Current chemotherapeutic approaches for androgen-independent prostate cancer

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This review describes the current state of chemotherapy for androgen-independent prostate cancer. Landmark clinical trials, including TAX 327, a randomized trial comparing docetaxel and prednisone with mitoxantrone and prednisone, and SWOG 9916, a randomized clinical trial comparing docetaxel and estramustine with mitoxantrone and prednisone, are reviewed. Novel combination therapies, involving taxane administered with compounds such as calcitrol and thalidomide, newer cytotoxic agents, vaccine therapies, and targeted modalities are also detailed. This review mainly focuses on agents with activity in phase II/III clinical trials.

Keywords Androgen-independence, chemotherapy, hormone-refractory, metastatic, prostate cancer, taxanes

Introduction

Adenocarcinoma of the prostate is the most common solid tumor in US males, and is second only to lung cancer as a cause of cancer death. In 2005, prostate cancer accounted for an estimated 33% of cancer cases and 10% of cancer deaths in the US [1]. Therapy directed at presumably localized disease is successful in the majority of cases, whether by operative means or radiation. Despite treatment involving radical prostatectomy, progression rates at five and ten years are estimated to be 22 and 25%, respectively, as measured by prostate-specific antigen (PSA) levels [2]. As with any metastatic malignancy, therapy for non-localized disease requires systemic treatment. Until recently, medical or surgical castration was the only tenable systemic therapy available to men with metastatic prostate cancer. The method of androgen deprivation dates back to 1941, when Huggins & Hodges reported the efficacy of castration and estrogens in the treatment of advanced prostate cancer [3•]. Unfortunately, the efficacy of androgen deprivation is limited by the progression to androgen-independent prostate cancer (AIPC). In men with metastatic prostate cancer, this progression typically occurs within 12 to 18 months, resulting in a median survival of two to three years.

The progression to androgen independence is multifactorial. When prostate cancer is androgen-sensitive, testosterone enters the cell and is enzymatically converted to dihydrotestosterone (DHT), which exerts its influence in the nucleus and activates genes involved in cell growth. As prostate cancer progresses to androgen independence, it develops various 'pathways' allowing for growth in the absence of testosterone. For example, cells may increase the synthesis of androgen receptors, allowing them to flourish with very low levels of testosterone. This is known as the 'hypersensitive pathway'. In the 'promiscuous pathway', the androgen receptor mutates and is activated by a broad range of other circulating steroids. The androgen receptor is inactive unless phosphorylated. In the 'outlaw pathway', the receptor is aberrantly phosphorylated allowing for constitutive receptor activation. In contrast, a 'bypass pathway' allows for cell survival in the absence of androgen receptor activation, allowing cells to avoid apoptosis in an anti-androgen environment [4].

Background to the treatment of AIPC

Reviews by Yagoda & Petrylak [5] and Raghavan *et al* [6] accurately portrayed the available cytotoxic agents as ineffective in treating AIPC. Clinical trials evaluating anthracyclines, alkylating agents, antimetabolites, platinum-based agents and topoisomerase inhibitors were reviewed [5,6]; overall response rates of 8.7% were noted in 26 clinical trials conducted between 1987 and 1991. The broad range of reported response rates and the lack of standardized objective responses confounded the reviewers, who described the chemotherapeutic landscape as 'chaos' [5]. Subsequently, the PSA response was accepted as the standard endpoint when measuring the efficacy of new chemotherapeutic agents. A 1999 consensus conference defined a partial response in a clinical trial as a minimum PSA decline of at least 50% confirmed by a second PSA value of similar levels 4 or more weeks later in the absence of clinical or radiographic evidence of disease progression during this time period [7]. This is what is typically meant by a 'PSA response' and is used as a measure of demonstrable activity in phase II clinical trials.

Clinical treatment with taxanes

Docetaxel (Taxotere) is a semi-synthetic taxane, which disrupts normal mitosis by binding to β-tubulin and preventing microtubule disassembly. This event leads to an arrest in the cell cycle at the G_2M phase and, ultimately, apoptosis. Various pro-apoptotic mechanisms of docetaxel, including inactivation of Bcl-2 by phosphorylation, induction of p53 and overcoming multidrug resistance have also been proposed [4]. Initial phase II clinical trials with docetaxel revealed more encouraging response rates than any previous agent in AIPC and led to two large phase III trials, both of which were reported in 2004.

