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Clinical trials in metastatic prostate cancer – Has there been real progress in the past decade?

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Abstract

Hormone refractory prostate cancer remains a challenge. While only palliative treatment strategies were available for the past several decades, many promising agents have been investigated over the past decade. Of those the taxanes appeared with significant anti-tumor activity and recently, two large randomized controlled trials demonstrated for the first time, a survival and palliative benefit with docetaxel based chemotherapy. In the current era, recurrent disease after local treatment for localized disease is diagnosed long before evidence of systemic disease. With earlier institution of hormonal treatments, patients are becoming ''hormone refractory'' earlier in the course of their disease with considerable long life expectancy. Hence, there is a greater need than ever for more treatment options for this expanding group of patients. A number of new systemic therapies have recently emerged, based on a deeper understanding of prostate cancer biology. Novel chemotherapeutics such as the epothilones, molecularly targeted therapies against angiogenesis, the proteosome and endothelin receptor antagonists, as well as biological agents such as anti-sense oligonucleotides are being tested as part of the armamentarium. Key to progress in the therapy of this fatal disease is the commitment and timely enrolment of prostate cancer patients in clinical trials.

Keywords: Chemotherapy; Docetaxel; Epothilone; Clinical trials; Prostate cancer; Hormone refractory; Targeted therapies

1. Introduction

Prostate cancer is the most common non-dermatological malignancy and the second leading cause of cancer-related death in men in the United States of America (USA). In Europe incidence rates are similar to that of the USA; prostate cancer is among the top three non-dermatological cancer diagnoses. During 2005, an estimated 232,090 men will have prostate cancer diagnosed (1 in 6 men), while 30,350 men will die of this disease in the USA [1].

Due to prostate-specific antigen (PSA) screening, the majority of patients present with localised prostate cancer and are candidates for definitive local therapy. Despite undergoing radical prostatectomy or radiation therapy for localised disease, the actuarial 10-year likelihood of biochemical disease recurrence for these patients is approximately 25% [2,3]. For patients who develop osseous or visceral metastasis, or less commonly for those patients who present initially with advanced disease, the surgical or medical ablation of androgens is regarded as optimal first-line treatment [4,5]. Unfortunately, androgen ablative therapy is palliative, with a median duration of response of 12–24 months [4,5]. Second-line hormonal manipulation in men who progress on androgen deprivation can result in a largely biochemical

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response [6–10] which is generally short-lived and has no demonstrable impact on survival. Hormone-refractory prostate cancer (HRPC) is a progressive morbid disease, leading to eventual death over a median of 12–18 months. Chemotherapy in this setting has been actively investigated over the last 2–3 decades and, until recently, was only palliative.

Recent studies of docetaxel-based chemotherapy in men with androgen-independent prostate cancer (AIPC) have demonstrated a survival benefit for the first time in this disease state. However, in order to assess whether progress has been made in HRPC, we have to pause and ask what we would accept as progress in this disease. The dimensions of progress, as for any metastatic cancer, would include palliation of symptoms, improvement in quality of life, prolonged clinical response, improvement of survival and, the ultimate goal, cure. While evaluating the progress made over the last decade, we will attempt to define which of these goals have been met and how much work remains in order to attain the remaining ones.

2. Pre-1990s: where the journey began

Estramustine is a synthetic fusion of a nitrogen mustard to an estradiol moiety. It was the first chemotherapeutic drug approved by the US Food and Drug Administration (FDA) in December 1981 for patients with HRPC. Being an oral pill, it gained widespread use around the world in subsequent decades. While palliative in nature, it had a wide spectrum of side-effects and low objective response rates, ranging from 5% to 19% [11,12]. Various other chemotherapeutic agents, including alkylating agents (cyclophosphamide), anthracyclines (doxorubicin, epirubicin) and vinka alkaloids (vinblastine, vincristine), were evaluated with some disease activity, but a major breakthrough was not obtained. Chemotherapy continued to carry the burden of ineffectiveness and toxicity. The seminal review nearly a decade ago, in 1993, by Yagoda and Petrylak [13] provided little optimism that HRPC was a disease sensitive to conventional cytotoxic agents. With average response rates below 15%, it was compared with another intrinsically chemo-resistant disease, renal cell carcinoma [14].

3. Chemotherapy for metastatic HRPC: lessons from the earlier part of last decade

3.1. Mitoxantrone-based chemotherapy

Mitoxantrone is a derivative of anthracyclines and originally approved for use in acute myelogenous leukaemia. Based on phase II data, two studies were initiated in the early 1990s to test the value of mitoxantone plus a corticosteroid in patients with hormone-refractory metastatic prostate cancer. The Canadian study [15] randomised 161 chemotherapy-naïve symptomatic patients to either prednisone 10 mg/d, or prednisone at that dose plus mitoxantrone 12 mg/m^2 every 21 d. The primary end-point of this study was pain palliation. Using a validated pain monitoring scale, this study demonstrated a statistically significant improvement in pain relief (29% *versus* 12%, $P = 0.01$), which was also more durable for patients receiving mitoxantrone (43 weeks *versus* 18 weeks, $P < 0.0001$). The patients who reported pain relief decreased their self-reported use of analgesic medications. Patients treated with mitoxantrone also reported in an unblinded fashion, prolonged improvement in physical and social functioning, global quality of life, anorexia, drowsiness, constipation and other symptoms [16]. However, this study was not designed or powered to show a survival advantage and the median survival for either arm was about a year. The study's crossover design allowed patients who did not respond to prednisone alone subsequently to receive mitoxantrone, and this may have diminished the possibility of seeing a survival benefit.

