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State-of-the-Art Treatment of Metastatic Hormone-Refractory Prostate Cancer

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Key Words. Hormone-refractory prostate cancer · Treatment · Resistance · Taxanes

ABSTRACT

Initial therapy for advanced prostate cancer includes androgen ablation by surgical or medical castration. Still, nearly all men with metastases will progress to hormone-refractory prostate cancer (HRPC). Current U.S. Food and Drug Administration-approved agents for the treatment of HRPC include mitoxantrone and estramustine, although the vinca alkaloids and the taxanes have shown promising activity in single-agent phase II trials. Combinations of these agents induce a biochemical response in greater than 50% of patients, but the median duration of response is approximately 6 months. Overall survival of patients treated with these combinations is approximately 18-24 months. Studies are ongoing to develop novel therapies that target specific molecular pathways or mechanisms of chemotherapy resistance. Novel agents under development include growth factor receptor inhibitors, antisense oligonucleotides, bisphosphonates, and cell differentiating agents. Evaluation and incorporation of these agents into existing treatment regimens will guide us in the development of more active regimens in the treatment of HRPC.

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INTRODUCTION

One in six men will be diagnosed with prostate cancer in their lifetime in the U.S. [1]. Nearly half of the patients with prostate cancer recur with advanced disease after definitive local therapy consisting of radiation or prostatectomy [2, 3]. Although patients with advanced prostate cancer are effectively treated with androgen ablation, the effect of androgen ablation on disease progression is temporary. These patients ultimately become unresponsive to androgen ablation and are then classified as having hormone-refractory prostate cancer.
and microtubule function appear to be particularly active in prostate cancer (HRPC) (Fig. 1). In the National Cancer Institute (NCI) Intergroup Study I, patients who received androgen ablation with leuprolide plus flutamide had a median time to progression to androgen-independent disease of 16.5 months [4]. Although dependent on prognostic factors, the median time to disease progression to HRPC in prostate cancer patients treated with androgen ablation ranges from 1 to 4 years in extensive and minimal disease, respectively [4, 5].

Standard options for patients with HRPC include secondary hormonal therapies or chemotherapy. For patients that progress on both a luteinizing-hormone-releasing hormone (LHRH) agonist and antiandrogen, the withdrawal of antiandrogen therapy results in an antiandrogen withdrawal response in 25%-50% of patients [6]. Other secondary hormonal options include the use of ketoconazole and hydrocortisone, the addition of an antiandrogen in patients progressing despite only an LHRH agonist, and corticosteroids [7]. Although secondary hormonal manipulations may produce a subjective response in approximately 25% of patients, it is short lived (approximately 4 months duration) [8, 9]. Therefore, both chemotherapy and the development of novel therapeutic options for the treatment of HRPC need to be explored in this patient population.

CHEMOTHERAPY IN HRPC

Several clinical trials have evaluated the role of both single-agent and combination chemotherapy in the treatment of HRPC [10, 11]. Recent clinical trials have demonstrated encouraging results in disease control and improvement in quality of life.

Estramustine

Chemotherapeutic agents that target the nuclear matrix and microtubule function appear to be particularly active in prostate cancer. Estramustine, a 17-β-estradiol phosphate derivative linked to a nor-nitrogen mustard molecule, is utilized in multiple chemotherapy regimens for prostate cancer. Originally developed as an alkylating agent, estramustine has shown activity in prostate cancer possibly unrelated to its hormonal or alkylating effects. Estramustine binds to microtubule associated proteins (MAPs) in the nuclear matrix and inhibits microtubule assembly and disassembly [12, 13]. The antimitotic effects of estramustine in prostate cancer have been shown in vivo in animals implanted with DU145 prostate tumor cell lines [14].

As a single agent, estramustine has shown an overall response rate of 14%-48%, with subjective improvements in pain and performance status [15, 16]. Differing response criteria have resulted in the wide response rates. For example, in the Danish Prostatic Cancer Group (DAPROCA) 9002 trial, patients with a decline in prostate-specific antigen (PSA) of only 25% were classified as responders, while in other studies patients were classified as responders based on palliative end points [17]. The addition of estramustine to other chemotherapeutic agents that affect microtubule function improves response rates [18-21]. For example, Hudes et al. completed a phase III trial treating patients with either estramustine with vinblastine or vinblastine alone [22]. They demonstrated that patients receiving estramustine had an increased response rate and decreased time to progression. Overall survival was not significantly improved on the initial report, but was significant on a recent analysis with longer follow-up. (Hudes et al., ASCO 2002). Similarly, Berry et al. treated patients with HRPC with estramustine and paclitaxel or paclitaxel alone [23]. They found a similar result; estramustine improved PSA response rate but not overall survival. Studies with estramustine in combination with other antimicrotubule agents have also been completed, as described later in this review.