Docetaxel plus estramustine versus mitoxantrone plus prednisone

The randomized clinical trial, Southwest Oncology Group (SWOG) 9916 trial, compared docetaxel and estramustine (D/E) with mitoxantrone and prednisone (M/P) in the

treatment of advanced refractory prostate cancer [8••]. The M/P arm was included based on previous demonstrations of a palliative benefit, although this was without any observable survival benefit. In a prior study conducted by Tannock *et al*, pain relief and a decline in average analgesic consumption were greater in patients receiving M/P than prednisone alone [9•]. In the SWOG 9916 study, 770 men with progressive AIPC received one of two treatments, each given in 3-week cycles: estramustine (280 mg three times daily) on days 1 to 5, docetaxel (60 mg/m^2) on day 2, and dexamethasone (60 mg) in three divided doses before docetaxel; or mitoxantrone (12 mg/m^2) on day 1 plus prednisone (5 mg twice daily). Median survival rates in the D/E and M/P groups were 17.5 and 15.6 months, respectively ($p = 0.01$). PSA response (50 versus 27%) and the objective response rate in patients with known soft tissue disease (17 versus 11%) were also significantly greater in the D/E arm [8••]. However, the D/E group had a statistically significant higher rate of grade 3 or 4 neutropenic fevers (5 versus 2%), cardiovascular events (15 versus 7%), nausea and vomiting (20 versus 5%), metabolic disturbances (6 versus 1%) and neurologic events (7 versus 2%). There was no observed difference in grade 3 or greater neutropenia between the treatment groups [8••]. Although the median survival benefit was only 2 months, this study set a new standard for the efficacy of chemotherapeutic agents in AIPC.

Docetaxel plus prednisone versus mitoxantrone plus prednisone

TAX 327 was a multi-institutional, prospective, randomized clinical trial comparing docetaxel and prednisone with mitoxantrone and prednisone [10••]. In this trial, 1006 men with AIPC received prednisone (5 mg twice daily) and were randomly assigned to three treatment groups: mitoxantrone (12 mg/m^2) every 3 weeks, docetaxel (75 mg/m^2) every 3 weeks or docetaxel (30 mg/m^2) weekly for 5 of every 6 weeks. Overall survival was the primary endpoint. There was no statistically significant difference in the weekly docetaxel group, but a difference was observed in the 3-week arm compared with mitoxantrone (18.9 versus 16 months; $p = 0.009$). Pain reduction frequency, as a secondary endpoint, was only significantly reduced in the 3-week docetaxel arm when compared with mitoxantrone (35 versus 22%; $p = 0.01$). The median duration of pain reduction was the same across all groups at 3.5 to 5.6 months. The rates of PSA response (45 to 48%; $p < 0.001$) were significantly greater in patients receiving docetaxel compared with mitoxantrone, regardless of the dosing schedule. An improvement in quality-of-life was more likely in patients receiving docetaxel compared with mitoxantrone (22 to 23% versus 13%; $p < 0.01$). The weekly docetaxel schedule was included to determine whether a reduced dose administered weekly would result in fewer adverse events or improved outcomes; however, this effect was not borne out in the data. The adverse event rate in the 3-week docetaxel arm was 26%, compared with 29% when administered weekly. Significantly more adverse events occurred in the docetaxel treatment arms than with mitoxantrone (20%). In summary, an every 3-week regimen of docetaxel (75 mg/m^2) with prednisone (5 mg) twice daily was superior to weekly dosed docetaxel and had a similar side-effect profile to mitoxantrone and prednisone [10••]. The US Food and Drug Administration (FDA) approved this regimen shortly thereafter for the treatment of AIPC.

Role of estramustine in AIPC

Results from the SWOG 9916 and TAX 327 studies defined the role of estramustine in the treatment of AIPC, and altered the treatment paradigm for this cancer type [11•]. In comparable patient populations, a similar efficacy (48 to 50% PSA response) was observed for patients receiving estramustine and docetaxel (SWOG 9916) and prednisone and docetaxel (TAX 327). However, the toxicity profiles in the two clinical trials differed significantly. In the TAX 327 study, none of the patients reported grade 3 nausea and vomiting, compared with a 20% incidence in the SWOG 9916 estramustine arm. Additionally, no patients in the TAX 327 study suffered grade 3 or higher cardiovascular or clotting adverse events, while a 15% incidence was noted in the SWOG 9916 study. Nausea, vomiting and cardiovascular/clotting events are well known complications of estramustine administration because of its high estrogen content [4]. Thus, estramustine, when administered with docetaxel, does not appear to offer increased efficacy over prednisone and docetaxel, and is likely the cause of increased gastrointestinal and cardiovascular toxicities. Therefore, it appears that the administration of estramustine with docetaxel for AIPC is unwarranted, and possibly harmful.

Docetaxel as adjuvant therapy

The benefits of adjuvant chemotherapy observed in breast and colon cancer patients led to this treatment option being evaluated in a phase II clinical trial of docetaxel after prostatectomy. Post-prostatectomy patients ($n = 77$) with a high risk of prostate cancer recurrence received docetaxel (35 mg/m^2) on days 1, 8 and 15 of a 28-day cycle. Docetaxel was well tolerated; however, the oncological outcomes of this study are pending. The TAX 3501 study is a phase III, randomized, controlled trial comparing observation, androgen deprivation therapy (ADT) and ADT/docetaxel in the adjuvant setting. Enrollment for this clinical trial began in late 2005. Those patients who progress in the observation group will be randomized to either ADT or ADT/docetaxel. The results of the TAX 3501 trial, with a projected enrollment of over 2000 patients, should highlight the roles of both hormonal therapy and chemotherapy in the adjuvant setting [12].

