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Review

Actual Chemotherapeutical Possibilities in Hormone-refractory Prostate Cancer (HRPC) Patients

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Abstract. *Androgen deprivation therapy still remains the gold standard in the treatment of advanced prostate cancer. Unfortunately, patients with metastatic prostate cancer treated with androgen deprivation therapy frequently develop androgen-independent prostate cancer. Cytotoxic chemotherapy has not been used routinely and the current standard regimens have not demonstrated any significant alteration in the development of hormone-refractory disease. Recent phase III randomized clinical trials have suggested that docetaxel-based therapy, demonstrating a real increase of survival in treated patients, could represent the new standard treatment for metastatic patients. There is also promising activity of new drug combinations, such as taxanes plus vinca alkaloids, and of classic chemotherapeutic agents plus biological drugs. This review focuses on the current therapies for the treatment of HRPC.*

Hormonal ablative therapy remains the primary therapy for metastatic androgen-dependent prostate cancer. However, the optimal timing for the initiation of androgen deprivation therapy has not been established yet. There are 3 randomized trials of "early" *versus* "deferred" androgen deprivation therapy with conflicting results (1-4).

Today, it is believed that androgen deprivation therapy can start at the time of prostate cancer recurrence after curative primary therapy, most often manifested by increase of the serum prostate-specific antigen (PSA) levels. This will allow the patient to exploit the benefits attributed to this therapy, but the possibilities to experience adverse effects will increase. In contrast, waiting for prostate cancer metastasis to occur might permit a longer period without treatment-associated symptoms, but will miss the advantages of the "early" initiation of the androgen deprivation therapy. The PSA doubling time may provide a tool for stratifying patients with a rising serum PSA for androgen deprivation therapy: patients with a shorter PSA doubling times require earlier treatment than patients with longer PSA doubling times (5).

The progression of metastatic androgen-resistant prostate cancer is a significant threat of morbidity and mortality. Because of the relative efficacy of chemotherapy in the hormone refractory disease (symptomatic relief, objective disease response and potential survival benefits), investigators have recently examined the role of chemotherapy in the progression of prostate cancer, when the disease is still hormonally responsive, in an effort to improve the impact on disease response and patient survival. The benefit of chemo-hormonal therapy *versus* hormonal therapy alone, is currently examined (6-8).

Androgen deprivation is only temporarily effective in metastatic prostate cancer secondary to the development of tumor resistance. The prostate cancer, that grows despite the castration levels of testosterone, no longer responds to any form of hormonal manipulation, requires non-hormonal approaches and can be precisely defined as hormone-refractory prostate cancer (HRPC) (9). Chemotherapy (CT) at this stage of the disease has been studied since the early 1970s, but there is still no single, widely accepted systemic treatment for patients with HRPC. Therefore, in the past, there has been reluctance to treat patients with HRPC using CT which was considered to be ineffective with unacceptable toxicity, especially in those elderly patients with a poor performance status. Moreover, many of these early studies suffered from important methodological flaws: some enrolled too few patients, others included heterogeneous groups of patients within the same study cohort and there were no definitive objective response criteria, because of the typical behaviour of the disease.

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For these reasons, until recently, there has been no standard chemotherapeutic approach for HRPC. However, there is evidence that newer chemotherapy agents and regimens do have some activity (10-12). The previous scepticism has been challenged by the development of new agents and combinations, attributed to the increasing understanding of the biology of this form of prostate cancer, to the evaluation of more appropriate response criteria, such as PSA and quality of life (QoL), and to the consequent definition of newer study end-points.

Clinical studies have used several indicators of response to demonstrate anti-prostate cancer activity: reduction in serum PSA, shrinkage in radiological-measured bi-dimensional disease, improvement in QoL and survival.

A 50% reduction in PSA sustained over several weeks is considered as a serum PSA response. An increase in serum PSA has been correlated with disease progression and a reduction has been correlated with a reduction in tumor mass, which has not been definitively correlated with increased survival and improvement in QoL. Many patients with metastatic disease have metastases to the bones, but it is very difficult to assess the chemotherapy response of bone tumors through traditional radiography. QoL parameters such as reduction in pain and improvement in performance status are accepted as measures of a positive response. However, the use of validated survey instruments is required to measure possible changes in QoL.

This review presents the recent and newly proposed therapeutical possibilities for the HPRC patients.