In a parallel US study [17] undertaken by the Cancer and Leukemia Group B (CALGB), 242 chemotherapy-naïve HRPC patients were randomly assigned to either hydrocortisone 40 mg/d, or hydrocortisone at that dose plus mitoxantrone 14 mg/m^2 every 21 d. This trial was larger than the Canadian trial and designed to detect an overall survival difference. However, none was found when comparing men treated on the chemotherapy arm (12.3 months) with men receiving hydrocortisone alone (12.6 months, $P = 0.77$). Mitoxantrone chemotherapy was associated with an improvement in progression-free survival (3.7 *versus* 2.3 months, $P = 0.025$) a higher PSA decline rate (38% *versus* 22%, $P = 0.008$) and a non-significant trend towards improvement in pain control in the chemotherapy arm. The end-points met by these two seminal trials are summarised in Table 1. The combined efficacy and safety data from the Canadian and the US study was convincing enough for the US FDA to approve mitoxantrone in 1999 for symptomatic HRPC, the first new chemotherapy approved for this deadly disease in over 15 years.

Mitoxantrone combined with a corticosteroid, given on an every-3-week basis hence became a new standard of care for symptomatic patients with metastatic HRPC from the late 1990s and further chemotherapeutic trials were compared with this new standard. While a survival benefit has not been demonstrated, the attainment of pain-relief and functional benefit is a very meaningful goal, particularly given the unremitting dysfunctionality and loss of quality of life patients suffer in the advanced stages of this disease. Hence, real progress towards the first two goals, namely palliation of symptoms and improvement in patients' quality of life was attained to

Table 1
End-points from phase III mitoxantrone

Trial	Patient characteristics	End-points			
		PSA response	Time to progression	Pain relief	Quality of life
Canadian trial 1996 [15]	Symptomatic HRPC patients	Yes	Yes	Yes	Yes
CALGB trial 1999 [17]	Asymptomatic and symptomatic HRPC patients	Yes	Yes	No	No

PSA, prostate-specific antigen; HRPC, hormone-refractory prostate cancer; CALGB, Cancer and Leukemia Group B.

some clinically significant extent with a fairly modest chemotherapeutic agent.

4. Trials evaluating chemotherapy agents based on rational pre-clinical observations

Various single agents have been tested in HRPC, based on pre-clinical activity. This was further facilitated by the routine use of PSA as a measure of disease activity. Table 2 summarises the results of the most commonly studied chemotherapy agents [18–36]. Based on single agent activity, the most widely tested contemporary regimens over the last decade have included a taxane. The taxanes were attractive candidates as they have both mitotic and non-mitotic effects, a feature that may be of importance in HRPC owing to the lower rates of cycling fraction. Among them, the most active agent appeared to be docetaxel, which has a 100-fold higher potency than paclitaxel in anti-apoptotic Bcl-2 inhibition. In phase II studies, the activity of docetaxel appeared to be independent of schedule. Greater than 38–46% of patients had more than 50% reduction in PSA and generally among the highest reported responses (28%) in measurable disease [18–21].

Another significant step forward in the 1990s was clinical evaluation of cytotoxic drugs based on rational pre-clinical observations from the laboratory. Estramustine destabilises the microtubule apparatus by binding microtubule-associated proteins and tubulin [37–39]. Combinations of estramustine with agents that target the mitotic spindle or nuclear matrix [39–41] were developed based on encouraging pre-clinical results. Hence, though estramustine had a difficult side-effect profile

Table 2
Selected single-agent activity in HRPC in phase II studies (mitoxantrone data from phase II and phase III studies)

Agent	Total patients treated (*n*)	PSA RR (%)	Overall measurable RR	Time to progression (months)	Survival (months)	Symptomatic improvement
Docetaxel [18–21]	138	38–46	36 (28%)	4.6–5.1	9.4–27	Yes
Paclitaxel [22–24]	126	4–39	29 (17%)	NR	9–13.5	NR
Mitoxantrone [15,17,25]	255	33–48	77 (13%)	3.7–8.1	12.3–23	Yes
Cyclophosphamide [26,27]	53	4	NR	NR	8–12.7	Yes
Estramustine [28]	42	21	NR	NR	NR	Yes
Vinorelbine [29–31]	140	4–17	46 (7%)	2.9–3	10.2–11.5	Yes
Doxorubicin [32,33]	135	NR	9 (22%)	3.5–4.3	8–10.8	Yes
Epirubicin [34–36]	260	24–32	61 (31%)	NR	9–13	Yes

HRPC, hormone-refractory prostate cancer; PSA, prostate-specific antigen; RR, response rate; NR, not reported.

Table 3
Selected combination chemotherapy agents in HRPC in phase II studies

Agents	Total patients treated (*n*)	PSA RR (%)	Overall measurable RR	Time to progression (months)	Survival (months)	Symptomatic improvement
Docetaxel + estramustine [43–45]	140	45–82	80 (57%)	4.2–10	12–20	Yes
Paclitaxel + estramustine [46–49]	119	53–62	39 (49%)	4.6–5.6	13–17.3	Yes
Estramustine + ectoposide [50–53]	211	14–58	66 (48%)	NR	11–14	NR
Paclitaxel, estramustine, etoposide [54,55]	74	41–65	39 (36%)	NR	12.8–16.9	NR
Paclitaxel, estramustine, carboplatin [56,57]	86	67–100	51 (51%)	5.25–11	19.9–21.9	Yes
Ketoconazole, doxoruicin, vinblastine, estramustine [55,58]	80	56–67	31 (61%)	NR	19–23.4	Yes
Vinblastine + estramustine [59]	95	25	30 (20%)	3.7	11.9	Yes
Vinorelbine + estramustine [60–62]	72	24–71	18 (6%)	3.5–5.8	10.5–15.1	NR

HRPC, hormone-refractory prostate cancer; PSA, prostate-specific antigen; RR, response rate; NR, not reported.