Vinca Alkaloids

Vinblastine, an agent that binds to tubulin to prevent microtubule assembly, has been extensively studied for the treatment of HRPC in combination regimens with estramustine. As a single agent, clinical trials with vinblastine report a modest 21% response rate when given as a continuous infusion [24]. However, based on in vitro data that show additive effects when given in combination with estramustine [21], the combination was evaluated in several phase II trials. The response rate, as measured by PSA, has varied from 40%-54% [17, 18, 25]. Two of the trials reported palliative improvements in pain measurements in patients with decreases in PSA [17, 18]. Hudes and colleagues reported a “major pain response,” defined as a 50% decrease in pain scores or narcotic use for 4 weeks, in 43% of patients with assessable pain. Hematologic toxicities were minimal with this combination; approximately
10% of patients experienced grade 3 or 4 neutropenia [18]. As expected, nausea was the major nonhematologic toxicity reported with this regimen.

Another vinca alkaloid, vinorelbine, has been evaluated utilizing the palliative end points of the clinical benefit response model by Fields and colleagues [26]. In this trial, vinorelbine produced a “clinical benefit response” in 6 of 15 evaluable patients. This included a decrease in the visual analogue scale (VAS) score and narcotic use, along with a corresponding improvement in performance status. Concomitant decreases in PSA were noted in all responders. Studies combining vinorelbine with other agents are ongoing. For example, Goodin et al. studied the combination of vinorelbine with docetaxel and demonstrated a PSA response in 20 of 30 evaluable patients [27].

Etoposide

Although not traditionally viewed as a chemotherapeutic agent that affects microtubule function, etoposide, a topoisomerase II inhibitor that acts at the nuclear matrix, has been found to act synergistically with estramustine. In vivo and in vitro, growth of prostate tumor cell lines is inhibited to a greater extent with the combination of etoposide and estramustine than with either agent alone [13]. Pienta and colleagues completed two phase II trials of this combination in patients with HRPC [28, 29]. Patients received 15 mg/kg/d of estramustine and 50 mg/m²/d of etoposide orally on days 1 to 21 every 28 days. In the first trial, 50% (9/18) of patients with soft tissue disease responded according to traditional response criteria [28]. Fifty-four percent of patients experienced a PSA decrease of 50% or greater during the trial; however, the decrease in PSA was calculated from baseline to the lowest point achieved in the trial (4-56 weeks). Because of this, interpretation of PSA response is difficult. The regimen was associated with major toxicities including grade 3 or 4 leukopenia and nausea in 25% and 29% of patients, respectively. In an effort to decrease the toxicity associated with the regimen, a second phase II trial of the combination, with a 25% dose reduction of estramustine, was completed [29]. Similar measurable response rates were reported in patients with soft tissue disease. Overall, 39% of patients had a 50% or greater decrease in PSA. The lower dose of estramustine was associated with decreased toxicity. The incidence of nausea was decreased to 24%, and grade 3 or 4 leukopenia was only reported in 8% of patients.

Doxorubicin

Doxorubicin has also been extensively studied in both early and modern clinical trials involving patients with HRPC. Early clinical trials with single-agent doxorubicin produced disappointing and erratic results of 5%-84% depending on response criteria used [30, 31]. Recent combinations of doxorubicin with either ketoconazole or cyclophosphamide have improved response rates over single-agent doxorubicin [32, 33]. A phase II trial of weekly doxorubicin plus ketoconazole was associated with a 50% decrease in PSA in 21 of 38 patients, as well as a partial response (PR) in 7 of 12 patients with measurable disease [32]. However, the regimen was associated with a high rate of toxicities, with 45% of the patients admitted to the hospital for chemotherapy-associated toxicities. The combination of doxorubicin and escalating doses of cyclophosphamide produced 46% and 33% response rates as measured by PSA and measurable disease, respectively [33]. Patients who experienced a PSA response had a statistically significant increase in survival when compared with nonresponders (23 versus 7 months, p = 0.02). In addition, an improvement in patient-reported pain scores was reported in 68% of patients. There was substantial hematologic toxicity experienced with this regimen; 33% of cycles were associated with grade 4 neutropenia, and 7.8% of all cycles required patient hospitalization for adverse effects.

