Systemic nonhormonal management of advanced prostate cancer and its likely impact on patients' survival and quality of life

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Prostate cancer is a hormonal sensitive disease with a response rate ranging from 80 to 90%; however, the majority of patients develop hormone resistance resulting in poor long term survival. Chemotherapy has demonstrated a benefit over steroids in improving the quality of life in the hormone refractory phase. Furthermore, the introduction of docetaxel succeeded in improving the survival of these patients in first-line therapy. Second-line treatment following docetaxel is challenging with no agent classified as standard in this setting. In the last 5 years, several drugs have shown promising results in initial evaluation. However, randomized phase III trials would be needed to answer this question. The majority of patients develop bone metastasis and the use of bisphosphonates has yielded encouraging results. Our understanding of the biology of hormone refractory prostate cancer has improved dramatically over the past few years and has translated into the developments of new therapeutic targets for this disease. Agents affecting several targets, including calcitriol, endotheline-1, bcl-2, and angiogenesis, are being studied currently and have the potential to change the treatment paradigms of this otherwise fatal disease. This review focuses on current and potential treatment options, including cytotoxic agents, bisphosphonates, and targeted agents, for patients with hormone refractory prostate cancer and the impact of these options on survival and quality of life. *Anti-Cancer Drugs* 19:645–653 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Prostate cancer is the leading cancer in the United States of America, accounting for 31% of all male malignancies and the second cause of cancer-related death in men [1,2]. Patients with advanced or metastatic disease are incurable. The standard of care for such patients is androgen blockade, which delays progression and relieves pain for 18–24 months [3]. Although the first manifestation of tumor resistance to androgen blockade is often an asymptomatic rise in serum prostate-specific antigen (PSA), nearly all patients eventually develop significant disease-related morbidity including fatigue, bone pain, and weight loss. This necessitates the development of other systemic nonhormonal agents to help these hormone refractory patients obtain better survival and quality of life (QOL). In this review, we will focus on nonhormonal agents in prostate cancer including chemotherapy, bisphosphonates, and targeted agents.

Chemotherapy

Mitoxantrone

Cytotoxic chemotherapy has been used in the treatment of prostate cancer for many years. The magnitude of benefit was not clear until 1996 when Tannock *et al.* [4] reported a randomized phase III trial defining a clear role for chemotherapy, particularly mitoxantrone in hormone refractory prostate cancer (HRPC). One hundred and sixty-one patients were randomized to receive mitoxantrone plus prednisone (M/P) or prednisone alone. The primary objective was a palliative response, which is defined as a 2-point reduction in the 6-point present pain intensity scale of the McGill–Melzack Pain Questionnaire maintained on two consecutive evaluations at least 3 weeks apart without an increase in analgesic score. It was observed in 23 of 80 patients (29%; 95% confidence interval, 19–40%) who received M/P, and in 10 of 81 patients (12%; 95% confidence interval, 6–22%) who received prednisone alone ($P = 0.01$). An additional seven patients in each group reduced analgesic medication ($\geq 50\%$) without an increase in pain. The duration of palliation was longer in patients who received chemotherapy (median, 43 and 18 weeks; $P < 0.0001$, log-rank). Eleven of 50 patients randomized to prednisone treatment responded after addition of mitoxantrone. Most of the responding patients had an improvement in QOL scales and a decrease in serum PSA levels. As for overall survival (OS), the trial failed to show any survival benefit of chemotherapy over prednisone alone. Despite this finding, this trial provided a window of opportunity for these patients in attaining a better QOL and served as

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a control regimen for subsequent randomized trials with other newer agents.

Antimicrotubular agents

Several antimicrotubular agents have evolved in the management of HRPC. Docetaxel, paclitaxel, estramustine, and ixabepilone all showed considerable activity in this setting. They are antimitotic agents and act on the phosphorylation of the antiapoptotic oncogene, bcl-2, which is frequently expressed in HRPC [5], rendering it inactive.

