Chemotherapy in patients with castration-resistant prostate cancer

Hielke J. Meulenbeld, Paul Hamberg, Ronald de Wit

Department of Medical Oncology, Erasmus University Medical Center, Daniel den Hoed Cancer Center, Rotterdam, The Netherlands

Introduction

Prostate cancer is, excluding non-melanoma skin cancer, the most common cancer among men, with approximately 301,500 new cases and 67,800 deaths annually in the European Union [1]. Prostate cancer is a major clinical problem, not only because of its high incidence and mortality, but also because of the severe morbidity associated with the advanced stages of this disease.

Treatment for clinically localised disease consists of early intervention with surgery, radiation therapy (external beam or brachytherapy), androgen suppression, or observation.

Treatment for metastatic prostate cancer is palliative. In patients with metastatic prostate cancer, androgen ablation therapy is almost universally accepted as the initial treatment of choice, with a response rate ranging from 80% to 90%. However, these tumours, at a median of 18 months, become androgen-independent and grow despite androgen ablation [2]. Because patients may respond to second- and third-line hormonal therapies, the Prostate-Specific Antigen Working Group (PCWG 2) advised the classification of tumours that are progressing with castrate levels of testosterone (serum testosterone levels <50 ng/dL) as castration resistant [3]. Hormone-refractory prostate cancer (HRPC) arises when disease progression continues despite secondary hormonal manoeuvres that may include anti-androgen withdrawal [4]. The mechanisms of the development of hormone resistance are largely unknown, although the molecular changes of the androgen receptor, e.g. mutation or amplification, can explain some observations [5].

Historically, clinical management for advanced prostate cancer has been primarily focused on controlling symptoms. Over the last two decades, treatment options for patients with CRPC have changed notably.

Prostate cancer was considered resistant to chemotherapy until the mid-1990s, when randomised trials showed that mitoxantrone with prednisone resulted in prostate specific antigen (PSA) responses greater than 50%, pain relief and improved quality of life (QoL) more frequently than prednisone alone [6,7]. In 2004, two landmark trials, TAX 327 [8] and Southwest Oncology Group (SWOG) 99-16 [2]0, showed for the first time a survival benefit in patients with advanced CRPC by docetaxel-based chemotherapy as compared to mitoxantrone plus prednisone.

Chemotherapy for prostate cancer

Mitoxantrone

Cytotoxic chemotherapy has been studied in the treatment of CRPC for many years. Until 1996, when Tannock and colleagues [7] reported a randomised phase III trial defining a clear role for mitoxantrone based chemotherapy, there was no convincing evidence to suggest that chemotherapy was of benefit to a meaningful proportion of patients with CRPC [9]. In the trial by Tannock and colleagues, 161 men were randomised to receive mitoxantrone plus prednisone or prednisone alone. Palliative response, defined as pain relief and/or reduction in analgesic requirement, was observed in 23 of 80 patients (29%) who received mitoxantrone plus prednisone, and in 10 of 81 patients (12%) who received prednisone alone. Most responding patients had an improvement in QoL and a non-significant decrease in PSA levels. There was no difference in overall survival. Toxicity of combined therapy included grade 3 or 4 neutropenia in 45% of all treatment courses, although only 1% was complicated by fever. These data were confirmed by the Cancer and Leukaemia Group B (CALGB) 9182 trial, in which 242 patients with CRPC were randomised between mitoxantrone plus hydrocortisone or hydrocortisone alone [10]. The PSA response was greater with the mitoxantrone plus hydrocortisone regimen, and there was a possible benefit with respect to pain control in those given mitoxantrone. However, no difference in overall survival was observed. Despite any survival benefit, the results of these trials led

to the adoption of mitoxantrone plus prednisone as the standard regimen prior to the development of docetaxel-based chemotherapy.

Proof-of-concept trials using docetaxel

Shortly after the reports of the mitoxantrone studies became available, proof-of-concept trials were being conducted to assess the feasibility and therapeutic potential of the taxanes. Several docetaxel-based regimens were investigated: a 3-weekly regimen, a weekly regimen (owing to the assumption that this regimen would be better tolerated in an elderly population), and a combination of docetaxel and estramustine. The PSA response rates in these phase I-II trials evaluating docetaxel-based regimens were higher (41–68%) than those reported previously in the mitoxantrone trials [11–16]. In addition, these trials were the first to report objective response rates of approximately 20–50% in patients with measurable disease [11–16]. Furthermore, a median survival of up to 27 months was reported in patients who received 3-weekly docetaxel [11]0. These results prompted the initiation of two large randomised phase III studies, TAX 327 and SWOG 99-16, to further evaluate the anti-tumour activity of docetaxel in this setting [2,8].