Mitoxantrone

Mitoxantrone in combination with prednisone was approved for the treatment of HRPC based on palliative end points. Based on clinical trials that suggested an improvement in symptoms over either agent alone, the combination of mitoxantrone and prednisone was evaluated for palliation of symptoms in phase II and III trials [34-36]. Tannock and colleagues randomized patients to receive either prednisone, 10 mg orally each day, alone or in combination with mitoxantrone, 12 mg/m² i.v. every 3 weeks [35]. The primary end point was a two-point decrease in pain assessed on the McGill-Melzak Pain Questionnaire, which ranks pain from 0 to 5, without a corresponding increase in analgesic use. Patients who received mitoxantrone plus prednisone achieved a statistically significant greater palliation of symptoms, including pain, compared with those who received prednisone alone (29% versus 12%, p = 0.01) along with a significantly longer duration of symptom palliation (43 versus 18 weeks, p < 0.0001). Patients in the mitoxantrone plus prednisone group also reported secondary improvements in four quality-of-life scales. Toxicity was mild, with the exception of a decreased left ventricular ejection fraction (LVEF) reported in 5 of 130 (including crossover) patients who received mitoxantrone, with two patients developing symptomatic congestive heart failure. Although PSA decreased by 50% or more in 33% of the patients receiving the combination therapy, it was not statistically different from a decrease of 22% in PSA in the patients that received prednisone alone. In a similar trial by Kantoff and colleagues involving 242 patients...
with HRPC treated with mitoxantrone, 14 mg/m², combined with hydrocortisone or hydrocortisone alone, the difference in PSA decrease between regimens was not significant (19% versus 14%, respectively) [36]. There was no difference in survival between the groups in either of the trials. Nevertheless, these large randomized trials showed a significant improvement in the palliation of symptoms in patients with HRPC who received chemotherapy.

**Taxanes**

The taxanes have received increased attention for their potential role in treating patients with HRPC due to their ability to induce cell death in prostate tumor cell lines (Tables 1 and 2). More recently, the taxanes have also been shown to affect genetic markers of HRPC [37, 38]. Similarly, investigators have demonstrated chemotherapy resistance in tumors with elevated levels of the antiapoptotic gene, bcl-2. Tu and colleagues transfected Dunning-G rat prostate cell lines with bcl-2 and assessed for doxorubicin sensitivity. Marked resistance to doxorubicin was found when compared with control cell lines lacking bcl-2 [39].

Since the development of resistance in prostate cancer has been correlated with bcl-2 overexpression, agents that overcome this mechanism of drug resistance may improve outcome. The taxanes represent one class of agents that has been shown to induce changes in bcl-2. Haldar and colleagues demonstrated that paclitaxel could induce apoptosis in bcl-2-expressing PC-3 prostate cancer cells through phosphorylation of bcl-2 which may be a secondary effect from taxane induced cell cycle arrest [37]. However, initial clinical trials with single-agent paclitaxel administered every 3 weeks in patients with HRPC have not been effective. Roth and colleagues administered paclitaxel, 135-170 mg/m² (depending on prior radiation), to 23 patients with bidimensionally measurable HRPC every 21 days as a 24-hour continuous infusion until disease progression or a maximum of six cycles [40]. A majority of those enrolled had multiple metastatic sites (18 of 23 with bone metastases). Utilizing standard criteria for measurable disease, there was one PR (4.3% of 23 patients) and 11 patients (47.8%) with stable disease. The patient with a PR also experienced a decrease in PSA of greater than 50% (from 66.6 ng/ml to 13.7 ng/ml).

Although the response rate with administration of paclitaxel at an every-3-week dosing was low, more promising results came from studies with a weekly schedule. For example, Trivedi et al. treated 17 patients with progressive metastatic HRPC with 150 mg/m² paclitaxel each week for 6 of 8 weeks [41]. Four of eight patients with measurable disease had a PR (one in liver, two in lymph nodes) or complete response (CR) (one in lung).

### Table 1. Single-agent taxane studies in HRPC

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n of subjects</th>
<th>PSA response*</th>
<th>Measurable disease response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel 135-170 mg/m² over 24 hr, q 3 wk</td>
<td>23</td>
<td>1/23 (4%)</td>
<td>1/23 (4%)</td>
<td>[40]</td>
</tr>
<tr>
<td>Paclitaxel 150 mg/m² over 1 hr, q wk in 6 wk of 8-wk cycle</td>
<td>18</td>
<td>7/18 (39%)</td>
<td>4/8 (50%)</td>
<td>[41]</td>
</tr>
<tr>
<td>Docetaxel 75 mg/m² q 21 d</td>
<td>21</td>
<td>7/21 (33%)</td>
<td>NA</td>
<td>[51]</td>
</tr>
<tr>
<td>Docetaxel 75 mg/m² q 21 d</td>
<td>35</td>
<td>16/35 (46%)</td>
<td>7/25 (28%)</td>
<td>[52]</td>
</tr>
<tr>
<td>Docetaxel 36 mg/m² q wk × 6 of 8-wk cycle</td>
<td>23</td>
<td>9/19 (47%)</td>
<td>NA</td>
<td>[53]</td>
</tr>
</tbody>
</table>

*PSA response defined as a 50% or greater decrease in PSA from baseline measurement.