(frequent breast tenderness and enlargement, decreased libido, thrombo- embolism, among others) [42], it become the most common agent in combination chemotherapeutic trials during the past decade because of increases in PSA and overall response rates in combination trials, mostly undertaken in phase II settings. Table 3 summarises the most commonly used chemotherapy combinations and their reported activity.

5. Development of suramin: few lessons learnt

Suramin, a polysulphonated napthylurea, was evaluated extensively during the mid-1990s as an anticancer agent, with most interest in the treatment of prostate cancer. It was first synthesised in 1916 by Bayer AG [63] and was found to have activity in African trypanosomiasis and onchocerchiasis [64,65]. *In vitro* studies demonstrated that suramin had the ability to block the binding of various growth factors, such as fibroblast growth factors (FGF), platelet-derived growth factors (PDGF), transforming growth factors (TGF) alpha and beta and insulin-like growth factor I (IGF-I) to their receptors as well as decrease cell motility [65–67]. Antiproliferative activity was noted against the human prostate cancer cell lines (LNCaP, PC-3 and DU145) [68–70]. These pre-clinical findings supported the evaluation of suramin in patients with HRPC. The drug was initially administered using a continuous infusion targeting serum levels of >200 μg/ml, with significant clinical activity. However, this method of administration proved impracticable, and pharmacologically based bolus dosing algorithms were developed which rapidly achieved and maintained target drug levels [71,72]. Observed toxicities were significant and included lethargy, neuropathy, rash, fatigue, anaemia, hyperglycaemia, hypocalcaemia, coagulopathies, neutropaenia, renal insufficiency and transaminitis. Unfortunately, the initial suramin trials were performed before the recognition of the anti-androgen withdrawal phenomenon, and clinical trials evaluating suramin did not control for this effect. The independent activity of corticosteroids was also not recognised. Trials that controlled for these two factors, where patients were withdrawn from anti-androgens, and only treated with suramin after progression on corticosteroids, did not achieve the same level of clinical activity as the initial trials [73–75]. Based on the initial promising findings using fixed bolus suramin, a randomised trial was initiated comparing suramin combined with hydrocortisone *versus* hydrocortisone alone. The suramin arm of this study demonstrated significantly higher PSA decline rates and pain improvement [74]. Unfortunately, the toxicity of this drug precluded its approval by the FDA. Although the final results with suramin were disappointing and did not deliver on the initial promise of a new therapeutic agent, the development did provide some valuable insight into clinical trial design. Modern clinical trials now require that patients discontinue all forms of anti-androgen treatment for at least 4–6 weeks. Phase III studies have also been designed to administer corticosteroids in all treatment arms to control for their effect.

6. Closing a decade with a definitive step forward: docetaxel-based chemotherapy shows survival benefit

Taxanes have significant anti-tumour activity in men with HRPC, when administered either as single agents or in combination with estramustine. Initial studies using single-agent paclitaxel administered as a 24-h infusion at a dose of 135–170 mg/m^2 once every 21 d were disappointing, with only 4% response rate [22]. In contrast, when docetaxel was evaluated in men with HRPC at 75 mg/m^2 every 3 weeks, a greater than 50% decline of PSA was observed in 46% patients treated, while 28% of patients with measurable disease had a partial response (PR) [18]. Significant activity has also been demonstrated with both weekly docetaxel and paclitaxel, with PSA decline rates ranging between 20% and 46% (Table 2). Initial phase I and II studies evaluating the combination of docetaxel or paclitaxel and estramustine have demonstrated a trend towards a longer median survival (20–23 months) as well as higher PSA decline rates (50–80%) (Table 3). The promising activity of docetaxel, administered either as a single agent or in combination with estramustine provided the justification for two multi-institutional, randomised phase III trials, SWOG 99-16 and TAX 327 [76,77]. In the short time since their release, these two trials have already established docetaxel with prednisone as the new standard of care for metastatic HRPC.

In the Southwest Oncology Group (SWOG) trial [76], 770 eligible patients were randomly assigned to be treated either with docetaxel plus estramustine or with mitoxantrone plus prednisone. Treatment in the experimental arm consisted of docetaxel 60 mg/m^2 intravenously (i.v.) every 21 d and estramustine 280 mg orally 3 times per day on days 1 through 5. The control arm consisted of standard therapy: mitoxantrone 12 mg/m^2 i.v. every 21 d plus prednisone 5 mg orally twice per day continuously. Docetaxel and mitoxantrone doses were increased for patients who had no grade 3 or 4 toxicities during the first treatment cycle. A protocol amendment permitted the addition of anticoagulant therapy in the experimental arm. The trial was designed to detect a 33% improvement in median survival using a one-sided log-rank test at a p level of 0.025. Secondary study end-points were progression-free survival, objective response rate, and rate of decline in PSA. Treatment schema for this and the companion TAX 327 trial [77] are shown in Fig. 1.