Docetaxel

Taxanes represent an important milestone in the management of HRPC. In the 1990s, a series of phase II studies were conducted which demonstrated clear efficacy of docetaxel-based regimens in patients with HRPC [6] such as docetaxel plus estramustine (DE), an antimicrotubule agent available orally. On the basis of these positive findings with docetaxel-based therapies, two independent phase III studies were conducted to test these relative to a control arm of M/P. Study 9916 from the Southwest Oncology Group (SWOG 9916) [7] compared DE with M/P and the multinational study TAX 327 [8] used three treatment arms: docetaxel (30 mg/m^2) administered weekly (5 weeks out of six) versus docetaxel (75 mg/m^2) administered every 3 weeks versus mitoxantrone 12 mg/m^2, which is also administered every 21 days. In TAX 327, all treatment arms were given with continuous administration of prednisone. Both studies enrolled patients with advanced hormone refractory prostate cancer. Both studies showed superior results for the docetaxel-based combinations in terms of response rate defined as 50% reduction in PSA and, for the first time, survival. Results are summarized in Table 1. Furthermore, a meta-analysis of these two trials and a large phase II trial [9] showed that docetaxel-based therapy significantly reduces the risk of death by 8–21% at 3 years compared with mitoxantrone-based therapy [10]. On the basis of these results, the FDA and EMEA approved docetaxel and prednisone (DP) as the current standard treatment for patients with HRPC. Although the introduction of docetaxel proved to improve survival, many investigators had concerns regarding the quality of survival offered by docetaxel given its toxicity profile, expected comorbidities, and advanced age of the patients. In 1996, Tannock and colleagues [4] showed that the addition of mitoxantrone to prednisone significantly improved the QOL scores over prednisone alone ($P = 0.01$) providing proof of the concept that chemotherapy in HRPC has a significant palliative role. Although the introduction of docetaxel did offer a survival benefit, further improvement in QOL over M/P was not consistently demonstrated. Patients treated with DE in SWOG 9916 did not demonstrate statistically or clinically significant differences for pain palliation or global quality of life when compared with patients treated with M/P. A modest improvement in favor of DE was measured with the global quality of life scales. Consistent with the previously reported toxicity data [7], significantly more nausea and vomiting were reported by patients receiving DE. These findings contrast with those reported in the TAX327, where pain palliation was significantly greater in those patients treated with docetaxel either weekly or every 3 weeks than in those patients treated with M/P. As the patients treated in SWOG 9916 and TAX 327 had similar baseline characteristics, the reason for this difference in palliation may be attributed to the continuous administration of prednisone in both docetaxel arms in the TAX 327, superadded toxicity offered by estramustine, and incomplete QOL data collection in the SWOG 9916 study. Taking that into consideration, docetaxel seems to offer a meaningful survival benefit with less pain and superior QOL scores.

On the other hand, combining docetaxel with other chemotherapeutic agents was reported in several phase II trials. Vinorelbine [11] and capecitabine [12] were combined with docetaxel resulting in efficacy more or less similar to that obtained by DP. However, correlation between the use of biomarkers and effectiveness of chemotherapeutic agents might help in the optimum use of these agents. Recently, Marur and colleagues reported the preliminary results of a small phase II trial of oral capecitabine and weekly docetaxel [13]. Their primary objective was to correlate between response/survival and certain biomarkers such as thymidine phosphorylase, thymidylate synthase, and dihydropyrimidine dehydrogenase in tumor tissue and dihydropyrimidine dehydrogenase in serum. The final results of this study are awaited.

Table 1 Summary of phase III trials comparing M/P with docetaxel-based regimens

Trial	Treatment arms	Number	50% PSA reduction (%)	Pain reduction (%)	QOL improvement (%)	Median survival (months)
SWOG 9916	MP	336	27	No difference[a]	No difference[a]	15.6
	DE	338	50 ($P<0.001$)			17.5 ($P=0.02$)
TAX 327	MP	337	32	22	13	16.5
	DP (Q 3w)	335	45 ($P<0.001$)[b]	35 ($P=0.01$)	22 ($P=0.009$)	18.9 ($P=0.009$)
	DP (weekly, 5/6)	334	48	31 ($P=0.08$)	23 ($P=0.005$)	17.4 ($P=0.3$)

D, docetaxel; E, estrmustine; M, mitoxantrone; P, prednisone; PSA, prostate-specific antigen; QOL, quality of life; SWOG, Southwest Oncology Group.
[a]Data not shown.
[b]Combined docetaxel arms versus MP.