Anthracyclines

Doxorubicin alone may have a significant palliative effect, but it has minimal overall activity in HRPC patients. Doxorubicin (20 mg/m^2/week intravenously) produced objective radiological responses in 15% of men treated (10). This drug has been combined with escalating doses of cyclophosphamide in a phase II trial, that enrolled 35 patients (13). Five out of the 15 patients (33%) with measurable disease had evidence of a response. Sixteen out of 35 patients (46%) had a >50% decrease in PSA levels. This combination required growth factor support and was generally well-tolerated, although 33% of the cycles were associated with grade 4 neutropenia; febrile neutropenia occurred in only 7.8% of all cycles.

Culine *et al.* (14) have performed a study based on administration of doxorubicin with estramustine phosphate and showed that the biochemical response rate was 58% among 31 assessable patients, and the objective response rate was 45% in 11 patients with measurable lesions. The morbidity of this combination therapy was generally acceptable: only 2 patients had febrile episodes among 12 who developed grade 3-4 neutropenia during treatment. No cardiotoxicity was observed and these results suggested that a weekly regimen with low doses of doxorubicin was able to reduce side-effects.

Another phase II study reported the results of epirubicin, the 4'-epimer of doxorubicin, and estramustine phosphate in 24 assessable patients with HRPC. A biochemical response was noted in 54% of the patients although no objective response occurred (15).

Recchia *et al.* have found that the combination of epirubicin, mitomycin C and 5-fluorouracil is active in the treatment of HRPC patients, giving substantial palliation of symptoms (16).

Mitoxantrone is an anthracenedione structurally related to anthracyclines such as doxorubicin, with lower toxicity. A multicenter phase II Canadian study of mitoxantrone plus prednisone demonstrated a significant palliative benefit of this combination (17). A randomized phase III trial had compared mitoxantrone plus prednisone *versus* prednisone alone (18). One hundred and sixty-one patients were administered mitoxantrone 12 mg/m^2 *i.v.* every 3 weeks with prednisone 10 mg/day, or prednisone alone; the combination was associated with significant pain relief in 29% for an average of 43 weeks, compared to 12% in the prednisone-treated arm for an average of 18 weeks. Change in PSA and overall survival were not statistically different; minimal hematological toxicity and possible cardiac toxicity was noted in 4% of the patients treated with mitoxantrone.

In a Cancer and Leukemia Group B Study, Kantoff *et al.* randomized 242 patients to mitoxantrone (14 mg/m^2 every 3 weeks) plus hydrocortisone (40 mg/day) *versus* hydrocortisone alone (19). PSA declines (>50%) were seen in 33% of the patients receiving chemotherapy *versus* 18% on steroids alone. Median survival was similar in both arms. Pain control was significantly better with the combination therapy.

The studies of mitoxantrone plus glucocorticoids have shown that as many as 40% of the patients will have improvements in pain and QoL with this treatment, with a reasonable toxicity profile, although there does not seem to be any significant impact on the overall survival. For these reasons, the FDA approved the mitoxantrone/ corticosteroids combination as palliative treatment for patients with HRPC.

Doxorubicin and other anthracyclines were then recognized as active antineoplastic agents (liposomal anthracyclines). Liposomal encapsulation may enhance the therapeutic efficacy and reduce toxicity. McMenemin *et al.* have conducted a single phase II study using pegylated doxorubicin 50 mg/m^2 administered once every four weeks to 14 patients. Three PSA responses were documented in patients with non-measurable disease. No patient had an objective response in measurable disease (20).

Heidenreich *et al.* have recently conducted a prospective randomized phase II trial to evaluate the feasibility, toxicity and therapeutic efficacy associated with pegylated

doxorubicin. Forty-eight patients were randomized to receive pegylated liposomal doxorubicin at either 25 mg/m^2 every 2 weeks for 12 cycles (group A) or 50 mg/m^2 every 4 weeks for 6 cycles (group B). The results show that patients in group B had a significantly higher response rate with respect to pain (52.6 *vs.* 28.6; $p=0.04$) and the mean 1-year survival rate was also significantly higher (42% *vs.* 15%; $p=0.02$) (21).

