Management of Advanced Prostate Cancer After First-Line Chemotherapy

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ABSTRACT

Hormone refractory prostate cancer (HRPC) causes substantial morbidity and mortality. There are increasing options for both first- and second-line therapy in the palliative treatment of patients with HRPC. Medications to control symptoms should first be optimized in patients with late-stage disease, and radiotherapy applied to dominant painful bone lesions. Docetaxel, mitoxantrone, satraplatin, and ixabepilone are active chemotherapeutic agents in the first- and/or second-line setting for patients with HRPC, and this may be true also of older drugs such as oral cyclophosphamide and vinorelbine. Radioisotopes such as strontium and samarium are useful for treatment of more generalized bone pain. Third-line hormonal maneuvers including glucocorticoids, ketoconazole, and estrogens can lead to further palliation in some patients, and there are provocative data that chemotherapy might restore hormonal sensitivity in a subset of patients.

INTRODUCTION

Patients with metastatic prostate cancer who have disease progression after primary androgen- ablation therapy (usually by orchectomy or a gonadotropin-releasing hormone agonist), followed by addition and subsequent withdrawal of an antiandrogen, are generally considered to be refractory to hormonal therapy. Hormone-refractory prostate cancer (HRPC) causes considerable morbidity, with pain and fatigue as major symptoms, and median survival is generally in the range of 10 to 20 months. Chemotherapy can provide palliative benefit in this setting. Mitoxantrone and prednisone is a treatment with minimal acute toxicity that can provide relief of symptoms in about a third of patients. Two recent large phase III trials (TAX 327 and SWOG 9916) have demonstrated an improvement in survival, and greater effects to relieve pain, from docetaxel administered with prednisone or estramustine, when compared with mitoxantrone and prednisone, although the treatment has greater toxicity. This article will review potential methods of management for the many patients with HRPC who have progressive disease after first-line chemotherapy.

PRINCIPLES OF TREATMENT

At this stage of disease, patients can expect only a short duration of survival, and many are symptomatic. The goals of treatment are to improve the duration and/or quality of survival. Before considering specific measures directed toward the prostate cancer, it is important to optimize supportive measures to minimize symptoms. Patients with pain due to metastases in bone will generally require regular narcotic medication, titrated to provide maximum relief of pain. Constipation is a common problem in elderly men receiving narcotics and should be treated aggressively. Dominant sites of metastases causing narcotics and should be treated aggressively. Dominant sites of metastases causing pain, or those threatening complications such as fracture or cord compression should be treated with radiotherapy. Fatigue is a major problem and may respond to
medications such as methylphenidate.\textsuperscript{4,5} Bisphosphonates, reviewed elsewhere in this issue, may decrease bone loss due to continued anti-androgen therapy, and may reduce bone events, but have not been shown to have an overall effect on duration or quality of survival.\textsuperscript{6,7}

The development of specific treatments for patients with this stage of disease requires sequential clinical trials, as for other palliative cancer treatments. Initially it is important to demonstrate tolerance, followed by evidence of biologic activity in phase 2 trials. PSA response and time to PSA progression are appropriate outcome measures in such trials, but they do not indicate direct benefit to patients. Phase 3 trials should aim to demonstrate palliative benefit to patients, either through improvement in survival, or in quality of life or symptom control. Given that pain is a common and disabling symptom of the disease, assessment of pain, together with a measure of analgesic intake, is an appropriate and validated method for evaluation of symptom control in clinical trials directed toward patients with metastatic prostate cancer.\textsuperscript{1,2,8,9}

Potential therapies that might be used to treat patients with HRPC after progression after first-line chemotherapy include second-line chemotherapy, radioisotopes, and further hormonal approaches. These are reviewed briefly in the following sections.

**SECOND-LINE CHEMOTHERAPY**

Re-Treatment With Docetaxel

The majority of patients are likely to discontinue first-line treatment with docetaxel because of progressive disease or unacceptable adverse effects. A smaller number of patients might stop the treatment while still responding to the drug, with adverse effects that are manageable. If progression occurs in the latter group after a reasonably long interval, repeat treatment with docetaxel is appropriate.