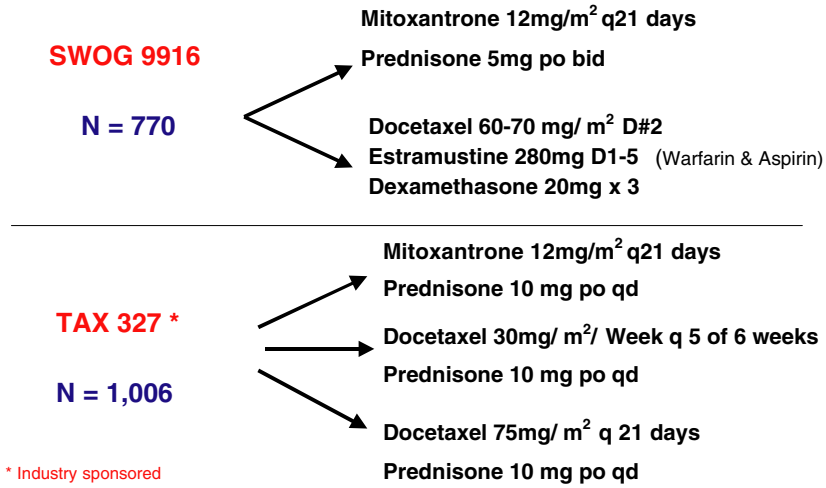

Fig. 1. Treatment schema of SWOG 9916 and TAX327 trials.

In SWOG 99-16, docetaxel and estramustine led to significantly improved median survival (18 months compared with 16 months; $P = 0.01$), longer median progression-free survival (6 months compared with 3 months; $P < 0.0001$), and superior median PSA decline (50% compared with 27%; $P < 0.0001$). Although the objective response rate was numerically superior in the investigational docetaxel arm, the difference did not achieve statistical significance. Hence, a 23% improvement in survival was seen in men treated with the docetaxel regimen compared with mitoxantrone plus prednisone.

Grade 3 and 4 toxicities were reported by more patients in the experimental arm than in the control arm (54% *versus* 34%), principally because of a higher incidence of cardiovascular and gastrointestinal toxicities. There was no difference in either toxic deaths or discontinuation of treatment between the two arms. The rate of cardiac ischaemia was decreased for patients treated with anticoagulants, but there was no reduction in the rate of thrombosis.

TAX327 was an international, multi-centre, three-arm study comparing two dosage schedules of docetaxel plus prednisone with standard mitoxantrone plus prednisone for metastatic HRPC [77]. Patients in the control arm were treated with mitoxantrone 12 mg/m^2 every 3 weeks plus prednisone 5 mg twice daily throughout the trial. The treatment arms consisted of docetaxel 75 mg/m^2 every 3 weeks or docetaxel 30 mg/m^2 weekly for 5 of every 6 weeks. Patients in both treatment arms also received prednisone 5 mg twice daily throughout the trial. A total of 1006 enrolled patients were randomly assigned to the three arms in almost identical numbers.

In an intent-to-treat data analysis at median follow-up of 28 months, the median overall survival rate for men treated with docetaxel every 3 weeks was 18.9 months, compared with 16.4 months for the patients treated with the control regimen ($P = 0.009$). Weekly docetaxel therapy did not result in significantly superior survival. Most importantly, the every-3-weeks dosing schedule of docetaxel was associated with a 24% reduction in risk of death ($P = 0.009$) compared with the control regimen. Docetaxel therapy was also associated with significant improvement in pain relief and in PSA response rate. There were no significant differences among the docetaxel arms with respect to the rate of tumour response. The most common toxicity was neutropaenia, which occurred frequently in the every-3-weeks docetaxel arm (32% *versus* 21.7%). Summary data from these definitive trials are presented in Table 4. On the strength of the data from these two trials, in the USA, the FDA granted approval for docetaxel on the every-3-weeks schedule in combination with prednisone for the

Table 4
Docetaxel and prednisone based regimens in phase III studies

Study	Treatment regimen	PSA RR (%)	Overall measurable RR	Time to progression (months)	Palliative response	Survival (months)
SWOG 9916 [76]	Docetaxel + estramustine	50	17%	6	17%[a]	18
	Mitoxantrone + prednisone	27	10%	3	11%	16
TAX 327 [77]	Docetaxel (q 3 weeks) + prednisone	45	12%[a]	7.9[a]	35%	18.9
	Docetaxel (q weekly) + prednisone	48	8%[a]	8.2[a]	31%	17.4
	Mitoxantrone + prednisone	32	7%[a]	7.8[a]	22%	16.5

PSA, prostate-specific antigen; RR, response rate.
[a] Did not reach statistical significance.

Table 5
Current multi-institutional randomised trials of chemotherapy in HRPC

Protocol	Regimen	Sponsor	Accural
ECOG 1899	Docetaxel + estramustine *versus* Ketoconazole + hydrocortisone in PSA-only relapse of HRPC	ECOG	Ongoing
ASCENT	Docetaxel *versus* Calcitrol + docetaxel	Novacea	Ongoing
EORTC 30021	Docetaxel *versus* Genasense (anti bcl-2) + docetaxel	EORTC	Ongoing
NEPRO	Docetaxel *versus* risedronic acid (oral bisphosphonate) + docetaxel	EORTC	Ongoing
MDA-ID-00156	Induction chemotherapy followed by consolidation with doxorubicin *versus* doxorubicin + strontium-89	MD Anderson Cancer Center	Ongoing

ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; ASCENT, AIPC study of Calcitrol-Enhancing Taxotere; AIPC, androgen-independent prostate cancer; HRPC, hormone-refractory prostate cancer; PSA, prostate-specific antigen; RR.

treatment of HRPC. In a short time since release, docetaxel on a 3-week treatment regimen has widely become the standard of care for first-line chemotherapy for HRPC in the USA, as well as across regions of Europe. Several ongoing phase III trials are evaluating docetaxel-based regimens in different settings of advanced prostate cancer (Table 5).