Estramustine

Estramustine phosphate is a nitrogen mustard derivative of estradiol-17-beta-phosphate. Its mechanism of action in prostate cancer combines the hormonal effect of estrogen with a cytotoxic action through disruption of microtubule function and nuclear matrix binding (22-24). As a single agent, it has a moderate activity in treating prostate cancer, with most studies reporting rates of approximately 20% (25).

In a randomized multicenter trial, the Danish Prostatic Cancer Group studied the effect of estramustine phosphate (560 mg/day) as a supplement to standard palliative therapy for patients with HRPC (26). This study showed similar subjective responses (18% *vs.* 7%) and overall (9.4 *vs.* 6.1 months) and cancer-specific (10.3 *vs.* 6.1 months) survival between estramustine and placebo. Out of 61 patients in the estramustine phosphate-treated group, 29 achieved a reduction of 25% in PSA levels at 1 month of follow-up, compared to only 3 out of 68 patients receiving placebo. A decrease in PSA levels after 1 month correlated significantly with survival.

In order to target microtubule proteins at different loci for maximal efficacy, estramustine has been combined with other antimicrotubule agents and has been evaluated in phase I and II trials. The semisynthetic podophyllotoxin derivative etoposide is an inhibitor of topoisomerase II, a nuclear matrix associated enzyme involved in DNA replication and repair. Pienta reported the results of a phase II trial, using the combination of oral estramustine 15 mg/kg/day and oral etoposide 50 mg/m^2/d in 52 CT-naïve patients with HRPC (27). The response rate was 45% in those with soft-tissue disease, and 54% of the patients showed at least a 50% decrease of the PSA levels, but a significant toxicity was noted. In an attempt to reduce this toxicity, the authors performed a second phase II study using the same dose of etoposide but with a reduction in the dose of estramustine to 10 mg/kg/d, including patients who had previously received CT (28). Eight (53%) out of 15 patients with measurable disease had a partial response. Out of the 47 patients with disease limited to the bones, 16 patients (34%) showed at least a 50% reduction from baseline PSA level.

In a recent phase II study Bracarda *et al.* have treated 32 HRPC patients with estramustine phosphate (10 mg/kg/day) and low-dose cyclophosphamide (2 mg/kg/day) (29). This combination produced PSA responses in 44% of men with a median duration of response of 30 weeks. Seventeen percent of men with measurable disease had an objective radiological response. Some patients had complete resolution of bone pain. The toxicity was mild and mainly gastrointestinal, thanks to the intermittent administration of estramustine phosphate and to the capacity of cyclophosphamide to preserve bone marrow stem cells.

Hovey *et al.* have evaluated an intravenous preparation of estramustine in combination with docetaxel (30). Weekly estramustine 1000 mg/m^2 was combined with weekly docetaxel 20 mg/m^2, with doses increasing by 500 mg/m^2 and 10 mg/m^2 for estramustine and docetaxel, respectively, in 4 patients with HRPC. Three patients achieved a 50% PSA level decline within 4 weeks of treatment. No vascular events were observed.

A multinational phase II study evaluated weekly intravenous estramustine (2000 mg/m^2) in patients with HRPC (31). Out of 31 evaluable patients, 11 (37%) achieved a 50% or higher PSA level decline, which was maintained for at least 4 weeks. Moreover, pain relief was achieved in 36% of patients. Thus, single agent weekly estramustine appears to be active and well tolerated.

Vinca Alkaloids

Vinca alkaloids are microtubule-targeted drugs derived from the periwinkle plant (*Cantharanthus roseus*). Two vinca compounds, vinblastine and vinorelbine have been evaluated in clinical trials for the treatment of prostate cancer. Vinblastine is an antitubulin agent, which has been used in combination with estramustine because of its complementary effects, distinct molecular targets and different toxicity profile (32).

In 1999, Hudes *et al.* showed the results of a randomized trial of 201 patients with HRPC, in which estramustine with vinblastine were compared to vinblastine alone (33). The combination was associated with improved, but not statistically significant, survival and a significant PSA decline (25% *vs.* 3%).

Albrecht *et al.* have evaluated estramustine *versus* estramustine/vinblastine in an EORTC trial. The conclusions showed much less favorable results with a median survival of 93.5 and 46.6 weeks, respectively, in 92 patients with HRPC (34).

Fields-Jones *et al.* have performed a phase II trial with vinorelbine and showed a durable clinical benefit with a response rate of 39% (35).

