chemotherapy.

3.5 Cost assessment

The Dutch Foundation for Pharmaceutical Statistics (Stichting Farmaceutische Kengetallen, SFK) has been evaluating data concerning the use of pharmaceuticals in the Netherlands since 1990 (41). Since 2006, SFK monitors costs of expensive drugs in hospitals. Expensive drugs in hospitals has been defined as drugs that are incorporated in the 'Beleidsregel Dure Geneesmiddelen', which in practice are drugs that cost more than €2.5 million. In 2008, total costs of expensive drugs in Dutch hospitals were €379.5 million, with an increase of 19.5% compared to 2007 (42).

Total costs of docetaxel in the Netherlands have been steadily increasing from 2004 to 2008 (see Figure 1). Recently, generic preparations have become available. It is therefore expected that direct costs of docetaxel will decrease.

	Manufacturer	Presentation	Price (€)
Docetaxel	Actavis	20 mg = 1 ml	184,26
		80 mg = 4 ml	737,03
		140 mg = 7 ml	1289,81
	Hospira	160 mg = 16 ml	1474,06
		2□ mg = 2 ml	17□,68
		80 mg = 8 ml	737,02
	Sandoz	160 mg = 16 ml	1410,08
		20 mg = 2 ml	176,26
		80 mg = 8 ml	705,04
	Teva	55.46 mg = 2 ml	174,64
		221.84 = 8 ml	698,75
Mitoxantrone	PCH	20 mg = 10 ml	263,43
		25 mg = 12.5 ml	345,00
	Ebewe	20 mg = 10 ml	299,08
		10 mg = 5 ml	182,47
Estramustine	Pfizer	140 mg tablet	66,30*

Table 9 Direct costs of docetaxel, mitoxantrone and estramustine in the Netherlands, based on G-standaard handelsproducten January 2011

* 40 tablets

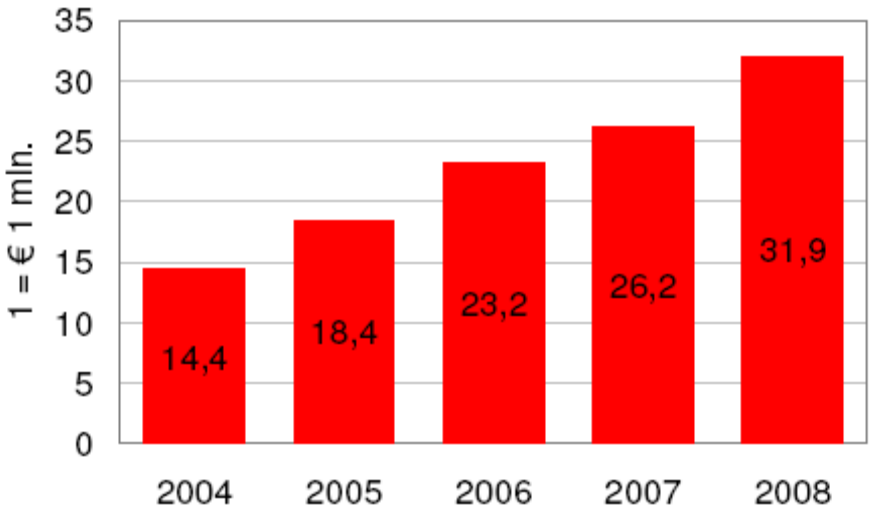

Figure 1 Total costs docetaxel for all indications, all hospitals in the Netherlands, 2004-2008 (Adapted from Stichting Farmaceutische Kengetallen, april 2010)

An illustrative calculation on actual direct costs of docetaxel in the treatment of prostate cancer per annum is provided below.

Assumptions on incidence rates and stage grouping are based on epidemiological data from the Netherlands (See Section 1.2.1; (4)). Direct costs of docetaxel are provided in Table 9. No value-added tax was included. We assumed 10,000 new prostate cancer patients per annum, with 18.5% stage IV tumors. We assumed 100% of patients treated per standard protocol. For this illustration, standard first-line therapy for CRPC is 3-weekly docetaxel 75 mg/m2 according to the regimen used in the TAX 327 trial (15). We assumed that the average body surface area is 1.8 m2.

In Table 10 an overview of total costs of gemcitabine based on our calculation is provided.