7. Moving ahead with novel agents and treatment strategies

A new generation of clinical trials has commenced to evaluate a variety of newer agents against traditional targets (e.g., epothilones against the mitotic spindle), as well as against entirely new targets based on a deeper understanding of the biology of HRPC. While several of these agents have been reviewed previously [78,79], some recent updates and phase II level clinical activity which validates a given mechanism are discussed in this section and in an accompanying article by Dr. Beer in this issue. It is too soon to assess what role these agents will play in the treatment of HRPC, either as single agents or in novel biotherapy–chemotherapy combinations with more traditional cytotoxic agents such as docetaxel. However, the clinical community has reached an understanding that more effective and less toxic treatments would emerge from a better understanding of the key molecular events leading to prostate cancer and the evolution to androgen independence, as well as tumour – microenvironment interactions (e.g., prostate cancer cell with bone) that leads to debilitating systemic disease. The challenge now is to prioritise and enroll patients in order to swiftly weed out marginal agents and enable promising therapies to be taken to definitive phase III clinical trials and integrated into clinical practice.

8. Cytotoxic agents

8.1. Third generation anti-microtubule agents

Like the taxanes, epothilones target the mitotic spindle, where they induce microtubule stabilisation resulting in mitotic arrest at the G2/M transition. BMS-247550 is a semi-synthetic analogue of epothilone B, which has been shown in pre-clinical studies to have activity against taxane-resistant and taxane-sensitive cell lines. In clinical trials, BMS-247550 has cytotoxic activity against a range of tumours, both sensitive and resistant to taxanes. Two phase II studies [80,81] demonstrate that epothilone-B (BMS-247550) has activity in chemotherapy-naive patients with metastatic HRPC. SWOG 0111 showed a 41% PSA and in patients with measurable disease a 30% objective response rate [80]. Another multi-institutional phase II study reported a 56% PSA and a 23% measurable disease response rate for epothilone-B alone, and a 69% PSA and a 44% measurable disease response rate for the combination of epothilone-B with estramustine [81]. Both studies reported a high incidence of neuropathy. These studies demonstrate significant activity for this agent, although further studies will need to validate its role in the treatment of HRPC patients in light of the docetaxel data. Pre-clinical data and an ongoing study [82] suggested that patients treated initially with epothilone remained responsive to taxane-based chemotherapy, indicating that the two agents are not cross-resistant and might be useful in tandem.

9. The promise of targeted therapy: novel agents

Observations on the biology of metastatic prostate cancer in general and on the mechanism of tumour progression and prostate cancer cell–bone interactions have fuelled the active investigation of novel agents targeting critical pathways. The promising ones under current clinical development are discussed below.

9.1. Proteosome inhibition

The proteasome is a ubiquitous enzyme complex that is a hub for the regulation of many intracellular regulatory pathways, particularly regulating apoptosis; because of its essential function, this enzyme has become a new target for cancer treatment. Proteasome inhibition

has been proposed as a therapy target for the treatment of HRPC given encouraging pre-clinical and clinical data. A phase II study of the proteasome inhibitor bortezomib, which has important activity in multiple myeloma, reported a 36% PSA response rate and 17% measurable disease response rate when combined with docetaxel [83]. Considering that the majority of these patients had prior chemotherapy and half had prior taxane-containing chemotherapy, this result is intriguing and requires further evaluation.

9.2. Anti-angiogenesis

An essential step in the metastases of solid tumours is the growth of new blood vessels. New blood vessels must be generated in order for metastases to grow. Vascular growth factors, including vascular endothelial growth factor (VEGF), matrix metalloproteins and integrins regulate the process of angiogenesis. Inhibition of these targets can arrest tumour growth, as well as inhibit metastatic spread. These vascular growth factors are expressed in both the tissue and serum of patients with prostate cancer. Agents with anti-angiogenic activity that are currently in development include thalidomide, CC5013, bevacizumab (anti-VEGF rhuMAb), and cilengitide, a potent and selective integrin inhibitor.

Thalidomide has activity in malignancies such as multiple myeloma and prostate cancer. The exact mechanism of the anti-tumour effect of thalidomide is unclear, and may be related to platelet-derived growth factor (PDGF) rather than VEGF pathway. As a single agent in heavily pre-treated patients, thalidomide has a PSA decline rate of >50% in 18% of patients [84]. A randomised phase II study evaluated the combination of thalidomide 200 mg/m^2 orally daily with weekly docetaxel 30 mg/m^2 weekly for 3 out of 4 weeks to weekly docetaxel alone [85]. The combination arm achieved higher PSA response rates (53% *versus* 37%), longer median progression-free survival (5.9 months *versus* 3.7 months; $P = 0.32$) and a trend towards an improved median survival (28.9 months *versus* 14 months) than docetaxel alone. Of the first 43 patients treated with docetaxel/thalidomide, 12 developed a deep venous thrombosis. Prophylaxis with low molecular-weight heparin prevented further instances of deep venous thrombosis in the docetaxel/thalidomide patients in this study. The randomised phase II design of this study precludes definitive conclusions regarding the true effects of the docetaxel/thalidomide combinations. Second generation compounds such as lenalidomide (Revimid) are also being evaluated as single agents or in combination with docetaxel in HRPC.