Paclitaxel

Despite the fact that most of the phase II trials using paclitaxel demonstrated efficacy results close to those encountered by docetaxel [14], the drug has not been evaluated in large phase III trials. In breast cancer, in comparison with the 3-weekly regimen, the weekly administration of paclitaxel was associated with better tumor cell kill via the enhancement of the antiangiogenic [15] and antiapoptotic [16] properties of paclitaxel with better toxicity profile. On the contrary, in prostate cancer the weekly regimen was not associated with encouraging results. In 2002, Vaishampayan and colleagues reported a median survival of 13 months with weekly paclitaxel and estramustine [17]. Similar survival was later reported with weekly paclitaxel alone by Chiappino and colleagues [18]. It is generally not sound to compare results across trials, but available evidence does not favor that paclitaxel (regardless of the schedule) could achieve beyond that achieved by docetaxel and this might explain the lack of enthusiasm in exploring paclitaxel further in HRPC.

Estramustine

Estramustine is a nonnitrogen mustard estradiol conjugate that inhibits the microtubule function and mitosis. It is designed to act as a targeted alkylating agent with its metabolites preferentially taken by the prostate cells. It exerts its function by an estrogenic component (20%) and chemotherapy component (80%). Single agent trials have demonstrated unique activity in HRPC with a PSA response rate in the range of 50% [19]. Furthermore, in-vitro studies showed an additive effect when combined with other active agents like docetaxel, paclitaxel, vinblastine, and etoposide [20]. This additive effect was further demonstrated in the clinical setting by Berry and colleagues when they compared the combination of paclitaxel and estramustine with paclitaxel alone [14]. In this trial, 166 patients were randomized between both arms with the combination showing almost a doubling of the PSA response at 48% (vs. 25% for paclitaxel) and 1 year progression-free survival (PFS) of 29% (vs. 8% for paclitaxel). The same was demonstrated with docetaxel in more than one trial [21,22]. In a recent study reported by Eymard *et al.* [22], the combination of DE had a PSA response of 68% (vs. 30% with docetaxel) and a median time to progression (TTP) of 5.7 months (vs. 2.9 with docetaxel). Although these trials failed to show a survival benefit of the combination over single agent chemotherapy, this was thought to be attributed to the small sample size of the randomized phase II trials. However, these small studies provided proof of the concept that the combination may improve clinical outcome. This was demonstrated in the SWOG trial when the combination of DE was shown to be superior to M/P in response rate, TTP, and survival. However, the same magnitude of benefit was seen with DP combination over M/P in the TAX 327 study. Moreover, QOL analysis of these two trials hypothesized that the addition of estramustine might have had a detrimental effect on QOL. The results of the SWOG 9916 and TAX 327 trials, although succeeding in standardizing docetaxel, failed to address the role of estramustine in upfront therapy. Fizazi and colleagues examined in a meta-analysis the magnitude of benefit offered by estramustine in HRPC [23]. The analysis included five randomized trials and the results showed that the addition of estramustine to chemotherapy particularly antimicrotubular agents had a significant improvement in OS [hazard ratio = 0.82 (95% confidence interval: 0.69–0.97); $P = 0.02$]. On the other hand, Machiels and colleagues recently presented a randomized phase III trial comparing DP with or without estramustine [24]. The results showed a PSA response of 73 and 69%, median PFS of 186 days and 195 days, and median survival of 617 days and 629 days for estramustine versus no estramustine, respectively. The results of this study failed to show any clinical relevant advantage in terms of efficacy in adding estramustine to DP. Moreover, DP with estramustine was significantly more toxic than DP alone ($P = 0.003$). To date, there is no standard second-line therapy, and given the activity of estramustine in this aggressive disease, its use as a single agent or in combination with synergistic chemotherapeutic agents with no cross-resistance to docetaxel seems rational. In a recently published retrospective analysis, the addition of estramustine to vinorelbine in patients previously exposed to taxanes as first-line therapy was able to significantly improve median survival over single agent vinorelbine (8.5 vs. 4.1 months; $P = 0.05$) [25].