### Table 2. Estramustine and taxane regimens studied in HRPC

<table>
<thead>
<tr>
<th>Therapy</th>
<th>n of subjects</th>
<th>PSA response*</th>
<th>Measurable disease response</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estramustine 600 mg/m²/d po, paclitaxel 120 mg/m² continuous infusion over 96 hr q 21 d</td>
<td>34</td>
<td>7/32 (53%)</td>
<td>4/9 (45%)</td>
<td>[44]</td>
</tr>
<tr>
<td>Estramustine 280 mg bid d 0-2, paclitaxel 90 mg/m² q wk × 6 q 8 wk</td>
<td>63</td>
<td>36/62 (58.1%)</td>
<td>6/22 (27.3%)</td>
<td>[45]</td>
</tr>
<tr>
<td>Estramustine 280 mg bid d 1-3, 8-10, 15-17 and paclitaxel 100 mg/m² d 2, 9, 16 versus paclitaxel 100 mg/m² d 2, 9, 16</td>
<td>166</td>
<td>48%</td>
<td>NA</td>
<td>[23]</td>
</tr>
<tr>
<td>Estramustine 280 mg po tid d 1-5, docetaxel 40-80 mg/m² d 2 q 21 d</td>
<td>34</td>
<td>20/34 (63%)</td>
<td>5/18 (28%)</td>
<td>[54]</td>
</tr>
</tbody>
</table>

*PSA response defined as a 50% or greater decrease in PSA from baseline measurement.
Seven of 17 patients (41%) had a PSA decline of >50%. In this study, myelosuppression was minimal, and the major toxicity was neuropathy with six patients developing grade 3 toxicity.

Based on clinical studies demonstrating activity of weekly paclitaxel and preclinical studies demonstrating enhanced activity of paclitaxel with estramustine [42], further studies investigated this combination in HRPC. Results of phase I trials suggested that paclitaxel plus oral estramustine was active against HRPC [43], leading to phase II evaluations of paclitaxel plus estramustine, estramustine/carboplatin, or estramustine/etoposide.

Hudes et al. studied the combination of estramustine, 15 mg/kg/d, and paclitaxel, administered as a 96-hour continuous infusion, in 24 patients with HRPC [43]. This schedule of administration was chosen since prolonged exposure of the agents was used in the preclinical studies. PSA decreases of 50% or greater for 6 consecutive weeks were seen in 65.2% of patients. The major toxicities noted were edema and mild to moderate nausea, attributed to estramustine, and leukopenia, attributed to paclitaxel. The subsequent phase II trial by Hudes et al. evaluated 34 patients with advanced HRPC [44]. Patients received paclitaxel at a dose of 120 mg/m² by 96-hour infusion every 3 weeks plus oral estramustine, 600 mg/m²/d. Overall, 17 patients (53.1%) had a >50% decline in PSA, with a median duration of response of 22.5 weeks and a median survival time of 69 weeks. Grade ≥2 nausea, fluid retention, and fatigue occurred in 33%, 33%, and 24% of patients, respectively. Further study of paclitaxel/estramustine using a weekly paclitaxel infusion was suggested to potentially improve the activity, ease of administration, and tolerability of this outpatient regimen [45].

Hudes et al. studied the combination of 90 mg/m² paclitaxel, administered in 6 weeks out of an 8-week cycle, and estramustine at a dose of 280 mg/m² orally twice a day, administered the day before, day of, and day after each administration of paclitaxel. Therapy was well tolerated, with the most common toxicities greater than grade 1 being nausea (14%) and fatigue (39%). The incidence of thromboembolism was 8%, with grade 3 or 4 occurring in 6% of patients. Thirty-six of 63 patients (58%) had a decline of >50% in PSA and 4/22 patients with measurable disease had a CR or PR. With a median follow-up of 15 months, the mean time to progression was 6 months and the median survival was 17.2 months [45].