Phase III trials of docetaxel-based therapy in advanced castration-resistant prostate cancer

TAX 327 [8]

The TAX 327 study was a large international randomised trial which compared the effectiveness of three schedules: 3-weekly mitoxantrone (12 mg/m^2), 3-weekly docetaxel (75 mg/m^2) and weekly docetaxel (30 mg/m^2), all combined with prednisone (5 mg twice daily) in patients with CRPC [8]. The treatment duration was 30 weeks in all treatment schedules. A total of 1006 patients were randomised from March 2000 to June 2002. The median overall survival was 16.5 months in the mitoxantrone group, 17.4 months in the group given weekly docetaxel and 18.9 months in the group given docetaxel every 3 weeks. This improvement in overall survival was statistically significant ($P = 0.009$) in the group given docetaxel every 3 weeks, with a significant reduction in the risk of death of 24%. A recent published updated survival analysis of the TAX 327 confirmed the significantly better survival with extended follow-up [17]. Median survival time was 19.2 months in the 3-weekly docetaxel arm, 17.8 months in the weekly docetaxel arm, and 16.3 months in the mitoxantrone arm. More patients survived $\geqslant$3 years in the groups treated with 3-weekly docetaxel and weekly docetaxel (18.6% and 16.6%, respectively) compared with patients treated with mitoxantrone (13.5%). Due to crossover between the treatment arms after disease progression in more than 30% of the patients the survival benefit of the docetaxel-based treatment groups is likely underestimated as compared to the mitoxantrone group. A subset analysis showed that the survival benefit with 3-weekly docetaxel remains in all subgroups; with similar trends in survival for patients above and below the age of 65 years, for those with or without pain at baseline, and for those with baseline PSA greater than or less than the median value of 115 ng/mL. Hence, there is no indication that specific subgroups (e.g. elderly patients, significant pain at entry) had less benefit from treatment with docetaxel-based chemotherapy. A reduction in pain was significantly more frequent among patients receiving docetaxel every 3 weeks than among patients treated with mitoxantrone (35% versus 22% respectively; $P = 0.01$). The rates of PSA response were significantly higher in both docetaxel groups compared with mitoxantrone (docetaxel every 3 weeks, 45%, weekly docetaxel 48% and mitoxantrone 32%; $P < 0.001$ for both comparisons). Also, the QoL assessment showed a significant improvement with the 3-weekly schedule of docetaxel compared to those treated with mitoxantrone (22% versus 13%; $P = 0.009$).

Grade 3/4 neutropenia was significantly more common in patients treated with the 3-weekly docetaxel (32%) than for those patients receiving weekly docetaxel or mitoxantrone (2% and 22%, respectively), although the incidence of febrile neutropenia was less than 3% in all treatment arms. Nausea and vomiting were common with all regimens (38% to 42%) and diarrhoea was significantly more frequent with both docetaxel schedules. Discontinuation of treatment with docetaxel was incidentally due to fatigue, musculoskeletal events, nail changes, sensory neuropathy, and infection whereas for mitoxantrone cardiac dysfunction was the major reason to discontinue therapy.

SWOG 99-16 [2]

The multicentre phase III study SWOG 99-16 was built on the prejudice that the combination of docetaxel plus estramustine had the greatest therapeutic potential. SWOG 99-16 compared docetaxel (60 mg/m^2, day 2) plus estramustine (280 mg, three times daily, days 1–5) with mitoxantrone (12mg/m^2,

day1) plus prednisone (5 mg twice daily). Both were given on a 21-day cycle, and dose escalation to docetaxel 70 mg/m^2 or mitoxantrone to 14 mg/m^2 was allowed on cycle 2 if no grade 3/4 toxicities were detected in the first cycle. A total of 770 men were randomised; of whom 69 patients were found ineligible. Median overall survival was significantly longer in the group treated with docetaxel plus estramustine than the group treated with mitoxantrone plus prednisone, 17.5 months versus 15.6 months, respectively (P = 0.020), with a 20% reduction in the risk of death in the group treated with docetaxel plus estramustine. The median time to progression was 6.3 months in the group given docetaxel and estramustine and 3.2 months in the group given mitoxantrone and prednisone ($P < 0.001$). The rates of PSA response were significantly higher in the docetaxel plus estramustine group compared with the mitoxantrone plus prednisone group (50% versus 27%; $P < 0.001$). Patients treated with docetaxel plus estramustine did not demonstrate statistically or clinically significant differences for pain palliation or improvement of global QoL when compared with patients treated with mitoxantrone plus prednisone. As the patients treated in SWOG 99-16 and TAX 327 had similar baseline characteristics, the reason for this difference in palliation may be attributed to incomplete QoL data collection in the SWOG 99-16, the continuous administration of prednisone in the TAX 327, and the additional toxicity caused by estramustine. As compared with the group given mitoxantrone and prednisone, the group given docetaxel plus estramustine had significantly higher rates of toxicity, with an increase in grade 3/4 nausea and vomiting (20% versus 5%, respectively; $P < 0.001$), neutropenic fever (5% versus 2% respectively; $P = 0.01$) and cardiovascular events (15% versus 7% respectively; $P = 0.001$). The most frequent vascular toxicities were pulmonary embolism and thrombosis, which were attributable to the oestrogenic effects of estramustine [2].