Elevated VEGF levels portend a poor prognosis in HRPC. Bevacizumab, a humanised monoclonal antibody directed against VEGF, is active in combination with chemotherapeutic agents in advanced colorectal carcinoma. A similar therapeutic approach has been undertaken with bevacizamab in prostate cancer. A trial by the Cancer and Leukemia Group B (CALGB) found promising activity in HRPC with the combination of docetaxel 70 mg/m^2 every 3 weeks, estramustine 280 mg orally three times per day on days 1–5 and bevacizumab 16 mg/kg every 3 weeks [86]. Seventy-nine patients were enrolled and nine of 17 evaluable patients demonstrated a partial radiographic response (53%). Of 20 patients evaluable for PSA decline, 65% had a confirmed PSA decline by 50%. At the time that this trial was reported, the trial had yet to mature and the median survival was not reported. Based on these preliminary observations, the CALGB is planning a phase III trial comparing the combination of docetaxel and prednisone with docetaxel/prednisone/bevacizumab.

Cilengitide (EMD121974) is a potent selective integrin antagonist [87]. Integrins are cell surface receptors that mediate a variety of cell activities [88] and the integrins $\alpha_V\beta_3$ and $\alpha_V\beta_5$ (vitronectin receptors) are involved in endothelial cell proliferation and migration. Thus, these are crucial molecules in the process of neovascularisation. Blocking the ligation of vitronectin by antagonists promotes apoptosis of proliferative angiogenic cells, thereby suspending new blood vessel formation [89]. Phase II studies in patients with metastatic and non-metastatic AIPC are opening for this agent and may show the benefit of targeting this mechanism for disease progression.

9.3. Endothelin-1 as a target

The endothelins, a family of potent vaso-constricting peptides, have been implicated in the pathophysiology of advanced prostate cancer. Two endothelin receptors, ET_A and ET_B are found in normal prostate tissue. Malignant prostate cells are notable for the loss of ET_B receptors and increased levels of ET_A and endothelin-1 [ET-1]; this distortion of the endothelin system may be a significant factor in the progression of prostate cancer [90]. Proposed roles for endothelin in prostate cancer include growth promotion, apoptosis inhibition, bone formation, and stimulation of nocioceptive (pain) receptors. Through interaction with the endothelin-A receptor (ET_A) endothelin-1 plays a key role in bone-tumour interactions producing osteoblastic lesions. Atrasentan (Abt-627) is a potent, orally bioavailable and selective ET_A receptor antagonist, which in a dose-dependent fashion reduces bone metabolism markers in patients with HRPC. One randomised phase II clinical trial has been published [91] and the preliminary results of a larger phase III trial reported [92]. The phase II trial [91], with 288 patients, demonstrated for the primary end-point of time to progression, in intent-to-treat analysis, a trend toward prolongation in disease progression and a statistically significant delay in PSA pro-

gression and attenuation of bone turnover markers, lactate dehydrogenase (LDH) and acid phosphatase.

The phase III study [92] with the higher dose level of atrasentan at 10 mg was conducted in 809 patients. It revealed a trend towards delayed time-to-progression and significant delayed bone turnover markers. Again, atrasentan was generally well tolerated. The final published report of this phase III trial is awaited and further development would validate the role of endothelin-1 targeting in the treatment of HRPC. A phase I trial with atrasantan and docetaxel is ongoing at Duke University (Dan George, Duke University).

9.4. Targeting bcl-2 with anti-sense oligonucleotides

Bcl-2 protein over-expression is a common manifestation of malignancies and represents an attractive molecular target for therapy. In experimental prostate cancer models, increased expression of Bcl-2 protein mediates, at least in part, the transition from androgen-dependent growth to androgen-independent growth [93–95]. Furthermore, in several human tumour cell lines, Bcl-2 protein expression mediates resistance to the cytotoxic effects of a diverse spectrum of hormone and cytotoxic chemotherapeutic agents. In advanced HRPC pathological specimens, the frequency and intensity of Bcl-2 protein over-expression is markedly increased compared with hormone-sensitive disease [96–98]. These findings raise the intriguing possibility that Bcl-2 over-expression mediates, at least in part, both HRPC resistance to androgen-ablation therapy and chemotherapy. Oblimersen (G3139, Genasense) is an 18-base synthetic oligodeoxyribonucleotide strand (sequence 5′-TCTCCCAGCGTGCGCCAT-3′) that hybridises to the first six codons of the *bcl-2* mRNA. The oligodeoxyribonucleotide-mRNA hybrid recruits endogenous RNase H, mediates scission of the *bcl-2* mRNA, and thereby depletes Bcl-2 protein [99]. The impetus for pursuing the clinical development of oblimersen sodium combined with docetaxel includes the prevalence of Bcl-2 protein expression in HRPC, the intrinsic resistance of HRPC to chemotherapeutic agents, and the marked enhancement of docetaxel anti-cancer activity in pre-clinical models when combined with oblimersen [100]. Phase I trials of oblimersen and docetaxel have been completed [101] with interesting biological correlates. Seven out of 12 taxane-naïve patients had a PSA response and Bcl-2 protein inhibition was seen in peripheral blood mononuclear and HRPC tumour tissue cells. This interesting agent is reaching more advanced stages of development in HRPC (Table 5).