Based on encouraging results with estramustine-based combination regimens and utilizing the synergistic and platelet-sparing effects of paclitaxel plus carboplatin, investigators at Memorial Sloan-Kettering Cancer Center (MSKCC) initiated a phase I/II trial evaluating weekly paclitaxel plus estramustine and carboplatin (TEC) in patients with advanced prostate cancer [46]. Based on the tolerability and activity observed in the phase I dose-escalation trial, weekly paclitaxel, 100 mg/m², was combined with oral estramustine, 10 mg/kg three times daily days 1 to 5, plus carboplatin at an area under the plasma concentration-time curve (AUC) of 6 every 4 weeks. In the multi-institutional phase II portion of this trial, response criteria included PSA levels, measurable disease, and bone scan results. Overall, 56 patients with androgen-independent disease were enrolled (eight in phase I, 48 in phase II). A majority (75%) of patients had received two or more prior hormonal therapies, and 25% had received prior chemotherapy. The median PSA level was 100 ng/ml. Of 54 patients evaluable by PSA measurements, 34 (67%) achieved a >50% reduction and 25 (48%) achieved a >80% reduction in PSA levels, and the median duration of PSA decline was 21 weeks (range: 8 to 85+ weeks), with a median survival of 20 months. Among patients treated for more than 4 weeks, declines in PSA levels of >50% and >80% occurred in 72% and 53% of patients, respectively, and patients achieving a >80% reduction sustained this response for a median of 27+ weeks. A CR was observed in two patients (6%), and a PR was observed in 13 patients (39%), for an overall response rate of 46%. Stable disease was reported in nine patients. Grade 3/4 pulmonary embolism/deep vein thrombosis, which occurred in 25% of patients, was most likely related to estramustine administration. Grade 3/4 leukopenia also was reported in 22% of patients [46].

Additional combinations with paclitaxel have been investigated [47, 48]. When used in combination with estramustine, 280 mg three times a day, and etoposide, 50 mg/m²/d, both for 14 days, paclitaxel, 135 mg/m² over 1 hour on day 2, was administered every 21 days in 37 patients [47]. In patients with measurable disease, 45% (10 of 22 patients) had a PR, and a PSA decrease of 50% or greater was seen in 65% of patients. Despite these encouraging response rates, the median time to progression was 2.5 months, and the median survival was 13 months. Finally, in a preliminary report, the combination of mitoxantrone, 12 mg/m², and paclitaxel, 175 mg/m², over 3 hours, was evaluated in 17 patients [48]. A PSA reduction of 50% or more occurred in 64% of patients in association with pain relief and improved quality of life.

Despite improved response rates with these combination regimens, the duration of response is short, secondary to the development of chemotherapy resistance, warranting novel approaches. Based on data suggesting that 13-cis-retinoic acid (isotretinoin, Accutane™) plus interferon alfa decreases the expression of the resistance protein, Bcl-2, in prostate cancer and the hypothesis that this decreased Bcl-2 expression will enhance the cytotoxic activity of paclitaxel, we conducted a series of trials with these agents. A phase I trial of 13-cis-retinoic acid, interferon alfa, and an every-21-day schedule...
of paclitaxel in patients with advanced prostate cancer and other malignancies was well tolerated, with no hematologic dose-limiting toxicity observed [49]. Of the 10 patients with advanced prostate cancer who received at least three cycles of therapy, one had a greater than 50% decrease in PSA level that was maintained for >1 month, and two patients had stable disease (defined by PSA at 3 months). In addition, results showed that 13-cis-retinoic acid/interferon alfa modulates Bcl-2 expression in peripheral blood mononuclear cells, allowing development of a potentially useful biologic marker of Bcl-2 modulation in patients with solid tumors. A second phase I trial with weekly paclitaxel, 13-cis-retinoic acid, and interferon demonstrated that the weekly regimen was well tolerated [50]. Based on these data, the Eastern Cooperative Oncology Group (ECOG) recently activated a randomized phase II trial comparing weekly paclitaxel plus 13-cis-retinoic acid and interferon alfa with the combination of estramustine, mitoxantrone, and vinorelbine. The results of these trials should contribute to an assessment of the value of weekly paclitaxel plus 13-cis-retinoic acid and interferon alfa in the treatment of prostate cancer.