Mitoxantrone After Docetaxel and Vice-Versa

Most patients will receive docetaxel-based treatment as primary chemotherapy, in view of the survival advantage demonstrated in recent phase 3 trials.\textsuperscript{2,3} However, mitoxantrone and prednisone remains an appropriate initial regimen for many patients, especially those with slowly progressing disease and those who are averse to potential adverse effects of docetaxel. Only a small proportion of patients crossed over from mitoxantrone to docetaxel chemotherapy in the phase III studies, so there is no information as to the effect of order of administration of these drugs on overall survival.

A few relatively small studies have evaluated prostate-specific antigen (PSA) response rate after cross over from docetaxel to mitoxantrone and vice versa, and these are summarized in Table 1.\textsuperscript{10-13} Overall, the PSA response rate to docetaxel after initial treatment with mitoxantrone seems similar to that achieved with first-line treatment, whereas a relatively low proportion of patients respond to mitoxantrone after first receiving docetaxel. The relationship between PSA response and palliation of patients will likely depend on its extent and duration, and on patient-based factors such as performance status. There is little direct information about pain response or other assays of palliative benefit after second-line treatment. Tolerability seems to be somewhat worse than for first-line chemotherapy, with about 45% to 65% of patients requiring a delay, dose reduction, or cessation of chemotherapy in the second-line setting.

**Older Drugs With Activity Against Prostate Cancer**

Other types of chemotherapy that might reasonably be used after initial treatment with docetaxel include those with first-line activity against the disease, that are well-tolerated, and in which the mechanism of action and dose-limiting toxicity are different from those of docetaxel. Oral cyclophosphamide, used alone or with other agents such as vincristine and a glucocorticoid, has shown consistent activity as first-line treatment, with minimal toxicity.\textsuperscript{14,15} Vinorelbine was reported to give comparable palliative benefit to mitoxantrone when evaluated in a randomized trial with hydrocortisone versus hydrocortisone alone,\textsuperscript{16} although neurotoxicity might be dose limiting in patients who have received prior docetaxel. Etoposide may also be a useful and well-tolerated drug, although it...
has usually been evaluated in combination with estramustine, a drug that adds considerable toxicity.

Current interest is focused on evaluating newer drugs for second-line treatment, such as satraplatin and ixabepilone, but it is not clear that these new agents are more active or less toxic than some of the older drugs.

**Satraplatin**

Satraplatin (JM-216) is a third-generation platinum analog that has structural similarities to cisplatin, and is orally bioavailable. Like other platinum analogs, satraplatin acts by binding to DNA-forming intra- and interstrand cross links, resulting in cell-cycle arrest in the G2 phase and eventual apoptosis. While satraplatin-DNA adducts are efficiently repaired by the nucleotide excision repair pathway, they are not recognized by the DNA mismatch repair system that acts on cisplatin and carboplatin adducts. Phase I trials of satraplatin have established a recommended dose and schedule in chemotherapy-naive patients of 80 to 120 mg/m²/day for 5 consecutive days, repeated every 4 to 5 weeks. The dose-limiting toxicity is myelosuppression, which is dose-dependent and reversible.

Five phase II or phase III trials of satraplatin in prostate cancer were initiated or are ongoing, but three of the studies were terminated before achieving their planned accrual. In a phase II trial of satraplatin in 39 chemotherapy-naive patients with progressive HRPC, 7 (32%) of 22 assessable patients had a PSA response. Toxicty was mainly hematologic, with grade 3/4 nonhematologic toxicities including transient increases in aspartate transaminase and bilirubin. These results led the European Organisation for Cancer Research (EORTC) to initiate a phase III trial of satraplatin plus prednisone (10 mg twice daily) versus prednisone alone for first-line treatment of patients with HRPC. Although the target accrual was 380 patients, only 50 patients were enrolled when the study was terminated early by the sponsoring company. This trial demonstrated that the combination of satraplatin and prednisone resulted in a significant increase in PSA response compared with prednisone alone (33% vs 9%; P = .046), and improvement in progression-free survival (5.2 months vs 2.5 months; P = .023). A phase III trial, known as SPARC (Satraplatin and Prednisone Against Refractory Cancer), is a multinational, double-blind, placebo-controlled trial, initiated in 2003, that compares satraplatin plus prednisone to prednisone alone for second-line treatment of patients with HRPC. Patients are randomly assigned in a 2:1 ratio in favor of satraplatin and the primary end point is time to progression (TTP); the trial is powered to detect a 30% increase in TTP with ≥ 85% power. Secondary trial end points are overall survival and time to pain progression. Target accrual for this trial, which involves 137 sites worldwide, is 912 patients.