Other taxane combination trials

After the encouraging results from investigations of the effect of single-agent docetaxel in the TAX 327 study, interest has turned to several taxane combination therapy protocols. The combination of calcitriol or thalidomide with docetaxel has generated considerable interest. Calcitriol, the most active metabolite of vitamin D, decreases prostate cancer cell proliferation and increases the cytotoxicity of taxanes independent of Bcl-2 [13]. Based on encouraging phase II trials data, the Androgen-Independent Prostate Cancer Study of Calcitriol Enhancing Taxotere (ASCENT) trial was initiated. This randomized, placebo-controlled clinical trial was designed to evaluate the efficacy of high-

dose calcitriol combined with docetaxel. Patients with AIPC (n = 250) were randomized to receive either placebo and docetaxel, or a capsule formulation of calcitriol (DN-101 (Novacea Inc), 45 µg orally once weekly) and docetaxel. Docetaxel was administered according to the 30-mg/m^2 weekly dose schedule described in the TAX 327 study, rather than the every-3-week regime. The primary endpoint of this study was PSA response. Interim results of this study have been reported in abstract form [14]. PSA response within 6 months was 58% for patients receiving calcitriol/docetaxel compared with 49% for those receiving placebo/docetaxel; however, this was not a statistically significant difference ($p = 0.16$). In patients with measurable disease, a trend toward improved objective response rate was noted (28 versus 20%; $p > 0.05$). Serious adverse events were less common in the DN-101 group (24 versus 36%; $p = 0.038$). A full report on the ASCENT trial is pending, particularly details of secondary endpoints and progression-free survival.

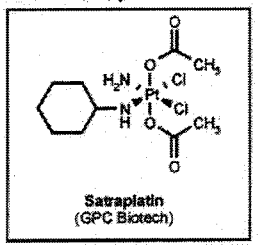
Several trials are currently evaluating docetaxel in combination with agents that interfere with tumor neovascularization. Thalidomide is a potent teratogen with anti-angiogenic properties, as evidenced by the stunted limb growth in exposed fetuses. A randomized, phase II clinical trial of docetaxel plus thalidomide versus single-agent docetaxel has been reported [15]. In this study, 75 patients with AIPC were randomized to receive docetaxel (30 mg/m^2), or thalidomide (200 mg) daily plus docetaxel (30 mg/m^2). The PSA response was 37% in the docetaxel alone arm and 53% in the combination arm, although this did not reach statistical significance ($p = 0.32$). However, the response rates did satisfy criteria for further evaluation. The 18-month survival rate was 42.9 and 68.2% for the docetaxel alone and combination arms, respectively ($p = 0.11$). Although the observed response did not reach statistical significance, improvement was demonstrated in all the standard outcome measures: PSA response, time-to-progression (TTP) and overall survival. Only a small number of patients were included in this study and it was not designed to evaluate overall survival; therefore, larger, randomized clinical trials are necessary to better evaluate the efficacy of this regimen in patients with AIPC.

Future treatment modalities

Cytotoxic agents

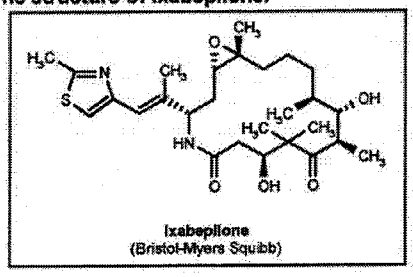
Satraplatin (GPC Biotech AG; Figure 1) is a third-generation oral platinum(IV) complex anticancer agent, with clinically demonstrated antitumor activity [16]. On the basis of promising phase II clinical trials data, the Satraplatin and Prednisone Against Refractory Cancer (SPARC) trial was initiated in 2003, and expanded in 2004 to include several more European sites. SPARC is a multicenter, randomized, double-blind, phase III study designed to evaluate satraplatin as a second-line chemotherapy in patients with metastatic AIPC that have failed previous cytotoxic chemotherapy [17]. Currently there are no approved agents for the second-line treatment of hormone-refractory prostate cancer, and the US FDA has granted accelerated approval status to satraplatin in the SPARC clinical trial, which is currently ongoing.

Figure 1. The structure of satraplatin.