Carles *et al.* have treated 24 patients with a combination of estramustine and vinorelbine. A decline greater than 65% was observed in the PSA levels in 37.5% of patients, without objective response (36).

A clinical response rate of 32% and a biochemical response rate of 56% was obtained with the combination of estramustine, oral etoposide and vinorelbine (37).

In a recent randomized trial comparing vinorelbine (30 mg/m^2 days 1 and 8 every 3 weeks) and hydrocortisone with hydrocortisone alone in 414 men with progressive androgen-resistant disease, a statistically significant difference of 1 month (3.7 *vs.* 2.8 months; $p=0.005$) in median progression free-survival favoring vinorelbine treatment, with no difference in overall survival (median 15 months), was detected (38). PSA response rates were also significantly higher for vinorelbine treatment (30.1% *vs.* 19.2%; $p=0.01$), as well as the clinical benefit, defined as a decrease in pain intensity or analgesic consumption or an improvement in performance status (30.6% *vs.* 19.2%; $p=0.008$). Additionally, vinorelbine therapy was generally well tolerated in the trial, with approximately 7% incidence of significant neutropenia and less than 1% incidence of cardiotoxicity.

Currently, combinations of vinorelbine with estramustine, docetaxel and other agents are under clinical development (39, 40).

Alkylating Agent

The alkylating agent cyclophosphamide is active against a number of malignancies including breast cancer and lymphoma. Oral cyclophosphamide has been tested in several clinical studies on prostate cancer treatment. Cyclophosphamide as a single agent (100 mg/m^2/day given 14 of every 28 days) is still well tolerated. In a phase II trial, objective response was 6 out of 30 (20%) and subjective improvement was 18 out of 30 (60%). The median survival from the time of diagnosis was 33.3 months (41).

In another phase II trial conducted by Maulard-Durdux *et al.*, 20 patients with HRPC were orally treated with cyclophosphamide (100 mg/d) and etoposide (50 mg/d) for 14 days every 28 days (42). The performance status improved in 26% of the patients, and bone pain was relieved in 71%. A 50% reduction of the PSA levels was demonstrated in 35% of the patients, and the toxicities were minimal.

The combination with other drugs has also been investigated: the study conducted by Bracarda *et al.*, previously described (29), and a more recent trial carried out by Nishimura *et al.* with the combination of cyclophosphamide, uracil plus tegafur and estramustine phosphate; this combination therapy was shown to be active and well-tolerated (43).

Platinum Compounds

There is scientific evidence about the use of cisplatin in advanced prostate cancer.

In preclinical models there has been evidence of synergism between cisplatin and anthracyclines. The non-overlapping toxicities of cisplatin and epirubicin prompted Huan *et al.* to conduct a phase II study of this combination in patients with HRPC (44). This study produced a biochemical response in 32%, symptomatic improvement in 38%, and a partial response of measurable diseases in 14% of the patients.

Veronesi *et al.* have evaluated a multidrug regimen comprising cisplatin, epirubicin and estramustine phosphate in terms of feasibility, toxicity and activity in younger (<70 years) patients with HRPC (45). The overall response rate was 39%, and an improvement of symptoms was obtained in 17 out of 19 (89%) patients. A moderate toxicity was observed without any fatal events.

Miglietta *et al.* have carried out a trial using carboplatin, a second-generation less toxic analog of cisplatin; a palliative response was achieved in 56% of the patients (46).

A combination regimen with etoposide, epirubicin and carboplatin was used to treat 12 patients with advanced prostate cancer (47), which showed a partial response rate of 25%, with pain relief obtained in 44% of the patients; the regimen toxicities were primarily hematological.

A randomized, multicenter phase II study of 54 patients with HRPC has been performed using oxaliplatin (a new analog of cisplatin) alone (130 mg/m^2/day) and an oxaliplatin –5-fluorouracil combination (1000 mg/m^2/day, continuous intravenous infusion, days 1-4) every 3 weeks (48). Clinical benefit response was assessed in 20 and 22 patients, respectively, with more responders in the combination therapy arm. Median time to progression was 2.6 and 3.4 months, and the median overall survival was 9.4 and 11.4 months, respectively. Hematotoxicity was common, but mostly mild to moderate.

Antimetabolites

5-Fluorouracil (5-FU) has not shown promising response rates in HRPC, but produced a significant toxicity profile (49, 50).