**Ixabepilone**

Ixabepilone (BMS-247550) is an epothilone, a new class of antineoplastic drugs that induce microtubule bundling, formation of multipolar spindles, and mitotic arrest. Like paclitaxel and docetaxel, epothilones function by stabilizing the polymerized microtubules, but they are structurally distinct. Ixabepilone has potent cytotoxic effects on paclitaxel-sensitive and insensitive cells, and in taxane-resistant tumor cell lines overexpressing P-glycoprotein.

Phase I trials of ixabepilone have established a dose schedule of 40 mg/m² given intravenously every 3 weeks. In a phase II single-agent trial performed by the Southwest Oncology Group (SWOG), 16 (39%) of 41 patients with chemotherapy-naive metastatic HRPC had a PSA response, and median progression-free survival was 6 months. The primary adverse effects were hematologic and neurologic, with grade 3 neuropathy reported in 7 patients (17%).

Ixabepilone with or without estramustine was evaluated in a multicenter trial of chemotherapy-naive patients with progressive HRPC. PSA response was achieved in 21 (48%) of 44 patients (95% CI, 33% to 64%) on the ixabepilone arm, and 31 (69%) of 45 patients (95% CI, 55% to 82%) in the ixabepilone + estramustine arm. Time to PSA progression was 4.4 months and 5.2 months, respectively. Neutropenia and neuropathy were the main adverse events, with 9% of patients in the estramustine arm having a grade 3-4 thrombotic event.

An ongoing randomized phase II study is evaluating ixabepilone as second-line treatment in patients who have experienced treatment failure with prior taxane therapy; ixabepilone is compared with mitoxantrone and prednisone. A large international phase III trial is planned to compare ixabepilone with mitoxantrone (each administered with prednisone) in patients with HRPC who have received prior docetaxel.

**RADIOPHARMACEUTICALS**

Most patients with metastatic bone disease have multiple involved sites in the skeleton. External beam radiotherapy is useful in treating dominant sites of pain, but often pain will be relieved in one area, only to reappear rapidly in another. Infusion of bone seeking radiopharmaceutical agents has been shown to relieve bone pain in multiple metastatic sites. Strontium-89 and samarium-159 are incorporated into sclerotic bone metastases, and have no effect against soft-tissue disease. They are β-emitters, and this short-range radiation may kill prostate cancer cells in bone, leading to relief of pain. In two randomized phase III studies, strontium-89 was shown to give better and more durable relief of pain than limited field radiotherapy, although in a recent Dutch study, strontium was not found to be superior to local radiotherapy. In two phase III trials samarium was superior to placebo in providing
pain relief. These agents are well tolerated but they cause hematologic toxicity, especially thrombocytopenia, because of radiation effects on bone marrow. Toxicity may be less for samarium than for strontium, perhaps due to the shorter half-life and shorter range of the emitted energy. Because these agents can lead to prolonged bone marrow depression, and especially thrombocytopenia, it seems reasonable to use these agents in patients who are not appropriate candidates for second-line chemotherapy, or in those where such chemotherapy has proven ineffective in palliating bone pain.

α-emitting agents such as radium-223 are being investigated. The have shown promising preclinical results and a phase I trial has shown low hematologic toxicity.