Treatment	Patients	Cost per treatment	Total costs	Sensitivity analyses
Palliative	740 patients (370-1110)	€9,030 (€7,740 -€11,610)	€6,682,200	€2,863,800 To €12,887,100

Table 10 Calculation on total costs of docetaxel in prostate cancer in the Netherlands

Palliative chemotherapy is indicated in 1,850 patients (10,000 patients * 18,5%). We assumed that 40% of these patients actually start treatment with docetaxel, due to bad clinical condition or denial of chemotherapy (based on experience and the structured interviews). Resource use was derived from the TAX 327 trial (15) and a retrospective analysis (43). The median number of cycles docetaxel in the TAX 327 trial was 9.5 and in the retrospective analysis 7. Based on our experience we assumed the median number of cycles to be 7.
We assumed that 740 patients (1,850 * 40%) will actually receive palliative docetaxel, consisting of 7 infusions. Dose reductions were required in 12% of patients in the TAX 327 trial, which is consistent with our experience. We assumed the average dose of docetaxel administered to be 72.5 mg/m2, and therefore 130.5 mg per infusion (72.5 * 1.8 m2). Direct costs of one infusion of docetaxel are calculated at €1,290 (1 vial of 140mg). One palliative treatment is calculated at €9,030 (7 infusions * 1,290). When treating 740 patients, total direct costs of docetaxel are calculated at €6,682,200. When varying the percentage of patients treated from 20% to 60% and the number of cycles from 6 to 9, total costs range from €2,863,800 to €12,887,100.

4. Discussion and conclusion

Discussion and conclusion

Relative survival in prostate cancer has been improving in the Netherlands since the start of registration in 1988, as shown in Figure 2. Although prostate cancer is the second most common cause of cancer in men (after non-melanoma skin cancer), the majority of patients will never develop metastatic disease and subsequently mortality rates are much lower than incidence rates. However, in an ageing society incidence rates are expected to increase (9). In the Netherlands approximately 10,000 patients are diagnosed with prostate cancer and approximately 2,500 patients will die from prostate cancer (4). In 2008, 18.5% of prostate cancer patients were staged in stage IV and those patients will eventually develop CRPC. Chemotherapy is indicated in metastatic CRPC only.