Epothilones are microtubule inhibitors with an action similar to that of taxanes but with the added advantage of activity in taxane-resistant tumors. The epothilone B analog ixabepilone (BMS-247550, Bristol-Myers Squibb; Figure 2) has demonstrated clinical activity in a phase II clinical trial [18]. PSA response was observed in 21 out of the 44 patients receiving ixabepilone, and in 31 out of the 45 patients receiving ixabepilone plus estramustine phosphate [18]. Phase II and III clinical trials are ongoing.

Figure 2. The structure of ixabepilone.



Vaccines

As cancer is increasingly being viewed, at least in part, as a breakdown of immune system surveillance, researchers are seeking ways to increase the effectiveness of the immune system. Thus, tumor vaccine therapy is a promising area of research.

GVAX (Cell Genesys Inc) is a vaccine in which irradiated patient-derived prostate cancer cells are transduced *in vitro* with granulocyte-macrophage colony-stimulating factor. The role of this vaccine is to recruit and stimulate peripheral blood monocytes and macrophages against malignant cells. A phase III clinical trial comparing GVAX with docetaxel plus prednisone is underway. Additional combination studies of docetaxel and GVAX are also being designed [4].

Provenge (APC-8015; Dendreon Corp) has been designed to help the body develop an immune response to prostate cancer cells. Autologous antigen-presenting cells (APCs) are loaded with a fusion protein combining a prostate-specific protein and a molecule specifically targeting an APC surface receptor. Results from a phase II clinical trial are encouraging, with reports of a median time to progression of 118 days. One patient with AIPC had a decrease in PSA from 221 ng/ml to undetectable levels, which remained undetectable for four years [19]. A randomized, phase III trial in patients with asymptomatic, metastatic AIPC is underway, in which 275 patients will be randomized to Provenge or inactivated APCs [20•].

Onyvax-P (Onyvax Ltd) is a cell vaccine composed of three irradiated allogeneic cell lines. Cells from primary and metastatic disease are included in this vaccine, and theoretically, the broad range of antigens will improve its efficacy and help avoid resistance. Based on encouraging phase II clinical trials data in AIPC patients, a phase III trial is to be initiated [4].

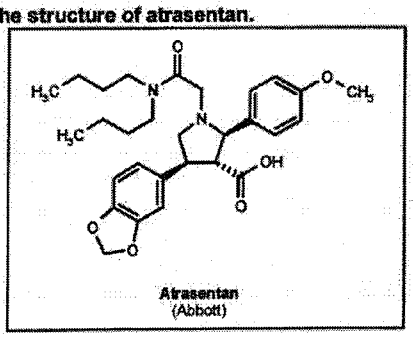
Targeted therapies

Targeted therapy refers to the inhibition of specific signal transduction molecules that are important for cell growth. Vascular endothelial growth factor (VEGF) and endothelin-1 (ET-1) are two targets that are being evaluated in clinical trials.

Bevacizumab (Avastin) is a monoclonal antibody that targets VEGF, binding and inactivating it, thereby neutralizing its primary pro-angiogenesis effects. The effect of bevacizumab in combination with docetaxel and estramustine (CALGB 90006) was initially evaluated in 79 patients with AIPC. Of this patient set, 32 had measurable disease, with nine (53%) of these demonstrating a partial response. Furthermore, a > 50% decline in PSA levels was noted in 65% of 20 evaluable patients [21]. CALBG 90401 is a randomized, phase III clinical trial currently accruing patients with AIPC. The trial will compare the effect of combining bevacizumab with docetaxel plus prednisone with docetaxel plus prednisone on overall survival [22].

ET-1 is a potent vasoconstrictor that plays a role in the mediation of osteoblast growth and function. Blocking the ET-1/ET_A receptor pathway may therefore block the role of osteoblasts, which play a pathological role in bone metastases in AIPC [23]. Atrasentan (Xinlay, Abbott Laboratories; Figure 3) is an orally administered, selective ET_A receptor antagonist, which has demonstrated activity in clinical trials [24,25]. A randomized, phase III clinical trial comparing daily administration of atrasentan (10 mg po) with placebo in 941 patients with AIPC (M00 244), with a primary endpoint of time to progression, is underway [20•]. To investigate the effect of combination therapy in patients with AIPC, a randomized, placebo-controlled, phase III clinical trial comparing atrasentan in combination with docetaxel plus prednisone with docetaxel plus prednisone is planned (SWOG S0421). The trial has been approved but is not yet underway [20•]

Figure 3. The structure of atrasentan.



Conclusion

After decades without significant progress in the treatment of AIPC, new and innovative therapies are being developed in earnest. Encouraging response rates have been obtained from landmark clinical trials evaluating docetaxel in combination with estramustine or prednisone, and results from these studies have influenced future treatment regimens for AIPC. Promising chemotherapeutic agents, emerging tumor vaccines, targeted therapy, and novel combination regimes are all under active investigation. These studies will hopefully play a role both in current investigational therapy and as a bridge to future modalities.

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