Epothilones

Epothilones are nontaxane, microtubular stabilizing agents that can induce microtubule inhibition, mitotic arrest, and apoptosis at the G2/M phase transition of the cell cycle [26,27]. They are generally 5–25 times more potent than paclitaxel in inhibiting cell growth in cultures. Epothilones and taxanes differ in their drug-resistance mechanisms. Cytotoxic effects of the epothilones are preserved in multidrug resistance, expressing cell lines and in cells harboring tubulin mutations, which demonstrate resistance to paclitaxel. Single agent ixabepilone was evaluated in two first-line studies. PSA response was observed in 30–35% of cases with an objective clinical response rate $\geq 15\%$ in patients with measurable disease. The estimated median PFS is about 6 months and the median survival ranges between 16 and 18 months [28]. Eighty patients with taxane-resistant HRPC were assigned in a randomized phase II study to either ixabepilone or mitoxantrone/prednisone. PSA decline of $> 50\%$ was seen in 20% and median survival of 13 months in patients on the mitoxantrone arm as compared with a PSA decline of $> 50\%$ in 17% and median survival of 12 months in the ixabepilone arm [29]. A logical next step would be a randomized phase III trial to determine whether a survival benefit could be achieved by any of them over the other. Another way of

using the drug is to combine it with other active agents, particularly estramustine. In a randomized phase II trial in 90 patients with chemo-naïve HRPC, the addition of estramustine to ixabepilone was associated with a PSA response of 69% (vs. 48% for ixabepilone alone) [30]. The main adverse event encountered with ixabepilone is neurotoxicity. In phase I studies with ixabepilone, no grade III neurotoxicity was reported when the drug was administered daily for 5 days [31]. Furthermore, in a recent phase II trial with ixabepilone administered daily for 5 days in patients with breast cancer, the grade III peripheral sensory neuropathy was only 3% [32]. This seems to be less than that observed in the every 3 weeks schedule, which reached 20% in some reports [28].

Platinum salts

Platinum salts have a long history of use in many cancers, including prostate cancer [33]. Although earlier studies suggested a lack of activity, more recent studies using palliation and PSA endpoints have suggested that a greater degree of clinical benefit could be achieved by carboplatin. In 2006, Castagneto *et al.* [34] demonstrated a 26.9% decline in serum PSA by more than 50%. However, with the establishment of taxanes as first line therapy, less enthusiasm is drawn to platinum salts as a single agent and instead several phase II trials combined them with taxanes with appealing results [35,36]. Although the combination seemed promising and was tolerated reasonably well, it remains unclear as to the extent to which carboplatin enhances the efficacy of docetaxel and estramustine. Recently, new generation platinum salts showed some interesting data in taxane refractory settings. Satraplatin is the first orally available platinum drug that has shown cytotoxic activity *in vitro* in cisplatin-resistant cell lines. In a large phase III trial (SPARC) [37], 950 patients were randomized in a 2:1 fashion to receive satraplatin/prednisone or prednisone alone. Fifty-one percent of the patients had received prior docetaxel. The results were clearly in favor of the satraplatin arm that was associated with a superior PSA response ($P = 0.00007$), objective tumor response ($P < 0.002$), pain response ($P < 0.005$), and duration of pain response ($P = 0.049$). Satraplatin was also associated with a 31% reduction in the risk of PFS events ($P < 0.00001$) and a 33% reduction in the risk of pain progression ($P = 0.00028$). It was generally well tolerated with grade IV toxicities occurring in less than 5% of cases. However, one must question if prednisone was an appropriate control arm. Nevertheless, this data supports the suggestion that satraplatin will have a role in the management of HRPC and it indeed extends the treatment options for these patients. Future trials should focus on comparison with other treatment options, particularly M/P which is probably the most common second line chemotherapy used nowadays.

Bisphosphonates

Prostate cancer metastasizes to bone more frequently than does any other solid tumor [38]. Bone metastasis occurs in almost all patients during the natural course of their disease and typically targets the lumbar spine, vertebrae, and pelvis [39]. Many causes exist for this high incidence of bone metastasis, including anatomic factors facilitating accessibility of the lumbar spine, innate characteristics of prostate cancer cells, and molecular interactions between prostate cancer cells and the bone microenvironment. Indeed, prostate cancer seems uniquely suited to growth in bone [40]. Bone lesions from prostate cancer are characterized by osteoblastic overactivity, exhibiting localized increases in osteogenesis [41]. In osteoblastic lesions, prostate cancer cells stimulate the maturation and activation of osteoblasts [42]. Osteoblasts, in turn, appear to stimulate prostate cancer growth and reduce proapoptotic signaling [43]. Although osteoblastic lesions are associated with pathologic new bone formation, this does not correlate with increases in bone strength. On the contrary, the new osseous tissue is often abnormally mineralized or inappropriately placed [44]. Furthermore, osteoblastic bone metastases can trigger localized increases in osteolysis to balance the excess activity of osteoblasts [45]. Excess osteogenesis can also cause systemic increases in osteolysis, resulting in generalized osteolysis at distant sites. The overall result is uncoupling of the osteogenesis and osteolysis processes. In most cases, disease progression in patients with bone metastases from prostate cancer is associated with mild hyperparathyroidism [46], perhaps from decreases in serum calcium levels caused by new bone formation.