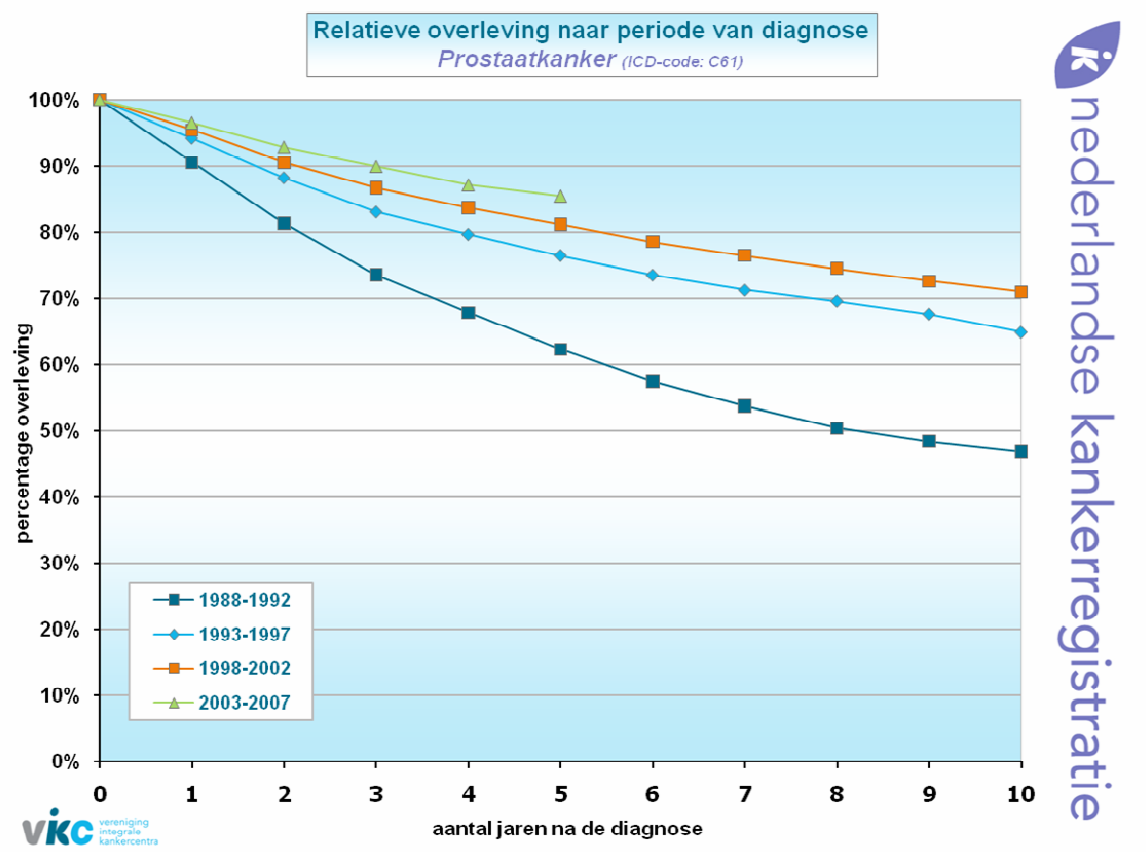

Figure 2 Relative survival to the period of diagnosis for prostate cancer in the Netherlands (4).

First-line therapy in CRPC

Before 2004, mitoxantrone had shown to improve palliative end points, especially pain control, over steroids only (13;14). However, survival was not improved. Cost-utility analysis (Canada, 1998) showed that mitoxantrone dominated prednisone as first-line treatment in CRPC (longer quality-adjusted survival and less costs) (32). Since 2004, docetaxel in a 3-weekly regimen significantly prolonged survival in CRPC as compared to mitoxantrone (OS improvement from 16.5 to 18.9 months) (15). Moreover, treatment with docetaxel improved quality of life and has an acceptable toxicity profile. Based on experience, docetaxel is generally well tolerated. The mean number of cycles given in the TAX 327 trial was 9.5. However, in a retrospective chart review in Canada the median number of cycles was 7 (43). Reasons to explain this difference may include the tolerance to docetaxel.

Docetaxel is administered in the outpatient clinic. A rechallenge of docetaxel treatment after an initial response and a minimum 3 months interval since the last docetaxel treatment is often considered in daily practice.

For first-line docetaxel in CRPC, a cost-utility analysis (UK, 2007) showed that the ICER per QALY was €38,478 (in sensitivity analysis the ICER ranged from €32,964 to €39,174) (34). Since generic preparations of docetaxel have become available, direct costs of docetaxel treatment are expected to decrease and therefore the cost-effectiveness of docetaxel in the Netherlands is expected to improve.

An illustrative economic evaluation was conducted to obtain actual yearly docetaxel costs on prostate cancer in the Netherlands. The other direct medical costs, including co-medication (e.g., anti-emetics), therapy of adverse events and outpatient clinic visits were not included in this evaluation. The calculations were limited due to assumptions. If possible, assumptions were made based on literature. One assumption was that no patients were treated in trial protocols, however it is estimated by the interviewed medical oncologists that 40% to 70% of patients are treated in clinical trials. Because a low expected rate of patients using the weekly docetaxel regimen (based on the interviews), we did not include this regimen in our calculation. Other assumptions, concerning percentages of patients treated and number of cycles given, have been tested in sensitivity analyses. However, more accurate data on direct costs of docetaxel in prostate cancer are not available. The impact of docetaxel for the indication prostate cancer on the Dutch health care budget is estimated to be €6,682,200 per year based on our calculation. This calculation is particularly sensitive in the upward direction to the number of patients treated (range €2,863,800 to €12,887,100). Our calculations suggest that approximately 21% of total costs of docetaxel in the Netherlands are for account of prostate cancer (see Figure 1).

Docetaxel is now standard first-line therapy in symptomatic, metastasized CRPC. Eligibility criteria of the TAX 327 trial included metastasized CRPC and a Karnofsky performance status score of at least 60% (ECOG 0-2). However, identifying the patient who benefits from docetaxel and the timing of treatment is a point of discussion. Retrospectively, risk factors predicting overall survival were anemia (hemoglobin < 8.1 mmol/l), progression by bone scan criteria, visceral metastases and presence of clinically significant pain. These risk factors could help to determine the subgroup of patients that would benefit from systemic cytotoxic therapy (44).