A number of trials have been completed with single-agent docetaxel in HRPC utilizing both the every-3-week and the weekly schedule [51-53]. When docetaxel, 75 mg/m², was administered on the every-3-week schedule, there was a PSA response of 50% or more in 38% and 46% of patients, respectively in the two studies [51, 52]. Toxicity was predominantly myelosuppression and fatigue when administered in the every-3-week schedule. In the study by Friedland et al., 86% of patients treated developed grade 3 or 4 neutropenia [51]. When administered on a weekly basis at a dose of 36 mg/m², for 6 out of 8 weeks in 25 patients, 48% had a palliative response, 46% had a PSA response of 50% or more, 25% had a PSA response of 75% or more, and two of five patients with measurable disease had a PR [53]. The weekly administration of docetaxel was associated with a decreased incidence of myelosuppression. In the study by Beer et al., only 25% of patients developed grade 3 or 4 hematologic toxicities [53]. These single-agent trials support the investigation of docetaxel as part of a combination regimen for HRPC.

In a phase I trial by Petrylak et al., escalating doses of docetaxel were used in combination with estramustine, 280 mg orally three times a day on days 1 to 5, in 34 patients with HRPC [54]. This trial was also associated with a palliative response, with 53% of patients on narcotic therapy reporting a decrease in narcotic use. Additionally, 63% of patients experienced a 50% or greater decrease in PSA. Interestingly, 7 of 13 responders were patients who had failed prior treatment with estramustine. Five of 18 patients (28%) with bidimensionally measurable disease had objective regressions of tumor. In another phase I trial, estramustine, 14 mg/kg daily, was combined with escalating doses of docetaxel every 21 days [55]. The dose-limiting toxicity was fatigue, and estramustine was associated with nausea and diarrhea that required an interruption of therapy. A reduction in PSA of 50% or more was observed in 14 of 17 patients (82%), and in patients with measurable disease, one of six patients had a PR. In a phase II trial involving 35 patients, a 74% PSA response was reported with a duration of response of 18 weeks [56]. Seven of the patients had measurable disease and four of these (57%) had a PR. Dose reductions were necessary in 31% of patients secondary to toxicity. Two patients had a cerebrovascular accident and two had deep vein thrombosis; there were two treatment-related deaths related to neutropenia sepsis. Coumadin and aspirin were administered to the last 15 patients. The median survival time was 22 months. These studies support the combination of estramustine and docetaxel in the treatment of HRPC.

The results of the phase II study of docetaxel, 70 mg/m² every 3 weeks, oral estramustine, 280 mg three times a day for 5 days beginning 1 day before docetaxel, and hydrocortisone, 40 mg daily, in men with HRPC were recently reported [57]. Forty-six patients were evaluable, 24 with measurable disease. In patients with measurable disease, there was a 50% response rate (three CR, nine PR). A 50% or greater decrease in PSA was seen in 68% of patients, and 57% of patients had a 75% or greater decrease in PSA. The combined measurable disease and PSA response in all assessable patients was 54%. The most common toxicity was neutropenia, and the incidence of thromboembolic events was 9%. The median survival was 20 months with a median time to progression of 8 months. This is the first multicenter trial demonstrating the combination as effective and tolerable.

Therapy with weekly docetaxel in combination with estramustine has also been evaluated in HRPC [58]. Weekly docetaxel, 35 mg/m², with oral estramustine, administered on days 1 to 3 each week, was evaluated in 18 patients. A PSA response of 50% or greater occurred in 72% (13/18) of patients, and a response of 75% or greater occurred in 50% (9/18) of patients. Therapy was well tolerated, with a median overall survival of 16 months.

Additional combination therapy with docetaxel continues to be investigated [59, 60]. The combination of docetaxel, estramustine, and trastuzumab was associated with a PSA response in 69% of patients, and when weekly docetaxel was combined with thalidomide, a PSA response in 53% was reported. Ongoing trials will help determine the optimal combination therapy and schedule for docetaxel.

Although these data support a role for chemotherapy combinations, such as estramustine and docetaxel or paclitaxel, in the treatment of HRPC, further studies are needed
to determine the effect on overall survival. An ongoing Southwest Oncology Group (SWOG) trial is treating patients with HRPC with either mitoxantrone and prednisone or docetaxel combined with estramustine. The main objective of this trial is to determine a 30% improvement of overall survival in the taxane arm.