Zoledronic acid [47], clodronate [48], pamidronate [49], and ibandronate [50] have all been investigated in patients with bone metastasis from prostate cancer, and all have shown some benefit in terms of pain palliation. However, and unlike other solid tumors, only zoledronic acid has demonstrated long-term objective benefits compared to placebo. Saad *et al.* [47] demonstrated a 36% reduction in the risk of having a skeletal-related event at 24 months for patients with HRPC treated with zoledronic acid over placebo. As patients developing a pathological fracture have a poorer survival rate compared with those who did not [51], zoledronic acid might function as a cornerstone tool in the management of HRPC in improving the QOL and possibly survival. Saad *et al.* failed to show a survival benefit over placebo ($P = 0.09$), yet the study was not originally designed to evaluate an effect on survival. On the other hand, the addition of clodronate failed to demonstrate any improvement in QOL scores, palliative responses, and survival when added to M/P regimen compared with placebo [48]. The same results were reported with pamidronate as well [49]. In hormone sensitive tumors, the benefit of adding zoledronic acid to antiandrogens is

not yet clear and a randomized controlled trial (CALGB/CTSU 90202) is currently ongoing to define a role for zoledronic acid in this setting. As for clodronate, the MRC Pr05 trial showed no benefit from the addition of oral clodronate to androgen deprivation compared with placebo [52]. After a median follow-up of 59 months, the clodronate group had nonsignificant improvements in PFS and OS. Men in the clodronate group reported more gastrointestinal problems and required more frequent dose modification of the study drug ($P = 0.002$).

In prostate cancer, bone turnover markers in urine and serum have been extensively studied as indicators of bone metastases, and they correlate with the number of lesions [53,54]. In general, markers of bone resorption are distinguished from markers of bone formation, and under normal conditions they are coupled to each other. Bone formation markers are direct or indirect products of osteoblast activity. Bone resorption markers physiologically result from bone collagen degradation [55]. Bone metastasis deregulate the balance between bone formation and bone resorption. Therefore, biochemical markers of bone turnover can provide an insight into tumors and their dynamic effects on bone interactions. In a recently reported prospective trial, Hegele and colleagues compared the value of bone turnover markers in different stages of prostate cancer [56]. The study included 219 men: 129 with localized disease amenable to surgery, 25 with bone metastasis, and 65 with benign urological disorders serving as controls. Two bone formation markers, namely alkaline phosphatase (ALP) and osteocalcin, and two bone resorption markers, namely tartrate-resistant acid phosphatase type 5b (TRACP5b) and serum C-terminal telopeptide of type I collagen (S-CTX), were assayed before commencing any form of therapy. The control group had the lowest bone turnover marker levels, and patients with bone metastases had the highest levels of ALP ($P < 0.001$), osteocalcin ($P < 0.05$), and TRACP5b ($P < 0.001$), but there was no statistically significant difference in S-CTX levels ($P = 0.16$) from the controls. Patients with localized prostate cancer had significantly higher levels of TRACP5b ($P < 0.001$) than the controls, but not higher levels of ALP ($P = 0.1$), osteocalcin ($P = 0.58$), and S-CTX ($P = 0.35$). Patients with lymph node-positive prostate cancer had significantly higher levels of TRACP5b ($P < 0.005$) and ALP ($P < 0.05$), but not osteocalcin ($P = 0.78$) and S-CTX ($P = 0.1$) than the controls. This study demonstrated that markers of bone formation and resorption might be helpful tools to detect bone disease and to initiate adequate therapy in time. TRACP5b and ALP indicated activated bone metabolism despite a normal bone scan. These markers could be useful to indicate occult bone metastases in high-risk patients earlier than the other clinical variables and a bone scan. Furthermore, it could guide in predicting which patient will develop bone metastasis and may advocate adjuvant bisphosphonates. These results have led to another study to define the clinical value of serum bone turnover markers in the follow-up of high-risk patients. Other markers were also shown by Lein and colleagues [57] to provide valuable information regarding progression of bone metastasis in men with metastatic prostate cancer under bisphosphonate therapy, including ALP, bone-specific ALP, terminal procollagen propeptides of type I collagen, and C-terminal telopeptides of type I collagen. In this trial, patients who responded to bisphosphonate therapy had a significant decrease in serum bone turnover markers with the exception of C-terminal telopeptides of type I collagen .