These two independent studies represent an important therapeutic milestone by demonstrating that docetaxel-based chemotherapy compared with mitoxantrone improves overall survival in patients with advanced CRPC. Given that both docetaxel-based regimens resulted in a similar survival benefit, the combination of docetaxel plus prednisone is preferred in routine clinical practice, due to the avoidance of estramustine-related toxicity. Although several phase II studies and small randomised trials have suggested that the docetaxel plus estramustine combination may improve the PSA response rate compared with docetaxel alone, this was not supported by the results of the two pivotal phase III trials [15,16,18,19]. No clinically relevant advantage of the addition of estramustine to docetaxel has been observed in a randomised trial [20]. In this study, 150 patients were randomised between docetaxel alone (35 mg/m^2 on days 2 and 9, every 3 weeks) or docetaxel in combination with estramustine (280 mg orally three times a day on days 1 to 5 and 8 to 12, every 3 weeks). All patients received prednisone (10 mg/day). The PSA response rate was not statistically different between the two groups. No significant differences were found for median time to PSA progression (docetaxel plus estramustine 6.9 months versus docetaxel 7.3 months) or median overall survival time (docetaxel plus estramustine 19.3 months versus docetaxel 21 months). More patients had at least one grade 3 or 4 toxicity with docetaxel plus estramustine (45%) compared with the docetaxel group (21%; $P = 0.005$); mainly as a result of grade 3 or 4 gastrointestinal toxicity ($P = 0.05$). Taking the data all together, in view of the apparent lack of superior activity and greater toxicity by the addition of estramustine, docetaxel every 3 weeks plus low-dose prednisone can be considered as the current standard treatment for patients with CRPC [21,22]. The optimal duration of docetaxel based chemotherapy for CRPC has not yet been established. In the Tax 327 patients were scheduled to receive 10 cycles of chemotherapy, in the SWOG 99-16 this was 12 cycles. As these studies are likely to define the standard of care in patients with CRPC, currently, standard practice is to treat patients with a fixed number of 10 cycles of chemotherapy.

The role of intermittent chemotherapy in the management of CRPC remains to be fully defined. A phase III trial of docetaxel plus either high-dose calcitriol or placebo permitted the use of intermittent chemotherapy and suggested that intermittent chemotherapy may be a feasible treatment strategy in selected patients who respond well on the initial cycles of chemotherapy, with treatment resuming when PSA begins to rise again [23]. However, there are no randomised phase III trials comparing intermittent versus continuous docetaxel-based chemotherapy. Further studies are needed to determine the value of this strategy on efficacy and cumulative toxicity of treatment.

Predicting outcomes in CRPC

CRPC is a heterogeneous disease with rather well characterised factors associated with outcome. Several prognostic models have been developed to estimate