Further Hormonal Manipulation

An operational definition of HRPC was provided earlier in this article as progression of disease after primary androgen ablation and addition and withdrawal of a peripheral anti-androgen. However, many studies have shown that even after such therapy, there is a low but definite response to further hormonal manipulations. Particularly for patients with slowly progressing disease, these may be appropriate measures after progression of disease after first-line chemotherapy. Hormonal manipulations that may be useful include prednisone or other glucocorticoids (although these are often administered with first-line chemotherapy), ketoconazole, and estrogens such as diethylstilbestrol.

Prednisone and Dexamethasone

Glucocorticoids may lead to PSA responses and/or relief of symptoms in patients with late-stage prostate cancer, and some investigators have suggested that the superior results of regimens with taxanes may be due in part to the dexamethasone that is administered to avoid toxic reactions to these drugs. Corticosteroids depress adrenocorticotrophic hormone secretion leading to suppression of release of adrenal androgens. A randomized EORTC phase III study compared flutamide with prednisone in patients with prostate cancer who were progressing symptomatically after androgen ablative therapy found similar PSA response rates, with prednisone superior in terms of pain control and overall quality of life. However, most patients have received substantial treatment with glucocorticoids concurrent with first-line chemotherapy, so their potential benefit in later stages is probably minimal.

Ketoconazole

Ketoconazole is an inhibitor of steroid synthesis and must be administered with hydrocortisone or prednisone. A phase III study has shown that it may increase the probability of an anti-androgen withdrawal response, although this did not translate into improved survival. When used after prior chemotherapy it is associated with occasional PSA responses, although these responses are usually transient.

Estrogens

Estrogens, such as oral diethylstilbestrol (DES) have been shown to be associated with PSA responses and improved symptoms in several small trials when used after failure of other hormonal measures in the treatment of prostatic cancer. They must be used with caution, because of their ability to stimulate thrombosis and cardiovascular events in susceptible elderly men, although this is not usually a major problem if the dose of DES is at or below 3 mg/day. The active components of various products such as PC-SPES (no longer available), are probably phytoestrogens from plants, and these agents clearly have activity, even in late stages of disease. The drug estramustine, which contains estrogen and alkylating moieties, was found equivalent to estrogen in several studies, and its activity is probably largely due to the estrogen component, whereas the alkylating component adds toxicity.

Re-Induction of Hormonal Sensitivity

The mechanisms leading to the hormone-refractory state are multiple and complex. A model in which clones of hormone-sensitive and hormone-resistant cells are present is overly simplistic, and adaptation to the hormonal environment has been shown. This is one reason that some patients may respond initially to addition of a peripheral anti-androgen and then subsequently to its withdrawal. Primary anti-androgen therapy is usually continued with chemotherapy to suppress any hormone-sensitive cells that may be present, although there are few data from clinical trials to support (or refute) this widespread (and expensive) practice.

There is a provocative report that chemotherapy might lead to restoration of hormonal sensitivity in some patients. In a phase II study where all hormonal manipulations were suspended while patients were treated with chemotherapy using chlorambucil and lomustine, Shamash et al reported re-induction of hormonal sensitivity after chemotherapy. After progressing on chemotherapy, 17 patients who initially were hormone refractory were re-treated with hormonal therapy and 47% demonstrated PSA response. This unexpected finding deserves further investigation.

Conclusion

Hormone-refractory prostate cancer is common, and causes suffering and death of many men. Treatment is palliative and medication to obtain optimal control of symptoms should be prescribed to all patients. Docetaxel is used most often as first-line treatment for HRPC, and older drugs with activity as first line treatment, such as mitoxantrone, vinorelbine, or oral cyclophosphamide...
are options for patients with progression after treatment with docetaxel. New drugs, especially satraplatin and ixabepilone, are promising agents that are being compared with prednisone alone or mitoxantrone plus prednisone for second-line treatment of patients with HRPC. Patients who are candidates for second-line therapy will be those who have a reasonable performance status, and who either have symptoms or are likely to soon develop symptoms from their disease. External radiotherapy and radiopharmaceuticals provide consistent relief for localized and more generalized pain respectfully and are an important component of supportive care. Further hormonal manipulations may decrease PSA and improve symptoms after prior chemotherapy, and formal studies should be undertaken to evaluate changes in hormone sensitivity after treatment with chemotherapy.

Authors’ Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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