In summary, there is increasing evidence to suggest that bone turnover markers may serve as an important tool in monitoring of therapy [57], predicting recurrence [56], and even survival [58].

Targeted agents

Vitamin D receptors

Vitamin D receptors (VDRs) are expressed in a broad range of malignancies including prostate cancer, and calcitriol is considered a natural VDR ligand. Several studies have shown that calcitriol and other synthetic VDR ligands have significant antitumor activity through inhibiting proliferation, inducing apoptosis, and reducing tumor invasiveness and angiogenesis [59,60]. Furthermore, the antineoplastic activity of VDR ligands is synergistic or additive with the activity cytotoxic chemotherapy drugs, such as paclitaxel [61], docetaxel [62], platinum compounds [63], and mitoxantrone [64]. In the clinical setting, the addition of calcitriol with docetaxel was associated with an impressive 50% PSA decline or more in 81% of patients and a 1-year survival rate in 89% [65]. These results encouraged the initiation of the ASCENT trial, which is a randomized placebo-controlled phase II trial testing the safety and efficacy of calcitriol when added to weekly docetaxel [66]. In this trial, 250 patients were randomly assigned to weekly docetaxel 36 mg/m^2 for 3 weeks of a 4-week cycle combined with either 45 μg calcitriol or placebo taken orally 1 day before docetaxel. PSA responses were seen in 58% in the calcitriol arm and 49% in the placebo. Although the difference in response rate was not statistically significant ($P = 0.16$), patients on the calcitriol arm had a hazard ratio of death of 0.67 ($P = 0.04$). The median survival of the placebo arm was 16.4 months whereas that of the calcitriol was not reached at the time of reporting the results and is estimated to be 24.5 months. The number of serious gastrointestinal events was reduced in the calcitriol arm (2.4%) as compared with the placebo arm (9.6%; $P = 0.02$). It was hypothesized that calcitriol induced temporary cell cycle arrest in the rapidly proliferating cells of the gastrointestinal tract, rendering them less sensitive to the cytotoxic effects of

docetaxel. This hypothesis is based on preclinical animal models, which showed that higher levels of vitamin D metabolites are associated with a reduced proliferation of gastrointestinal epithelial cells [67,68].

Given the superior efficacy and lesser toxicity profile witnessed in phase II trials, this regimen is now being investigated in a phase III study (ASCENT-2).

Endotheline-1

Endotheline-1 (ET-1) is a potent vasoconstrictor produced by the bone cells and responsible for stimulation of mitogenesis in the osteoblasts [69]. ET-1 exerts its effect by binding to ET_A and ET_B receptors, which are expressed on the prostate [70]. Nelson and colleagues found that plasma ET-1 concentrations are higher in men with metastatic prostate cancer to the bone compared with those with organ confined disease suggesting that ET-1 may be a mediator of the osteoblastic response of bone to metastatic prostate cancer [71]. Preclinical trials were later able to show that metastatic cancer cells in the bone microenvironment secrete ET-1, which binds to the ET_A receptor and stimulates osteoblast proliferation and new bone formation. Stimulation of osteoblast activity enriches the local microenvironment with growth factors, which, in turn, could increase tumor burden and ET-1 secretion with further osteoblastic proliferation leading to a vicious cycle [72]. Moreover, ET-1 modulates apoptosis [69], nociception [73], and blood flow [74] indicating other potential benefits of ETA receptor antagonism in prostate cancer.