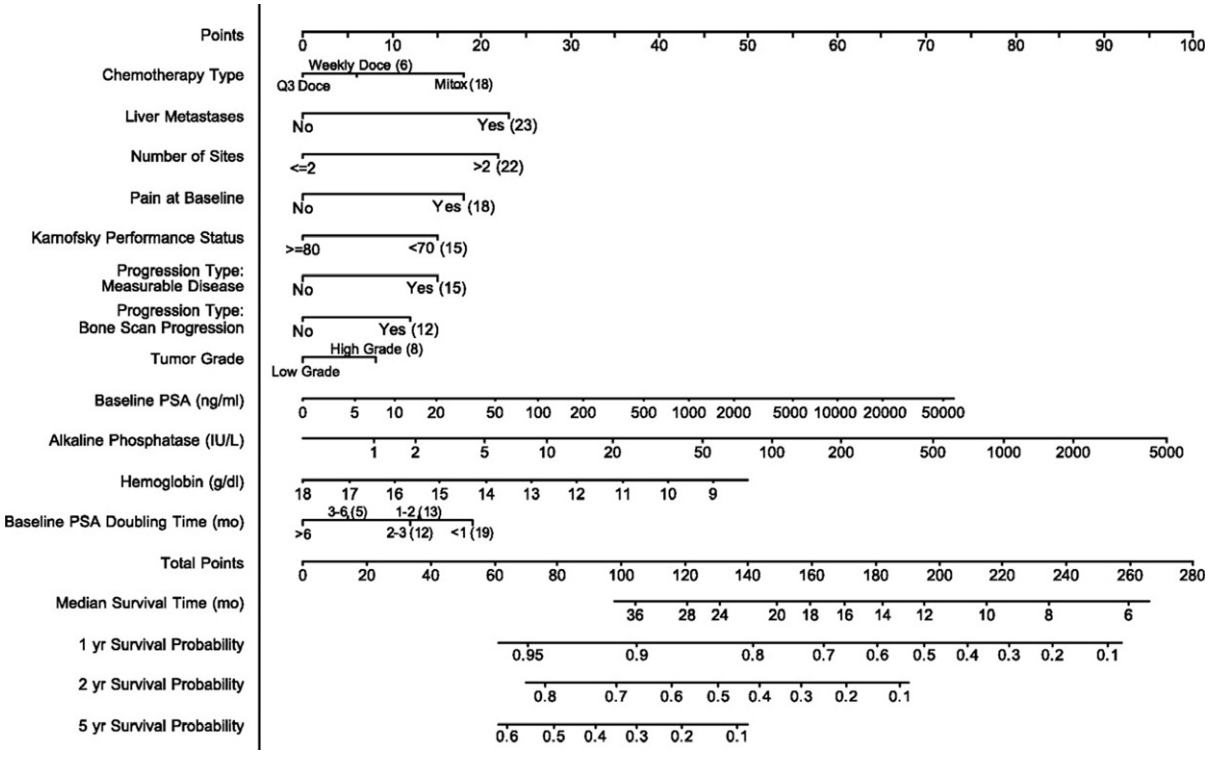

Fig. 1. Nomogram for survival of patients treated with cytotoxic agents for progressive CRPC (689 patients, 518 mortality events). Note: a pain intensity of $\geqslant$2 and/or an analgesic score of $\geqslant$10 were defined in the original protocol as indicative of the presence of significant pain. Reprinted with permission from Armstrong AJ and colleagues; A contemporary prognostic nomogram for men with hormone refractory metastatic prostate cancer: a TAX 327 study analysis. *Clin Cancer Res* 2007;**13**:6396–403, fig. 3 [26].

survival in patients with CRPC. The CALGB co-operative study group performed a pooled analysis combining data from six trials involving 1101 patients with metastatic CRPC treated between 1991 and 2001 and created a prognostic model for risk stratification of metastatic CRPC, by comparing the predicted probability with the actual survival probability on the basis of pre-treatment factors [24]. The factors used in this nomogram to estimate 12- and 24 month survival probability included the following: lactate dehydrogenase (LDH), PSA, alkaline phosphatase, Gleason score, performance status, haemoglobin, and the presence of visceral disease. Patients were classified into one of four risk groups. The observed median overall survival durations were 7.5, 13.4, 18.9, and 27.2 months for the first, second, third, and fourth risk groups, respectively. The corresponding median predicted overall survival times were 8.8, 13.4, 17.4, and 22.8 months for the four risk groups.

The significant better overall survival in the TAX 327 for patients without pain at entry [17]0, treated with docetaxel-based chemotherapy, was confirmed in a recent study, showing a median overall survival of 17.6 months and 10.2 months in men with low and high pain scores, respectively [25].

A subset analysis of the TAX 327 cohort, to investigate the significance of novel predictive variables, resulted in the TAX 327-based predictive nomogram (Fig. 1) [26]. Ten factors were associated with survival (Table 1) [26]. Univariately, PSA-doubling time (PSA-DT) is a prognostic factor for overall survival, but in the multivariate analysis PSA-DT retained only borderline significance (Fig. 2) [26]0. As shown in the nomogram baseline PSA, alkaline phosphatase, visceral metastases, progression type, and haemoglobin at baseline have stronger predictive value (Fig. 1) [26]0.

In contrast to the Halabi nomogram, which is regarded as a prognostic nomogram of the untreated underlying disease, the TAX 327 nomogram can be seen as a prognostic nomogram if it is assumed that the patient with CRPC is going to be treated with docetaxel-based chemotherapy. The TAX 327 nomogram should not be used for patients that do not receive treatment with docetaxel.

Recent data from TAX 327 risk group analysis, to develop and validate clinically applicable predictive

Table 1
A multivariate Cox proportional hazards analysis of ten independent prognostic markers showing a significant association with overall survival

Variable	Multivariate HR (95% CI)	*P*
Liver metastases	1.66 (1.09–2.54)	0.019
Number of metastatic sites (>2 vs. ⩽2)	1.63 (1.23–2.15)	0.001
Pain at baseline	1.48 (1.23–1.79)	<0.001
Performance status (⩽70 vs. ⩾80)	1.39 (1.06–1.82)	0.016
Progression type		
Measurable disease	1.37 (1.10–1.70)	0.005
Bone scan progression	1.29 (1.06–1.57)	0.010
Baseline PSA-DT (<55 vs. ⩾55 d)	1.19 (0.99–1.42)	0.066
Baseline log PSA (for every unit rise in log (PSA) in ng/dL)	1.17 (1.10–1.25)	<0.001
Tumour grade (Gleason ⩾8 or WHO 3–4 vs. Gleason ⩽7 or WHO 2–3)	1.18 (0.99–1.42)	0.069
Alkaline phosphatase, log scale (per log unit rise, IU/L)	1.27 (1.15–1.39)	<0.001
Haemoglobin (per unit decline, g/dL)	1.11 (1.03–1.19)	0.004

Adapted with permission from Armstrong and colleagues; A contemporary prognostic nomogram for men with hormone refractory metastatic prostate cancer: a TAX327 study analysis. *Clin Cancer Res* 2007; 13: 6396–403, Table 3 [26].
PSA-DT, prostate specific antigen-doubling time; vs., versus; d, days; PSA, prostate specific antigen; WHO, World Health Organisation; HR, hazard ratio; CI, 95% confidence interval.