In a phase II randomized study performed by Breul *et al.*, monotherapy with 5-FU was compared with the combination of 5-FU and high-dose folinic acid (FA) (51). Both regimens led to pain remission in nearly 70% of the patients; mucosal side-effects like diarrhea and stomatitis occurred more often in the combination arm, whereas leukopenia was more frequent in the monotherapy arm.

Shinohara *et al.* have treated 21 patients with 5-FU and low-dose recombinant IFN-α2a, and showed a median overall survival time of 18 months, a decrease in the PSA levels >50% of baseline in about 45% of men, and bone pain remission in about 50% (52).

Treatment with gemcitabine was correlated with a significant benefit on pain at the dose and schedule indicated (1200 mg/m^2 over 2 hours on days 1, 8 and 15 out of a 28-day cycle). The use of analgesics yielded palliation for at least 8 weeks in 14 patients (32%) (53).

Taxanes

The taxanes (docetaxel, derived from the leaves of the European yew tree, and paclitaxel, derived from the bark of the Pacific yew tree) represent a relatively new class of chemotherapeutic agents that interfere with microtubule function. Microtubule function is required for mitotic chromosome segregation, and taxanes, as well as vinca alkaloids and colchicine, are well-known to trigger arrest at the G2/M phase of the replicative cell cycle and to promote apoptosis in rapidly dividing cells (54, 55). Drug disruption of microtubules and microtubule dynamics has been proposed to inhibit nuclear-cytoplasmic shuttling of regulatory proteins, limit angiogenesis and stimulate signalling pathways leading to phosphorylation and inactivation of the anti-apoptotic regulator bcl-2 (56, 57). Paclitaxel as a single agent and in combination with estramustine has been evaluated for the treatment of patients with HRPC. Paclitaxel as monotherapy showed a highly schedule-dependent activity. In one study, 23 patients with HRPC were treated with paclitaxel, given as a continuous infusion over 24 hours (135-170 mg/m^2) every 3 weeks for as many as 6 treatment cycles, with little benefit (a single partial response lasting 9 months) (58). The study conducted by Trivedi *et al.* (59) showed that weekly 1-hour administration of single-agent paclitaxel in 18 men produced higher response rates (4 major responses and 3 partial responses among 8 men with measurable disease) and median survival times, with significant serum PSA decline in 7 men; however, it is important to note that different methods of administration are associated with different toxicities. Myelosuppression is common with paclitaxel every 3 weeks, whereas neurotoxicity is increased with weekly administration.

The combination of paclitaxel, given as a 96-hour infusion, and estramustine showed a serum PSA response rate of 53%, a measurable disease response rate of 44% and a median survival of 17.3 months, in an initial phase II trial (60). Paclitaxel given at a different dose and infusion schedule (225 mg/m^2 by 3-hour infusion every 3 weeks) combined with estramustine provided a similar serum PSA response rate of 62% in another trial (61). Weekly paclitaxel (90 mg/m^2 by 1-hour infusion) combined with daily oral estramustine also gave significant rates of serum PSA declines (42%) in a recent trial on 66 men with HRPC (62). Combination regimens that include paclitaxel, estramustine and carboplatin or etoposide, or both, have also been evaluated recently, with PSA response rates ranging from 65% to 73% and measurable disease response rates ranging from 45% to 64% (63-65). Experience with paclitaxel is still limited and there are no phase III data showing improvement on survival.

Docetaxel has been largely assessed in a series of clinical trials both as monotherapy and in combination with other drugs. Docetaxel has a significantly longer cellular affinity and uptake, as well as a slower cellular affinity than paclitaxel, effectively prolonging the duration of the drug exposure. Moreover, it is approximately twice as efficient as paclitaxel in stabilizing microtubules against depolymerization and it appears to be a more potent inducer of bcl-2 phosphorylation and apoptotic cell death. Given every 3 weeks (75 mg/m^2) to 35 patients with HRPC, docetaxel therapy resulted in a 46% serum PSA response rate (66). In several studies of weekly docetaxel (35-40 mg/m^2), undertaken to make treatment more tolerable to elderly men, serum PSA response rates ranged from 41% to 64% (67, 68).