**MECHANISMS OF RESISTANCE IN HRPC**

In order to define potential therapeutic agents for the treatment of HRPC, an understanding of the mechanisms of resistance associated with HRPC is necessary. Several genetic alterations seen in advanced carcinoma of the prostate may lead to the development of hormone-refractory disease. Overexpression of oncogenes or mutations in tumor suppressor genes have been implicated in the development of hormone-refractory disease. For example, the bcl-2 oncogene is highly expressed in hormone-refractory disease [61]. Bcl-2 belongs to a family of proteins that controls the apoptotic process. Its overexpression prevents apoptosis and inhibits the death of prostate cancer cells [61, 62]. Apoptosis, or programmed cell death, is characterized by active participation of the cell in its own demise by providing the enzymes and energy for the process [63]. Bcl-2 protects cells from apoptosis by dimerization with Bax. Bax is a member of the family of proteins related to Bcl-2, called Bcl-2-related-proteins. Homodimerization of Bax promotes cell death, with the ratio of Bax to Bcl-2 paramount in determining cell survival or death.

McDonnell et al. demonstrated that hormonal resistance in prostate tumors after initial treatment with androgen ablation is associated with the overexpression of bcl-2 [61]. Patients with hormone-sensitive disease have low levels of expression, whereas patients with hormone-resistant disease have high levels of bcl-2 expression [64]. The overexpression of bcl-2 also has been correlated with resistance to chemotherapy [39]. Additional oncogenes have been implicated in the progression of prostate cancer. Although rare, point mutations in the ras gene family leading to abnormal growth and transformation of tissue have been found to correlate with the progression of prostate cancer [65]. In one study, two out of 29 (7%) prostate tumors and prostate tumor cell lines tested contained point mutations at codons 12 and 61 of the ras gene family [66].

Mutations in p53, a tumor suppressor gene, are also associated with the progression of prostate cancer to hormone-refractory disease [67, 68]. Increased levels of mutant p53 have been found in HRPC cells. Heidenberg and colleagues evaluated 47 prostate tumor specimens by immunohistochemistry for the presence of mutant p53 [68]. They demonstrated a statistically significant elevation of mutant p53 in 16 of 17 (94%) HRPC specimens compared with 6 of 27 (22%) untreated primary tumors. The increase in protein expression was associated with p53 mutations in exons 5 to 8 in 82% of specimens tested. These data suggest that p53 mutations may contribute to the development of hormone-refractory disease.

The Rb (retinoblastoma) gene, a tumor suppressor gene, and the myc oncogene, along with other genetic changes, play an as yet undefined role in the progression of prostate cancer to hormone-refractory disease [69, 70].

**NOVEL APPROACHES TO TREATMENT**

Although advances in palliation of symptoms and improvements in quality of life have been obtained with chemotherapy, innovative approaches are needed to improve survival rates. Novel approaches to the treatment of prostate cancer include the use of more targeted therapies to pathways critical to tumor cells. As mentioned above, the abrogation of bcl-2 mechanisms of resistance by the taxanes is one strategy. Additional strategies to reverse or prevent the development of bcl-2-mediated resistance include the use of chemotherapy in androgen-dependent prostate cancer, the administration of chemotherapy-modulating agents, growth factor pathway inhibitors, and antisense agents directed against bcl-2.

An additional method for decreasing the impact of bcl-2 overexpression and the associated resistance is the use of antisense oligonucleotides. These agents bind to target sequences of bcl-2 mRNA, thus inhibiting genetic expression and message translation. bcl-2 antisense compounds have been shown to decrease bcl-2 expression with and without corresponding increases in apoptosis and cell death. In prostate cancer cell lines, bcl-2 antisense compounds have been shown to inhibit cell growth in addition to increasing the sensitivity of prostate cancer cell lines to certain chemotherapeutic agents [71, 72]. Therefore, the administration of bcl-2 antisense compounds along with chemotherapy may improve the response rates over either approach alone. G3139, a phosphorothioate oligodeoxynucleotide antisense compound, targets the first six codons of the bcl-2 reading frame [73]. This sequence has been shown to have antitumor effects in human lymphoid cell lines [74]. More recently, two trials involving the use of this bcl-2 antisense oligonucleotide in combination with chemotherapy have been reported [75, 76]. G3139 was evaluated alone and in combination with weekly paclitaxel, 100 mg/m², in patients with HRPC (n = 23) and in patients with other advanced malignancies (n = 12) [75]. Therapy was well tolerated, and a decrease in bcl-2 expression in peripheral blood mononuclear cells was detected in some patients. A second dose-escalation trial involved the combination of G3139 with mitoxantrone [76]. No dose-limiting toxicities were reported, and one patient had a greater than
50% reduction in PSA with symptomatic improvement in bone pain. This agent appears to be well tolerated alone and in combination with chemotherapy, and studies continue to define the role of bcl-2 antisense oligonucleotides.