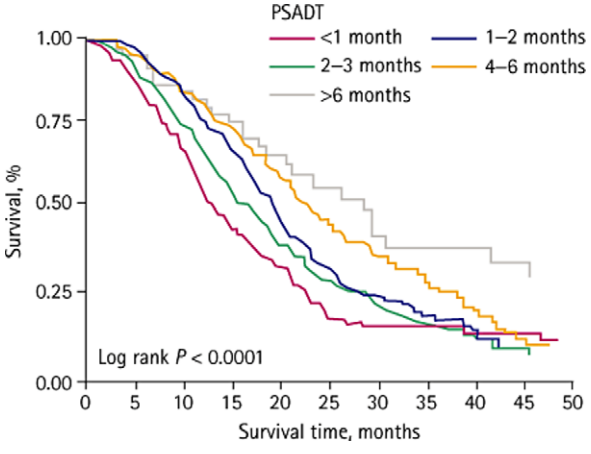

Fig. 2. Kaplan–Meier estimates of overall survival according to PSA-doubling time in the TAX 327 cohort ($n = 686$, 518 mortality events). The median PSA-DT in this study was 55 days. PSA-DT was separated into five cohorts: >6 months ($n = 44$, median OS not reached, mean OS 25 months), 3–6 months ($n = 118$, median OS not reached, mean OS 22.5 months), 2–3 months ($n = 151$, median OS 20.7 months), 1–2 months ($n = 264$, median OS 18.6 months), and <1 month ($n = 109$, median OS 13.3 months). Reprinted with permission from Armstrong and colleagues; A contemporary prognostic nomogram for men with hormone refractory metastatic prostate cancer: a TAX 327 study analysis. *Clin Cancer Res* 2007;**13**:6396–403, fig. 1 [26].

factors for response-based endpoints and assess the performance of a risk-group based classification in predicting PSA declines and overall survival in CRPC, identified three risk groups on the basis of four independent risk factors [27]. In this multivariate analysis, based on the 3-month PSA decline data in patients enrolled in the TAX 327, four independent risk factors were identified that predicted for not reaching a ⩾30% PSA decline in 3-month PSA: significant baseline pain, visceral metastases, anaemia (haemoglobin <13 g/dl), and bone scan progression at baseline. These risk factors were combined to develop three risk groups; a low-risk group consisted of patients with 0–1 risk factors, an intermediate-risk group of patients with two risk factors and a high-risk group of patients with 3–4 risk factors, with a median overall survival of 25.7, 18.7 and 12.8 months, respectively, with a concordance index of 0.64 ($P < 0.0001$ for trend).

When to start cytotoxic therapy

The widespread use of PSA monitoring has resulted in earlier detection of CRPC, often in asymptomatic patients. An important question for the management of asymptomatic disease is whether to initiate chemotherapy or to wait until symptoms occur. Although chemotherapy may halt or reverse progression, associated toxicity of the chemotherapy might lead to deterioration of QoL. Comparative data evaluating the merits of delaying the initiation of chemotherapy are lacking. As previously mentioned, survival benefit from treatment with docetaxel-based chemotherapy is equal for all subgroups of patients [17]0. Although the benefit is similar, there is a substantial difference in overall survival in patients with and without pain