In summary, extensive laboratory-based work over the past decade has provided various targets and agents based on a deeper understanding of the biology of HRPC.

10. Progress during the last decade: closing the 'attitude' gap

Cytotoxic chemotherapy in HRPC has gained more common acceptance in the larger oncology community over the past decade. In 1980s and early 1990s, chemotherapy was often not offered to patients with metastatic disease, particularly for older patients or those with a poorer performance status [102]. However, a recent survey from a cohort of 232 practising US physicians [103] indicated that the vast majority of physicians including medical oncologists, urologists and radiation oncologists (87%) would recommend, and are currently using chemotherapy for their patients with hormone-refractory disease. This shift was based on both perceived efficacy and manageable toxicity of the regimens available. Although, at the time of this survey (103), a survival benefit had not yet been demonstrated for cytotoxic chemotherapy in metastatic HRPC, most physicians strongly endorsed chemotherapy for palliative benefits, taking into account the toxicities of the available regimens. This attitude shift and acceptance has been the result of clinical trials demonstrating clinically meaningful benefits to systemic therapy in HRPC, not only in better symptom palliation but also durable responses and improving survival.

11. Advancement in tools for undertaking trials

11.1. Value of surrogate markers in designing clinical trials

The development of new treatments for advanced prostate cancer has been hampered by the inability to radiographically assess, radiographically, the response in the setting of bone-only disease, as we lack objective clinical criteria that could be easily and systematically evaluated to test new agents [104,105]. Definitive survival studies required for drug approval are large, expensive, and take a long time to completion. Availability of surrogate markers can aid in drug development by allowing smaller, quicker trials to screen for potentially active agents. While loosely and often incorrectly used, the classical definition of surrogacy, as described by Prentice [106] in 1989, defines a surrogate marker as "response variables that can substitute for a 'true' end-point for the purpose of comparing specific interventions or treatments in clinical trials". An ideal example, developed and validated among all patient groups, is that of low-density lipoprotein (LDL)-cholesterol as a surrogate marker for benefits for lipid lowering agents in coronary heart disease morbidity and mortality. In various other clinical settings (e.g., 30-day mean-arterial blood pressure reduction as a surrogate marker for antihypertensive agents benefit in cardiovascular disease

morbidity and mortality) surrogate measures can be used to detect a clinical benefit more quickly, easily and more cost-effectively, well before definitive survival benefits can be obtained months to years down the line.

The routine use of PSA as a disease marker for prostate cancer activity entered widespread clinical use in the early 1990s. In the pre-PSA testing era, response rates to investigational drugs were based on reductions in tumour burden, as determined by radiology studies. Since bone metastases and their response to treatment are difficult to quantify using standard radiographic tests such as bone scans or X-rays [104,105], pre-PSA era trials depended on radiographically measurable disease to assess for response. When PSA testing was adopted as a measure of disease burden, chemotherapy trials counted decreases in PSA values as responses to treatment. Initially driven by data from the Memorial Sloan-Kettering Cancer Center in New York [107], it was seen that $a > 50\%$ decrease in PSA was associated with longer median survival (23.6 *versus* 12.3 months, $P = 0.0002$). While other studies have not consistently confirmed these findings [108,109], the need to establish consistent guidelines lead a 26-member expert prostate cancer consensus panel (the Prostate-Specific Antigen Working Group) to recommend using >50% PSA decline confirmed over two time-points, at least 4-weeks apart in the absence of radiological progression as a valid end-point to screen for anti-tumour activity in phase II clinical trials [110]. Additionally, the Southwest Oncology Group (SWOG) investigators recently showed that a 50% decrease in PSA within 3 months of initiating docetaxel therapy and PSA velocity measured during the first 3 months of treatment were both independent prognostic factors for survival in SWOG 9916 trial [111]. These surrogate marker developments and the widespread use of PSA over the past decade has allowed chemotherapeutic drugs to be evaluated more quickly in phase I/II settings, as well as prevent non-responding or PSA-only progressing patients from being exposed to additional drug toxicities.

However, for a clinical or laboratory response variable to be truly valid as a surrogate marker, there needs to be prospective validation of the magnitude and direction of effect on the surrogate correlating with the magnitude of effect on the true clinical 'end-point' of clinical interest (reduced time-interval mortality or improved overall survival) [112].

11.2. Trial collaboration and patient enrolment

The timely completion of two of the largest chemotherapeutic prostate cancer trials, viz. SWOG 99-16 and TAX 327 [76,77], evaluating more than 1700 patients with metastatic disease in multi-institution and multi-national setting, as well as latest trials such as the atrasentan phase III trial with over 800 patients enrolled [92] attest to the fact that the clinical trial community in prostate cancer has matured over the past decade to undertake and execute such definitive trials in a rapid manner. Furthermore, such rapid collaboration and execution of trials via the established co-operative groups in the USA, Europe and Asia-Pacific will be paramount to evaluate the large number of novel biological and targeted therapeutic agents that are being developed in this disease. This is a significant and real challenge, given analysis which show that in spite of having roughly equal number of patients diagnosed each year in the USA with breast and prostate cancer, prostate cancer patients are four times less likely to be enrolled on a National Institutes of Health (NIH)-sponsored clinical trial compared with breast cancer patients [113].