A retrospective analysis of docetaxel-use in elderly patients (aged >75 years) has been done in France (45). Docetaxel was active and feasible in elderly patients (aged >75 year) with a good performance status. Patients older than 80 years and patients with poorer performance status (ECOG 2 or higher) were more often treated with an adapted regimen (mostly weekly docetaxel). The adapted regimen resulted in increased non-hematological toxicity and earlier discontinuation. The first conclusion was that the optimal treatment of frail patients with CRPC remains to be established. Secondly, these findings highlighted the need to integrate a geriatric assessment in the clinical decision-making process in frail patients. The consensus of the International Society of Geriatric Oncology (SIOG) Prostate Cancer Task Force is that older men with prostate cancer should be managed according to their individual health status, which is mainly driven by the severity of associated comorbid conditions, and not according to chronological age (46). Geriatric assessment (comorbidity screening, dependence status and nutritional status) and interventions could help in optimizing care in elderly patients with CRPC. According to our interviews, geriatric consultation is incorporated in the clinical decision-making in two out of five hospitals. Adequate selection of patients who may benefit of chemotherapy in CRPC will further improve the cost-effectiveness of treatment.

European (ESMO) and American (NCCN) guidelines concerning CRPC have been updated in 2010, whereas the Dutch guideline is outdated (2007) (1;2;5). In the Dutch guideline, all patients with CRPC who are fit for chemotherapy should be considered for treatment with 3-weekly docetaxel. However, it is explicitly mentioned that the modest survival benefit (2 months) and modest chance of improvement of quality of life (22%) needs to considered in the light of the potential adverse events and costs. In the ESMO guideline all symptomatic CRPC patients should be considered for treatment with 3-weekly docetaxel. Mitoxantrone is an alternative if docetaxel is contra-indicated. In the Dutch and ESMO guidelines second-line therapy is not mentioned. In the NCCN guideline Sipuleucel-T is considered appropriate for asymptomatic or minimally symptomatic CRPC patients, whereas 3-weekly docetaxel is the treatment of choice in symptomatic CRPC. Mitoxantrone and cabazitaxel are considered optional second-line treatments.
We conclude that due to rapid evolution of treatment options in CRPC, guidelines need to be updated on a regular basis. In all guidelines, there is no important difference in the position of docetaxel treatment in CRPC.

According to our interviews, docetaxel is considered by medical oncologists in all hospitals in daily practice in the Netherlands. Selection of patients and timing of treatment in CRPC is based on limited evidence and mostly on experience of medical oncologists. However, it is estimated that a subgroup of patients is not referred by urologists for treatment of CRPC. The quantity and characteristics of this subgroup and the implications of this selection are not known. Another remarkable conclusion from our interviews is the estimate that estramustine is not seldom prescribed by urologists. Estramustine as single-agent therapy has not proven to be effective in terms of survival or palliation as compared to best supportive care (12). The use of estramustine is not advised in guidelines (1;2;5). It may be worthwhile to evaluate the effect of the selection of patients for referral by urologists and the effect of estramustine prescription.

In the illustration on daily practice in one academic centre, 38% of all prostate cancer patients were treated with chemotherapy and 62% received other treatment. An extensive evaluation concerning treatment options was not carried out.

Second-line therapy
Mitoxantrone is indicated for pain palliation in CRPC, and is used by some oncologists as second-line treatment after treatment with docetaxel. However, the effectiveness and cost-effectiveness of mitoxantrone as second-line treatment have never been prospectively evaluated. In the TAX 327 study, 27% of patients treated with 3-weekly docetaxel crossed-over to second-line therapy (mitoxantrone) (17). The median number of cycles of mitoxantrone was 4. PSA response rates and PSA PFS were low (15% and 3.4 months, respectively). In a retrospective chart review in Canada 41% of patients treated with docetaxel received second-line treatment, of which 89% consisted of mitoxantrone with a response rate of 19%. (43).
New developments in treating CRPC have been achieved recently. Cabazitaxel has been registered as second-line treatment in CRPC in the US in 2010, and registration is expected soon in the Netherlands. Quality of life and cost-effectiveness has not yet been evaluated.
Based on the interviews, mitoxantrone or treatment in trial protocols are currently the most common second line therapies in the Netherlands.