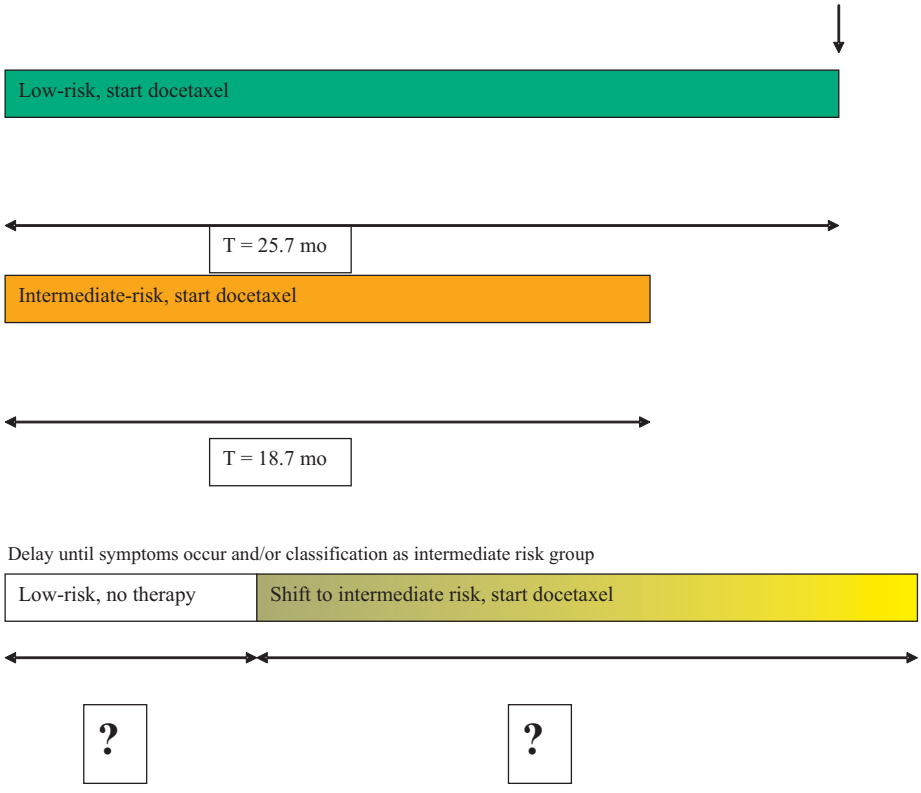

Fig. 3. To estimate the time expenditure in which the group of asymptomatic/low-risk patients is likely to become symptomatic, or to develop other adverse prognostic features with associated poorer survival outcome. T = Overall survival with docetaxel in patients with CRPC according to TAX 327 in different risk groups [27]. Postponing chemotherapy for the purpose of gaining some extra time without therapy, without impeding on survival expectancy when chemotherapy eventually starts, may be considered beneficial. The risk of postponing treatment for only some months at which time the patient has obtained significant worse features and associated decreased effects on survival probability must be avoided. Mo, months.

(14.4 months versus 21.3 months, respectively), but this does not necessarily imply benefit from early use of chemotherapy. Some patients had a decreased QoL after starting chemotherapy, and this was more often observed in patients with minimal symptoms [28]. Delaying cytotoxic therapy may be a suitable approach in CRPC patients with rather indolent disease, for which the following criteria were proposed: PSA only progression as a single sign of metastatic disease with low baseline PSA and a slow PSA-DT, a normal (or slightly raised) alkaline phosphatase and normal or (slightly lowered) haemoglobin. In patients who are more likely to develop symptoms and progression at an early stage (based on high PSA-DT and/or high baseline PSA and/or bone scan progression and/or visceral progression), the start of chemotherapy should not be postponed [21].

Therefore, to optimise management of advanced CRPC, it becomes increasingly important to understand the predictive factors influencing the outcome. It is difficult to estimate the time expenditure in which the group of asymptomatic/low risk patients is likely to become symptomatic, or to develop other adverse prognostic features with associated poorer survival outcome. Postponing chemotherapy and gaining significant time without therapy, without impeding on survival expectancy when chemotherapy eventually starts, may be considered beneficial, whereas the risk of postponing treatment for only some months at which time the patient has obtained significant worse features and detrimental effects on survival probability must be avoided.

Furthermore, the data derived from patients classified as intermediate risk cannot easily be applied to patients whose disease characteristics worsen from low to intermediate risk (Fig. 3). As long as these two questions remain unanswered, the decision with regard to the introduction of cytotoxic therapy in asymptomatic men can only be based on the circumstantial evidence available.

Assessing response for therapy

Assessing the response to treatment in prostate cancer is difficult as measurable disease, by standard oncologic criteria, occurs infrequently. The majority of men have bone metastases which are difficult to quantify objectively and reproducibly. The identification of surrogate endpoints, replacing solid endpoints, is crucial to the rapid evaluation of new cancer drugs. Recently, the PCWG 2 updated eligibility and outcome measures in trials that evaluate systemic treatment for patients with progressive prostate cancer and castrate levels of testosterone [3]0. Treatment should be continued for at least 12 weeks to ensure adequate drug exposure. PCWG 2 defined criteria of progression on the basis of changes in PSA, bone metastases, and measurable disease. PSA progression has been defined as a 25% or greater increase and an absolute increase of 2 ng/mL or more from the lowest documented PSA level, which is confirmed by a second value obtained 3 or more weeks later. When the bone scan is the sole indicator of progression, PCWG 2 defines progression in bone when at least two or more new lesions are seen on a bone scan compared with prior scans. Trials collecting data on measurable lesions should follow Response Evaluation Criteria in Solid Tumours (RECIST) [29]. An analysis based on the PSA data in patients entered in the SWOG 99-16 trial has demonstrated that a decline in serum PSA of 30% at 12 weeks and post-treatment PSA velocity were the optimal surrogate markers for survival [30]. This finding has been validated by analysis of the TAX 327 database, in which a $\geqslant$30% PSA decline within 3 months of treatment initiation provides the highest degree of surrogacy for overall survival with a HR of 0.50 after adjusting for treatment effect [31]. Another analysis of the TAX 327 database revealed that both PSA response (HR 0.59; $P < 0.001$) and pain response (HR 0.59; $P < 0.001$) were associated with longer survival [28]0. However, after adjusting for PSA and pain response, QoL response was not a significant predictor of survival (HR 0.97; $P = 0.84$).

Future directions

Different combinations of chemotherapy and numerous agents with novel mechanisms of anti-tumour activity have been studied in patients with CRPC; due to the rapid progress of this field it is beyond the scope of this review to cover all compounds under investigation.

Docetaxel-based combinations

Given the improved overall survival with docetaxel, several subsequent trials have administered docetaxel in combination with various agents to assess the additional benefit of these combinations relative to docetaxel alone.