In a pooled analysis of 86 patients with HRPC treated weekly with docetaxel in 2 different trials, patients over 70 years of age were as likely as younger men to enjoy serum PSA responses and no more likely to suffer side-effects (68). Docetaxel and estramustine combinations have shown high response rates in phase I and II trials, both for serum PSA responses (45-74%) and for measurable disease responses (11-57%) (69-72).

Savarese *et al.* (Cancer and Leukemia Group B: CALGB) have completed a phase II study of docetaxel, estramustine and low-dose hydrocortisone in 47 men with HRPC (73). The combined measurable and biochemical response rate was 54%. The toxicity of this combination regimen has been moderate and tolerable; the most common side-effect was neutropenia. The results showed a serum PSA response rate of 68%, a measurable disease response rate of 50% and a median survival of 20 months.

Docetaxel as monotherapy and in combination with estramustine showed high response rates in patients with HRPC, thus phase III randomized trials against mitoxantrone and corticosteroids were initiated. The two resultant large, randomized, multicentre, controlled phase III trials both showed improvements in overall survival for patients with HRPC treated with docetaxel-based chemotherapy over mitoxantrone-based chemotherapy. In the first trial (TAX-327 study), the drug was used with steroid only, with the comparator being mitoxantrone and prednisone, the currently accepted standard care (74). The 3-arm study compared 30 mg/m^2 weekly or 75 mg/m^2 every 3-weeks docetaxel, administered with prednisone, to a standard arm of mitoxantrone and steroid. One thousand and six patients were randomized to one of the 3 arms and it is noteworthy that the vast majority had a good performance status prior to treatment. The most effective treatment was the 3-weekly regimen, which produced a significant improvement of 24% in overall patient survival. This equated to an actual median survival improvement of 2.4 months duration by comparison with the control arm

(18.9 months docetaxel *vs.* 16.5 months control). In addition, docetaxel (75 mg/m^2 every 3 weeks) and prednisone provided a better median serum PSA response rate (45% *vs.* 32%) and better pain control (35% *vs.* 22%) than mitoxantrone and prednisone ($p<0.01$).

The other study (SWOG 99-16) randomized 770 patients to 3-weekly docetaxel in combination with estramustine, compared to mitoxantrone and steroid (75). A similar result to that seen in the TAX-327 study was observed, with a 23% improvement in survival and a 28% reduction in risk of death from HRPC. The toxicity rates in this study were higher in a number of areas (hematological, cardiovascular, neurological, *etc.*), probably related to the addition of estramustine.

The improvement in median survival attributable to docetaxel in the phase III trials has established docetaxel, given every 3 weeks, and prednisone as the standard treatment for men with HRPC. A recent meta-analysis of 3 randomized trials (1087 patients) showed that docetaxel significantly reduced the risk of death by 8-21% persisting at least 3 years after the start of chemotherapy (76).

Recently, a randomized phase II trial comparing docetaxel and estramustine to docetaxel alone (92 patients) found a serum PSA response rate of 68% for the combination *versus* 29% for docetaxel monotherapy, though no survival data have been reported (77).

Recently Goodin *et al*., have evaluated the combination of docetaxel and vinorelbine in 40 patients with proven adenocarcinoma of the prostate. Out of the 40 patients enrolled, 19 had no prior chemotherapy and 21 had received at least one prior chemotherapy regimen. Out of the 19 patients without prior chemotherapy and the 21 with prior chemotherapy, 7 (37%) and 6 (29%), respectively, demonstrated a decrease in PSA by >50% maintained for at least 4 weeks. Out of eight patients with measurable disease, one achieved a partial response and four demonstrated stable disease (78).

Bisphosphonates

Bone metastases are common in patients with advanced cancer (79) and bisphosphonates have became an integral tool in the management of malignant bone disease. However, until recently, they had failed to demonstrate significant and durable benefits in randomized, placebo-controlled trials (80).

Zoledronic acid was the first bisphosphonate to demonstrate objective and durable benefits for patients with prostate cancer. A trial conducted in 2002 demonstrated that, compared to placebo, a 4-mg dose of zoledronic acid resulted in a statistically significant reduction in the incidence and delayed the onset of skeletal-related events (81). In another placebo-controlled randomized trial, 4-mg of zoledronic acid reduced the incidence of skeletal-related events in men with hormone-refractory metastatic prostate carcinoma (82). The median time to the first skeletal-related event was 488 days for the zoledronic acid group *vs.* 321 days for the placebo group ($p=0.009$).