Atrasentan (ABT-627) is a selective ET_A receptor antagonist that blocks or reverses the biologic effects of ET-1 [75]. In a placebo-controlled randomized phase II trial, 288 patients with HRPC were randomized to atrasentan 2.5 or 10 mg/d or placebo [76]. Patients randomized to atrasentan 10 and 2.5 mg/d, respectively, had an improvement in TTP ($P = 0.021$; $P = 0.035$) and PSA progression ($P = 0.002$; $P = 0.055$) over placebo. Headache, rhinitis, and peripheral edema were the most common and statistically significant adverse events associated with atrasentan, yet most of the events were mild to moderate in severity, none of them leading to drug discontinuation. These results encouraged the initiation of a phase III trial that randomized 941 patients to atrasentan 10 mg/d or placebo [77]. Patients randomized to atrasentan showed longer PSA doubling time ($P = 0.031$). However, unlike the earlier phase II trial [76], the study failed to show a significant prolongation in TTP ($P = 0.288$). The discrepancy in results between the atrasentan phase II and phase III trials could be attributed to the high discontinuation rate in the phase III study as well as the different assessment methods. In the phase II trial, TTP was based on subjective progression whereas in the phase III trial it was based on objective progression on bone scan done after 12 weeks of initiation of therapy. Limited data are available on atrasentan combinations. In a randomized phase II trial, the addition of zoledronic acid to atrasentan failed to show any additive or synergistic effects [78]. Preclinical data showed encouraging results when atrasentan was combined with docetaxel [79]. A randomized controlled trial sponsored by SWOG-0421 in patients with HRPC who have bone metastases is underway to evaluate the possible synergistic effect of atrasentan in combination with docetaxel. A criticism that could be drawn to the atrasentan trials would be the absence of ET_A expression analysis done in any of them. As atrasentan is an ET_A blocker, it is rational to check ET_A expression before giving this drug. The degree of expression of ET_A is not yet known but available evidence suggests different degrees of expression in different tumor stages, that is, hormonal sensitive and hormone refractory [80].

Other targets

Vascular endothelial growth factor

Vascular endothelial growth factor is crucial for the development of tumor masses exceeding a diameter of 3–5 mms [81]. Anti-vascular endothelial growth factor monoclonal antibody therapy has been tested with a variety of agents and has shown compelling results. In a Cancer and Leukemia Group B (CALGB) trial, bevacizumab was given together with estramustine and docetaxel [82]. Preliminary results indicate a PSA fall to less than 50% of baseline in 77% with an estimated TTP of 10.3 months. This data provided a rational for the initiation of a phase III trial of bevacizumab and docetaxel compared with docetaxel alone. Other molecules showed some interesting data in preclinical models. The combination of sunitinib with docetaxel was associated with supra-additive effects in mice bearing well-established, PC3 prostate tumors [83], the fact that would encourage clinical application.

Bcl-2

The oncogene bcl-2 plays a major role in suppressing apoptosis, which may inhibit responses to therapy [84]. Therefore, suppression of bcl-2 in tumors may increase therapeutic efficacy [85]. In prostate cancer, abnormal expression of bcl-2 is associated with advanced stage, high Gleason score and shorter TTP [86]. In a recently completed phase II trial, the addition of bcl-2 antisense (oblimerson) to docetaxel in HRPC reported an encouraging 52% PSA response and a median survival of 19.8 months [87]. A randomized phase III EORTC trial is currently underway.

Epidermal growth factor receptor

Epidermal growth factor receptor (EGFR) is frequently expressed in prostate cancer and has been linked to poor prognosis and development of hormone resistance [88]. The two major categories of inhibiting EGFR are either antibodies to the external epitope or small molecule

inhibitors of the receptor tyrosine kinase. Gefitinib, which is a tyrosine kinase inhibitor, showed an encouraging antitumor activity in preclinical models [89]. However, gefitinib (250 and 500 mg/d) failed to demonstrate any PSA or objective response in 40 patients with HRPC [90]. When combined with docetaxel, the results were almost similar to those encountered with docetaxel alone [91]. The same results were reported with pertuzumab when given as a single agent for the same patient population [92]. Given these negative results, the therapeutic relevance of EGFR inhibitors in HRPC remains uncertain.

Conclusion

DP remains the standard first-line treatment in HRPC. Options for second-line treatment remain open including estramustine, satraplatin, ixabelipone, and M/P and a randomized phase III trial is needed in this setting. The high incidence of bone metastasis favors the addition of bisphosphonates, and zoledronic acid appears to be the most potent in HRPC. The incorporation of bone markers would help in optimizing the use of these agents. Many targeted agents evolved and appear very close to be incorporated in current treatment paradigms, particularly calcitriol and bevacizumab. Ongoing phase III trials are awaited to define an exact role.

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