Endothelin is a protein produced by vascular endothelium and is thought to play an important role in vascular homeostasis. The endothelin pathway is involved in several phases of prostate cancer development and progression [32].

Atrasentan is an oral selective inhibitor of endothelin-A receptor, and preclinical *in vivo* data have shown synergistic effects of atrasentan in combination with docetaxel chemotherapy [33]. A phase III trial comparing docetaxel with and without atrasentan, in patients with metastatic CRPC (SWOG S0421), is currently accruing patients.

Another endothelin receptor-A antagonist, ZD 4054, is also currently under investigation in a phase III study in combination with docetaxel for treatment of patients with metastatic CRPC.

Bevacizumab is a humanised monoclonal antibody to vascular endothelial growth factor (VEGF), a key activator of tumour angiogenesis. While single agent studies have failed to demonstrate significant results, a phase II study (CALGB 90006) added bevacizumab to docetaxel and estramustine in patients with metastatic CRPC with the result that 81% of the patients achieved a $\geqslant$50% PSA decline and overall median survival of 21 months [34]. The use of bevacizumab in the treatment of metastatic CRPC is currently being tested in a phase III trial comparing docetaxel with or without bevacizumab (CALGB 90401).

Several *in vitro* and *in vivo* models indicated that calcitriol (1,25-dihydroxyvitamin D3) inhibits the growth and stimulates the differentiation of prostate cancer cells [35,36]. The androgen-independent prostate cancer study of calcitriol enhancing docetaxel (ASCENT), a phase II trial of 250 patients with metastatic CRPC to compare docetaxel with or without high-dose calcitriol, suggested that the calcitriol-containing regimen was associated with improved survival, but the study was too underpowered to detect a survival difference and the primary endpoint PSA response did not reach statistical significance [37]. The subsequent phase III study (ASCENT-2) was closed by the Data and Safety Monitoring Board due to the higher number of deaths in the calcitriol plus docetaxel treatment group and the final analysis is awaited.

A Phase III study of Vaccine Immuno Therapy with Allogenic prostate cancer cell Lines 2

(VITAL-2), comparing docetaxel plus either prednisone or granulocyte-macrophage colony-stimulating factor gene transduced irradiated prostate cancer cells (GVAX), was recently closed because of a higher number of deaths in the docetaxel plus GVAX arm [38].

Bisphosphonates are inhibitors of osteoclast-mediated bone resorption that have been shown to decrease pain and the risk of skeletal complications by bone metastases in patients with breast cancer, prostate cancer and multiple myeloma [39]. Unlike bone metastases from breast cancer, most bone lesions in prostate cancer are osteoblastic. However, despite the osteoblastic nature of the metastatic bone lesions, morphologic studies suggest that most bone metastases from prostate cancer are characterised by excessive activity of both osteoblasts and osteoclasts [40,41]. Initial trials with first- and second-generation bisphosphonates (clodronate and pamidronate) have shown no significant effect on the prevention of skeletal-related events (SREs) [42,43]. In a phase III study zoledronic acid, a third generation bisphosphonate, significantly reduced SREs in patients with CRPC with bone metastases ($P = 0.021$) [44]. A follow-up study of 24 months confirmed its long-term efficacy with a 36% ($P = 0.002$) reduction in the ongoing risk of SREs in patients treated with zoledronic acid compared to the placebo group [45]. However, the study did not show a difference in survival or disease progression. Risedronate is an orally administered, third generation pyridinyl bisphosphonate, which reduces bone turnover and decreases resorption through osteoclastic effects, with no undesirable effects on cortical porosity or thickness or on cancellous bone volume [46]. Clinical studies with risedronate in patients with bone metastases have not been reported yet. Data from animal models have shown that risedronate can inhibit the formation and progression of bone metastases. In a mouse model, risedronate decreased breast cancer burden selectively in bone, which translated into a significantly longer survival for mice continuously treated with risedronate [47]. In another preclinical study, continuous administration of risedronate showed significant effects on the incidence and size of observed skeletal metastases in rats inoculated with ENU1564 mammary adenocarcinoma cells [48]. Pretreatment of prostate and breast cancer cells with risedronate and other bisphosphonates resulted in inhibition of tumour cell adhesion to unmineralised and mineralised osteoblastic extracellular matrices in a dose-dependent manner [49]. There is strong preclinical evidence that bisphosphonates and paclitaxel induce apoptosis in breast cancer cells in a synergistic manner when they are combined [50]. Therefore, an ongoing multicentre phase III trial, the Netherlands Prostate Study Group (NePro) study, is currently enrolling patients with CRPC with bone metastases to evaluate the addition of risedronate to docetaxel-based chemotherapy [51]. The primary endpoint in this study will be time to progression. Secondary endpoints will be PSA response rate, pain response, toxicity profile, objective response by RECIST when measurable disease, duration of PSA response and overall survival.