11.3. Clinical trial design

Another area of progress has been in the design of more targeted and smaller, but clinically relevant, phase I and phase II trials for evaluating drug activity in metastatic HRPC. While most single-institution phase II therapeutic trials in metastatic prostate cancer have adopted the 'mini-max' Simon optimised designs [114] to have early 'go-no go decisions' and minimise the number of patients who are exposed to an investigational agent, other novel trial designs are not noted in HRPC literature. These issues become relevant, as newer biological agents are more likely to be cytostatic rather than cytotoxic. Hence, classical criteria designed in the area of cytotoxic drug development, such as'Response Evaluation Criteria in Solid Tumours' (RECIST) radiological response criteria [115] are likely to miss potentially active biological agents with useful anti-tumour activity that may not translate into conventional responses via RECIST criteria. Combining surrogate marker development, novel trial designs such as neo-adjuvant trials primarily for assessing drug activity which can be confirmed with pathological tissue, randomised discontinuation phase II design which is optimised for evaluating the activity of an agent from preventing disease progression rather then tumour-mass shrinkage, are some of the unique trial designs proposed to assess cytostatic rather than cytotoxic biological agents [116].

12. Gap analysis – where do we need to be?

Although real progress has been made over the past decade in areas of therapeutic efficacy of chemotherapy, leading to better palliation and survival improvement, the expansion in basic science and clinical research and the change in attitude towards systemic therapy in prostate cancer must also be viewed as real progress. However, the absolute benefit attained thus far has been relatively modest. Questions about optimal length of

therapy, optimal combination regimens, optimal second and subsequent lines of treatment are all currently unanswered. Additionally, curative options for advanced prostate cancer are not on the current horizon. Efforts to enhance survival with combination-chemotherapy or newer approaches are the prime target of the prostate cancer research community. The question to be answered is 'what will our pace of progress have to be if we are to'win back' the lost years of life for an average man with HRPC?'

Currently, an average US patient with metastatic HRPC at age 72 years at diagnosis has approximately 10.9 years of life-expectancy remaining (Fig. 2). Overall survival, even with the state-of-the-art therapy with docetaxel is currently on the order of 18 months [76,77]. Median survival will need to be prolong by 25% every year, year-over-year up to 2015, if we are to'win the war' on HRPC (Fig. 3) and regain the years of life lost due to this deadly disease. While this annual pace of progress does not currently seem attainable and has not occurred for most other cancers over the past century, treatments discovered in metastatic HRPC and then integrated into earlier stages of disease, such as in adjuvant high-risk prostate cancer and ultimately chemoprevention studies may well be ways to'win the war' and prevent patients from progressing to metastatic disease in the first place.

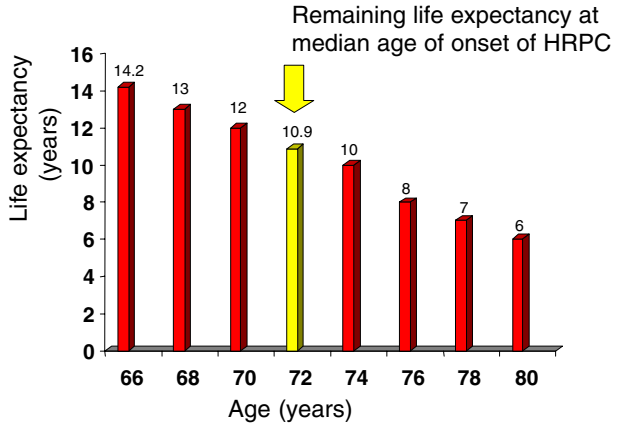

Fig. 2. US male life expectancy. HRPC, hormone-refractory prostate cancer. Figure used with permission of Dr. T. Beer. Presented at ASCO 2004 Educational Session: Advances in Systematic Therapy of Prostate Cancer.

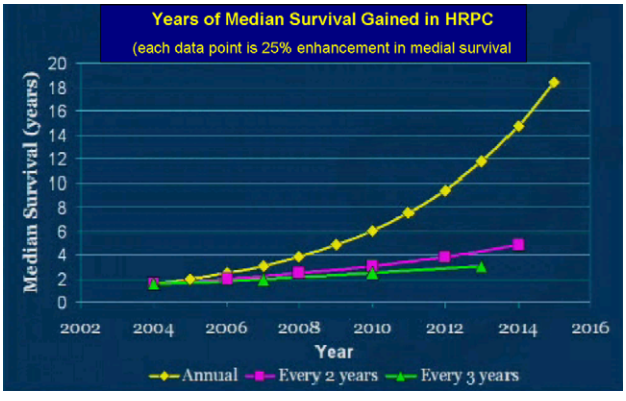

Fig. 3. Required pace of progress. HRPC, hormone-refractory prostate cancer. Figure used with permission of Dr. T. Beer. Presented at ASCO 2004 Educational Session: Advances in Systematic Therapy of Prostate Cancer.

13. Conclusion

Although advanced prostate cancer is still incurable, the last 15 years has witnessed modest but steady progress that has shifted the paradigms in treating this disease. Durable palliation and modest but real prolongation of survival have been achieved. HRPC is no longer considered a chemo-resistant disease, thus opening the doors for a wide range of basic and translational research activities aiming at developing rational therapies. We have begun to realise that the biggest impact on mortality is likely to come from a multi-modality treatment approach incorporating systemic therapy early in the course of the disease.

While real progress has been made over the past decade and we have run the first mile in the race for HRPC, the marathon has only just begun.

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