Differentiating Agents

One of the hallmark signs of tumors is the unregulated growth of cells leading to an increased number of undifferentiated, immature cells. Thus, agents that are capable of inducing the differentiation of malignant cells into cells capable of normal physiologic function may decrease the tumor burden. One agent being evaluated for its differentiating effects in prostate cancer is vitamin D. The hormonal metabolite of vitamin D3, 1-α, 25-dihydroxyvitamin D₃ (1,25-D₃), has been shown to induce the differentiation and proliferation of various human prostate cell lines and may be useful as a chemopreventative agent [77]. The antiproliferative effects of 1,25-D₃ are partly mediated by its binding to vitamin D receptors (VDR) found in prostate cancer cells. This is further supported by experimental evidence showing that the lack of functional VDRs can lead to the inhibition of the antiproliferative effect of 1,25-D₃ [78, 79].

Bisphosphonates

Bisphosphonates are potent inhibitors of osteoclastic bone resorption. They are an important new treatment modality of metastatic bone disease since they have decreased the number and rate of skeletal complications in multiple myeloma and advanced breast cancer, delayed the onset of progressive disease in bone after palliative chemotherapy for breast cancer and myeloma, and relieved metastatic bone pain caused by various solid tumors with consequent improvements in the quality of life [80, 81]. Laboratory data have revealed that bisphosphonates prevent and interrupt osteolysis induced by human prostate cancer cells, and that tumor growth can be inhibited by the use of bisphosphonates [82]. Saad et al. recently reported a phase III randomized trial treating patients with HRPC with zoledronic acid (Zometa®) or placebo. Zoledronic acid was shown to significantly delay the time to the first skeletal-related event [83]. Smith et al. studied pamidronate in patients with earlier disease starting androgen ablation therapy with or without pamidronate [84]. Patients treated with pamidronate had improved bone density. Ongoing trials will further determine the efficacy of bisphosphonates in the setting of HRPC and in earlier disease.

Other Novel Agents

Development of cytotoxic agents that are selectively activated by prostate tumor cells through PSA is a novel method for the treatment of HRPC. As a serine protease, PSA is responsible for liquefaction of semen through cleavage of proteins at specific amino acid sequences [85]. We recently studied a novel agent that is dependent on enzymatically functional PSA for activity [86]. The agent, L-377202, is a conjugate consisting of the peptide covalently linked to the aminoglycoside portion of doxorubicin, which is cleaved by PSA to produce the biologically active forms leucine-doxorubicin and doxorubicin. In a phase I trial of 19 HRPC patients, escalating doses of L-377202 were assessed for toxicity, response, and pharmacokinetics. Therapy was well tolerated, and at the maximum-tolerated dose, two of five patients had a greater than 75% reduction in PSA, and one patient had a stabilized PSA. Further studies of this or similar agents are warranted in advanced and earlier disease.

Epidermal growth factor (EGF) is another growth mediator that regulates prostate cancer growth. EGF acts via the EGF-receptor (EGF-R) to activate intracellular tyrosine kinase activity. Selective inhibitors of EGF-R tyrosine kinase activity are being studied in patients with PSA progression following androgen ablation therapy.

Immunotherapy approaches for the treatment of HRPC have also been investigated. Expanding the number or potency of T cells specific for tumor-associated antigen (TAAs) may lead to T cells infiltrating the tumor and destruction of the tumor cells. Presentation by the TAAs utilizing dendritic cells as the antigen-presenting cell has been investigated clinically [87]. A phase III randomized, double-blind, placebo-controlled trial presented at the 2002 Annual Meeting of the American Society of Clinical Oncology investigated APC8015 versus placebo in 127 men with HRPC with the primary end points of time to progression and cancer-related pain. Patients were randomized in a 2:1 ratio to APC8015 or placebo given i.v. in weeks 0, 2, and 4. Although additional events are necessary to evaluate the primary efficacy variable, fever and chills were the most common adverse events indicating that APC8015 is safe and well tolerated. Efficacy data from this trial are anxiously awaited.

Conclusions

Patients with HRPC now have multiple options of therapy beyond initial efforts at secondary hormonal agents. Combination chemotherapy regimens involving agents that affect microtubule integrity appear to have activity with tolerable adverse effects. In particular, combination regimens including taxanes represent a promising treatment option for patients, with response rates over 50%. Despite these high response rates, the median duration of response is limited to approximately 6 months. Additional survival benefits
reported in phase II trials have not yet been confirmed in phase III randomized trials. Additionally, novel agents, used either alone or in combination with these regimens, in patients with HRPC will be critical in efforts to improve duration of response and overall survival.

ACKNOWLEDGMENTS


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