Second-line treatment

There are no approved agents for second-line therapy in patients with CRPC who progress after first-line docetaxel-based chemotherapy. Several options for these patients have been suggested e.g. clinical trials of novel agents, other cytotoxic agents, docetaxel retreatment, additional hormonal manipulations, and best supportive care [52]. However none of them have proven to improve QoL or overall survival. Being the previous standard of care, second-line mitoxantrone chemotherapy has been utilised after docetaxel-based chemotherapy. Retrospective studies have reported limited efficacy and tolerability, with PSA response rates in 10–20% of patients [53,54]. Retrospective crossover results of the TAX 327 trial identified 237 (23%) patients, among the 1006 patients, who received the other drug as second-line therapy off-study [55]. Eighty-nine men received 3-weekly docetaxel followed by mitoxantrone, 76 men received mitoxantrone after weekly docetaxel and 67 men received docetaxel after mitoxantrone. Median survival after crossover was 10 months and did not depend on direction of crossover. Data on PSA response were available for 96 patients: PSA response ($\geqslant$50% reduction) occurred in 15% of 71 men receiving mitoxantrone after docetaxel and in 28% of 25 men receiving docetaxel after mitoxantrone. Median PSA progression-free survival was 3.4 months for mitoxantrone after docetaxel and 5.9 months for docetaxel after mitoxantrone. One prospective phase II trial tested second-line mitoxantrone chemotherapy for docetaxel-refractory CRPC in 41 patients [56]. In this study mitoxantrone also only had modest activity. In total, 20% of the patients treated with mitoxantrone and prednisone had a PSA decline $\geqslant$50%, the median time to PSA progression was 2.3 months, and the median response duration was 5.9 months. Median overall survival for patients treated with second-line mitoxantrone was 9.8 months. From these data,

although mitoxantrone has a limited PSA response ranging from 0% to 20%, time to progression is short and toxicity is significant with no clear data on any palliative effect. Mitoxantrone should, therefore, be considered to have minimal activity after first-line docetaxel-based chemotherapy. The potential role of retreatment with docetaxel in docetaxel pre-treated patients relapsing after an initial successful series of cycles remains undefined. Data from the ASCENT-1 study support the utility of retreatment after a response in some selected patients [37]0.

Only one phase III randomised clinical trial has been completed in the second-line setting in CRPC, the Satraplatin and Prednisolone Against Refractory Cancer trial (SPARC). In the SPARC trial, patients with metastatic CRPC in whom one previous cytotoxic chemotherapy regimen had failed were randomised to prednisone with or without satraplatin, an oral platinum complex [57]. Treatment with satraplatin was associated with a statistically significant improvement in progression-free survival, PSA response, pain response, time to pain progression, and duration of pain response. However, since this survival analysis, which was a co-primary endpoint, did not point towards a survival benefit, the Food and Drug Agency (FDA) and European Medicine Agency (EMEA) did not approve satraplatin in CRPC [58]. The survival data may have been adversely influenced by a greater number of patients in the placebo group who received a subsequent line of chemotherapy including docetaxel. Final data analysis and subset analysis is pending. Abiraterone acetate, a 17-hydroxylase and C17, 20-lyase inhibitor, to decrease serum androgen to undetectable levels, has shown activity in patients previously treated with docetaxel chemotherapy [59,60]. This agent is currently being explored in a phase III trial for patients with metastatic CRPC who have failed docetaxel-based chemotherapy, using overall survival as primary endpoint.

Conclusions

Following the results of the two landmark phase III studies, TAX 327 and SWOG 99-16, the combination of 3-weekly docetaxel plus low-dose prednisone has become standard treatment for patients with CRPC. These two independent randomised studies have demonstrated that 3-weekly docetaxel significantly improves overall survival compared with mitoxantrone-based chemotherapy, with acceptable toxicity. An updated survival analysis of data from TAX 327 showed that survival benefit was sustained at 3 years. The 3-weekly regimen with docetaxel also showed statistical significant improvement of pain and QoL in symptomatic patients.

An important question is when to start chemotherapy in asymptomatic patients. Delaying cytotoxic therapy may be a suitable approach in patients who are asymptomatic and at low risk for rapid progression and developing symptoms. In contrast, in those patients with fast disease progression the initiation of cytotoxic therapy should not be delayed. Several variables including baseline PSA and PSA-DT have been identified as prognostic parameters for overall survival and could facilitate the decision as to when to start cytotoxic therapy. Until our understanding of CRPC expands, nomograms may help to guide management in CRPC.

There is a need for robust clinical outcome measures in clinical trials for patients with CRPC.

Although an important and clinically meaningful first step, the impact on survival of docetaxel is modest and median overall survival for patients with advanced CRPC is still around 19 months. Novel agents in combination with docetaxel may provide further avenues through which CRPC can be treated more effectively. There are no second-line treatment options with demonstrated effectiveness and drug development is needed in this setting. There are numerous unanswered questions in the management of CRPC and patients should be enrolled in clinical trails whenever available.

Conflict of interest statement

Dr de Wit has received research grant support and consultancy fees from Sanofi-Aventis. Dr Meulenbeld and Dr Hamberg have no conflicts of interest to report.

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