For patients, quality of life and adequate information concerning treatment options in CRPC are pivotal. The patient association plays an important role in informing patients. Urologists and medical oncologists should explore and be aware of patient's preferences. Assistance of a case manager, e.g. a specialized nurse, can assist physicians and patients in informing and decision making.

New promising hormonal and immunological treatment options as both first-line and

second-line treatment in CRPC are evaluated. It is expected that treatment choices in CRPC will change dramatically in the coming years. Robust cost-effectiveness evaluations are needed to optimally incorporate these treatment options into clinical practice.

Future research should be directed at direct comparison of treatment options (e.g. docetaxel versus cabazitaxel in docetaxel-pretreated CRPC) and evaluation of the optimal timing and sequence of treatment options in CRPC.

Acknowledgements

We thank R. Otten, clinical librarian (VU Medical Center, Amsterdam), for his assistance in the literature search. We also thank J. Hugtenburg and C. Boons (VU Medical Center, Amsterdam) for cooperating in the preparation of the manuscript. Special thanks go to the medical oncologists and the patient representative from SCP (Stichting Contactgroep Prostaatcarcinoom), who were willing to participate in the structured interviews.

Biography contributors, conflict of interests

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Conflict of interests: paid for ad hoc participation in scientific advisory boards of BMS, Sanofi Aventis, Bayer, Roche, Johnson & Johnson, Astellas/Medivation, Bavarian Nordic, Amgen.

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Conflict of interests: none.

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Appendices

Appendix A: Dutch epidemiological data on subgroups

ICD-code: C61 PROSTATE

Relative survival of prostate cancer patients (18 years and older) in the Netherlands											
	tumor count	Years after diagnosis									
		0	1	2	3	4	5	6	7	8	9	10
Year of diagnosis*	**118226**											
1988-1992	10864	100%	91%	81%	74%	68%	62%	57%	54%	50%	48%	47%
1993-1997	26984	100%	94%	88%	83%	80%	76%	74%	71%	70%	68%	65%
1998-2002	34847	100%	95%	91%	87%	84%	81%	79%	76%	75%	73%	71%
2003-2007	45531	100%	97%	93%	90%	87%	85%					
2003	8201	100%	97%	92%	89%	86%						
2004	9386	100%	96%	93%	90%							
2005	8819	100%	96%	93%								
2006	9559	100%	97%									
2007	9566	100%	97%									
age group (1998-2007)												
18-44 years	2778	100%	98%	93%	90%	86%	85%	82%	79%	76%	75%	72%
45-54 years	18301	100%	98%	95%	93%	90%	89%	87%	85%	83%	82%	81%
55-64 years	33543	100%	98%	94%	91%	89%	86%	84%	82%	80%	78%	77%
65-74 years	21962	100%	95%	89%	85%	81%	79%	75%	73%	70%	68%	65%
>75 years	3794	100%	86%	79%	75%	68%	64%	63%	59%	60%	57%	56%
TNM-stadium 5th edition; 1999-2002												
I	631	100%	100%	100%	100%	101%	102%	103%	103%	103%	103%	104%
II	16380	100%	99%	99%	98%	97%	96%	95%	93%	92%	91%	91%
III	4229	100%	100%	98%	96%	94%	92%	90%	87%	85%	83%	80%
IV	5884	100%	86%	69%	56%	48%	42%	36%	33%	30%	27%	25%
unknown	274	100%	85%	78%	70%	69%	67%	65%	61%	54%	49%	46%
6th edition; 2003-2007												
I	623	100%	99%	100%	100%	99%	100%					
II	28525	100%	100%	100%	100%	99%	99%					
III	6883	100%	100%	99%	98%	96%	94%					
IV	8233	100%	87%	72%	60%	51%	45%					
unknown	206	100%	82%	74%	68%	65%	57%					

* standardised to age group
Table 2 derived from (4)

Appendix B: Performance scales (Karnofsky, ECOG-WHO-Zubrod)*

Status	Karnofsky	Grade	ECOG
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80		
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair 50% or more of waking hours
Disabled. Requires special care and assistance	40		
Severly disabled. Hospitalization indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20		
Moribund	10		
Dead	0	5	Dead

* Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

Appendix C: Literature search protocol

Pubmed/Medline (4 November 2010)

Search	Most Recent Queries	Result
#65	Search #10 AND #64	21
#64	Search "Costs and Cost Analysis"[Mesh] OR cost*[tiab] OR economic*[tw] OR cost[tiab] OR costs[tiab]	591598
#58	Search #45 OR #57	211
#57	Search #34 NOT medline[sb]	35
#45	Search #10 Limits: Humans, Clinical Trial, Meta-Analysis, Practice Guideline, Randomized Controlled Trial, English, Dutch, Publication Date from 2005 to 2011	176
#34	Search #31 OR #32	710
#33	Search #29 OR #30	6193749
#32	Search #10 AND #30 Limits: Publication Date from 2005 to 2011	676
#31	Search #10 AND #29 Limits: Publication Date from 2005 to 2011	470
#30	Search randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]	2705125
#29	Search (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR "latin square" [tw] OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [pt] OR evaluation studies [pt] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control[tw] OR controll*[tw] OR prospectiv* [tw] OR volunteer* [tw])	4940276
#10	Search #6 AND #9	1062
#9	Search #7 OR #8	6786
#8	Search 114977-28-5[EC/RN Number] OR 148408-66-6[EC/RN Number]	4742
#7	Search docetaxel[tw] OR docetaxol*[tw] OR taxotere[tw] OR taxoltere[tw]	6786
#6	Search #1 OR #2 OR #5	93264
#5	Search #3 AND #4	25045
#4	Search (prostate[tiab] OR prostatic[tiab])	110991
#3	Search Tumor[tiab] OR tumora*[tiab] OR tumorb*[tiab] OR tumorc*[tiab] OR tumord*[tiab] OR tumore*[tiab] OR tumorf*[tiab] OR tumorg*[tiab] OR tumorh*[tiab] OR tumori*[tiab] OR tumorj*[tiab] OR tumork*[tiab] OR tumorl*[tiab] OR tumorm*[tiab] OR tumorn*[tiab] OR tumoro*[tiab] OR tumorp*[tiab] OR tumorq*[tiab] OR tumorr*[tiab] OR tumors*[tiab] OR tumort*[tiab] OR tumoru*[tiab] OR tumorv*[tiab] OR tumorw*[tiab] OR tumorx*[tiab] OR tumory*[tiab] OR tumorz*[tiab]	786427
#2	Search (prostate[tiab] OR prostatic[tiab]) AND (cancer*[tiab] OR carcinoma*[tiab] OR neoplas*[tiab] OR tumour*[tiab] OR adenoma*[tiab])	77148
#1	Search "Prostatic Neoplasms"[Mesh]	72091

Embase (4 November 2010)

Search	Query	Result
#23	#8 AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2005-2011]/py	266
#18	#8 AND #17	39
#17	'cost benefit analysis'/exp OR 'cost effectiveness analysis'/exp OR 'cost utility analysis'/exp	118819
#8	#3 AND #7	3089
#7	#4 OR #5 OR #6	20894
#6	'114977 28 5':rn OR '148408 66 6':rn	19182
#5	docetaxel:mn,tn,ab,ti OR docetaxol*:mn,tn,ab,ti OR taxotere:mn,tn,ab,ti OR taxoltere:mn,tn,ab,ti	9366
#4	'docetaxel'/exp	20345
#3	#1 OR #2	118273
#2	prostate:ab,ti OR prostatic:ab,ti AND (cancer*:ab,ti OR carcinoma:ab,ti OR neoplas*:ab,ti OR tumor*:ab,ti OR tumour*:ab,ti OR adenoma*:ab,ti)	92854
#1	'prostate tumor'/exp	103442

Cochrane (4 November 2010)

ID	Search	Hits
#1	(prostate OR prostatic):ti,ab,kw and (cancer* OR neoplas* OR tumor* OR tumour* OR adenoma*):ti,ab,kw	3841
#2	(docetaxel OR docetaxol* OR taxotere OR taxoltere):ti,ab,kw	1150
#3	(#1 AND #2)	92
#4	(#3), from 2005 to 2010	70