Long term treatment with zoledronic acid is safe and provides sustained clinical benefits for men with metastatic hormone-refractory prostate cancer.

New Docetaxel Combinations, Angiogenesis Inhibitors and Other Oral Drugs

With the established efficacy of docetaxel in the treatment of HRPC and the uncertain overall benefit of the addition of estramustine to docetaxel, several new docetaxel combinations are under development and evaluation (83). For example, a phase II study of high dose calcitriol and docetaxel with dexamethasone found an 81% serum PSA response rate, with minimal toxicity (84). The preliminary results, presented at the American Society of Clinical Oncology (ASCO) 2005 Annual Meeting, showed a PSA response with DN-101 and docetaxel *versus* placebo and docetaxel (63% *vs.* 52%, $p=0.07$), with no increase in toxicity (85). Moreover the median survival was improved for DN-101-treated men.

Several trials have recently evaluated the role of docetaxel in combination with agents that interfere with tumor neovascularization; in fact neo-angiogenesis is a promising therapeutic target. The highest median survival reported in any phase II trial in HRPC was seen in a trial comparing weekly docetaxel plus thalidomide with docetaxel alone in 75 patients with chemotherapy-naïve HRPC: the median survival was 29 months in the docetaxel-thalidomide group; 69% of patients in the combination arm *versus* 42% receiving docetaxel alone were alive at 18 months follow-up (86).

The Cancer and Leukemia Group B (CALGB) have begun a phase III trial to evaluate the combination of docetaxel-prednisone-bevacizumab *versus* docetaxel-prednisone alone.

Atrasetan (ABT 627) is a selective endothelin-1 type A (ET-A) receptor antagonist that blocks the biological effects of endothelin (87-91). Recent studies, in fact, suggest that the endothelin B receptor is diminished, while expression of ET-A receptor increases with tumor stage and grade in prostate cancer. Endothelin 1 (ET-1) is a mitogen for prostate cancer cell lines and acts synergistically with other peptide growth factors. ET-1 is also a mitogen for osteoblasts.

Carducci *et al.* have conduced a randomized, phase II trial, to evaluate the efficacy and safety of atrasetan in the treatment of asymptomatic HRPC. This study demonstrated that 10 mg atrasetan (daily oral dose) had a trend toward prolonging time to disease progression and a statistically significant delay in PSA progression. These data substantiate the role of the ET-1/ET-A axis as a therapeutic target in hormone refractory prostate cancer (92). This promising

agent will be combined with docetaxel-prednisone and compared with the standard regimen of docetaxel-prednisone by an international group (SWOG) in the future.

The combination of vaccine therapy with docetaxel is also currently under investigation. GVAX is a vaccine in which irradiated prostate cancer cells are transfected with granulocyte/macrophage colony-stimulating factor. Preliminary data suggest that GVAX can delay time to progression in HRPC (93). Combination studies of docetaxel with GVAX are currently being designed.

Conclusion

When first- and second-line hormonal manipulation fails to alter the course of HRPC, chemotherapy is considered. Some patients prefer continuation of endocrine therapy alone or with supportive care when necessary, that influence QoL immediately. Alternatively, patients may be assessed to receive more aggressive therapies, in the hope of obtaining long-term benefits. The role of the urologist is to inform the patients of the available treatment options and potential benefits and side-effects.

Historically, prostate cancer was not considered to be a chemosensitive disease due to the poor survival outcomes for patients treated with chemotherapy. Single agent chemotherapy has been associated with palliative effects, but no single agent has been associated with a significant objective response rate. The use of palliation as a study end-point, along with the use of the PSA level as an indicator of disease response, has renewed the interest in chemotherapy as a treatment for HRPC and has led to many trials evaluating these end-points.

Important trials have recently shown for the first time that the taxane-based regimens also improved the overall survival of patients undergoing treatment. However, there are moderate improvements in efficacy, often accompanied by a significant increase in overall toxicity.

Several new docetaxel-based combination regimens are under evaluation in an effort to further improve outcomes for these patients. In addition, new agents are being investigated in the second-line setting in upcoming studies; targeted therapies are being developed in concert with translational research, which dissects the important molecular pathways in the evolution of the hormone-refractory phenotype.

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