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Chemotherapy in Androgen-Independent Prostate Cancer (AIPC): What's next after taxane progression?

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Summary

Prostate cancer is the most common non-cutaneous cancer in the United States. Although most are diagnosed at earlier stages of disease, a significant number of patients will eventually progress to metastatic androgen-independent prostate cancer (AIPC) and will receive chemotherapy. The benefit of chemotherapy in overall survival has been demonstrated in studies utilizing docetaxel. However, duration of response is short and therapeutic options are limited after taxane failure. There is a need for effective chemotherapeutic agents in the second-line setting, either alone or in combination. Some of these regimens may also ultimately translate to the front-line chemotherapeutic setting as an alternative or perhaps in combination with a taxane.

Keywords

Chemotherapy; prostate cancer; mitoxantrone; docetaxel; epothilones; satraplatin

I. Introduction

Prostate cancer is the leading non-cutaneous cause of malignancy in American men and it is estimated that 218,890 men will be diagnosed with prostate cancer and 27,050 would die from the disease in 2007 (Jemal et al, 2007). Since the advent of prostate specific antigen (PSA) screening, the majority of patients are diagnosed with localized disease and about 5% are diagnosed after the cancer has metastasized (Ries et al, 2006). Primary therapy for localized prostate cancer typically includes radical prostatectomy, external beam radiation therapy, brachytherapy, or active surveillance, but 30-40% of patients will eventually develop recurrent or metastatic disease (Dillioglugil et al, 1997). Androgen deprivation therapy achieved through medical or surgical castration has been the cornerstone of treatment for patients with metastatic disease (Huggins and Hodges, 1941; Figg et al, 1997; Sharifi et al, 2005) . However, almost all patients progress to androgen-independent phenotype after a medianof 18 – 36 months (Figg et al, 1997; Sharifi et al, 2005). Once metastatic androgen-independent prostate cancer (AIPC) develops, responses to alternative hormonal therapy or chemotherapy are not durable, with a median overall survival of approximately 18 months with docetaxel based chemotherapy. Several second-line hormonal treatment have been utilized in this setting, but responses had been short and non-durable (Goktas and Crawford, 1999; Klotz, 2000). In this population of patients where hormone-refractory state emerges, palliation with chemotherapy has been utilized.

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The use of chemotherapy especially during earlier analysis of single chemotherapeutic agents have been disappointing, with response rates of 8.7% and median survival of 10–12 months (Yagoda and Petrylak, 1993), until the recent introduction of taxanes (Gulley and Dahut, 2004). Among the first systemic agents studied was mitoxantrone, which was approved based on symptomatic improvement of quality of life (Tannock et al, 1996). Subsequently, treatment with docetaxel and prednisone was FDA-approved for the treatment of AIPC because of the demonstration of improved overall survival (OS) of 18.9 months versus mitoxantrone and prednisone with OS of 16.5 months (Tannock et al, 2004). The use of the docetaxel and estramustine showed similar survival advantage to docetaxel and prednisone, but with more toxicity (Gulley and Dahut, 2004; Petrylak et al, 2004). Despite the first clear advance in the treatment of metastatic prostate cancer, the median time to PSA progression with taxane therapy remains limited to about 6-8 months, with many patients progressing thereafter (Savarese et al, 2001). Therefore, there is a clear need for new therapeutic strategies for patients with advanced AIPC who have failed previous taxane chemotherapy.

This review will focus on several potential second-line chemotherapeutic agents that have shown promising results in the treatment of metastatic prostate cancer.

II. Chemotherapy in the second-line setting

Chemotherapy has recently been considered active in the treatment of prostate cancer. Although the use of taxanes (specifically docetaxel), has been shown to confer a survival benefit in AIPC, progressive disease after use of taxanes remain a vexing problem and present a hindrance to long-term survival in these patients. Several chemotherapeutic agents have been investigated in the 2nd line setting. With reported success of some of these agents, investigation with upfront use in first line treatment in AIPC will be in the foreseeable future. The following section will discuss the most commonly used or most promising chemotherapeutic regimens for AIPC in the second-line setting.

A. Mitoxantrone

The overall survival benefit demonstrated with the use of docetaxel in metastatic prostate cancer has become accepted standard of care in this population of patients. However, there are still a proportion of patients who may not tolerate the adverse effects and the use of the anthracenedione mitoxantrone, and prednisone may be considered appropriate initial regimen for these patients (Berthold et al, 2005). Although cross-over studies conducted using mitoxantrone and docetaxel are few in number, there is a suggestion that number of PSA declines of at least 50% achieved with mitoxantrone administered after first-line docetaxel may be inferior to first-line mitoxantrone (Michels et al, 2005). The percentage of patients who experienced a 50% or greater decline in PSA levels after therapy has been shown to occur from 6% (for 2nd line mitoxantrone) to 12% for first-line mitoxantrone use (Michels et al, 2005; Oh et al, 2005). However, the median total duration of PFS for both chemotherapy courses together, from the start of the first to progression after the second type of chemotherapy, was no different whether mitoxantrone or a taxane was used first (39.9 weeks versus 38.7 weeks, respectively, $P = 0.67$). The median OS also did not differ significantly between the two groups: 15.2 months for the mitoxantrone-first group versus 17.1 months for the taxane-first group. Therefore, mitoxantrone may still offer some benefit when used as 2nd line treatment after primary taxane therapy. Recently, Lin et al reported a trial using ixabepilone(discussed more extensively at later sections of this review) or mitoxantrone after primary taxane failure (Lin et al, 2006). PSA decline rates of 50 % were as high as 20% with mitoxantrone as 2nd line after taxane therapy, and 30% as 3rd line (after taxane and ixabepilone failures), with equivalent overall survival of 13 months or 12.5 months, using mitoxantrone or ixabepilone as 2nd line regimens after taxane failure, respectively. Furthermore, taxanes retain activity whether used before or after mitoxantrone in a retrospective analysis, with equivalent progression-free

survival and overall survival in either sequence (Oh et al, 2006). Thus, although the use of mitoxantrone and prednisone after docetaxel has some activity, response is modest, and other agents with better potency are needed after taxane-based chemotherapy.

B. Satraplatin and other platinum agents

Satraplatin, formerly known as JM-216, is a third-generation orally available platinum analogue that has similar but improved properties compared to other platinum agents like cisplatin, carboplatin, and oxaliplatin (Kelland, 2000). Similar to other platinum agents, satraplatin exerts its biological activity via reactive biotransformation products that bind to DNA , forming DNA adducts that cause the inhibition of DNA replication, cell cycle arrest, and induction of apoptosis, and repaired by the nucleotide excision repair (NER) mechanism, but not recognized by the DNA mismatch repair system that acts upon cisplatin and carboplatin adducts (Kelland, 2000). Unlike the older platinum generations, satraplatin is more lipophilic and more chemically stable, offering improved oral bioavailability which enables satraplatin to be administered orally. Preclinical studies with satraplatin demonstrated cytotoxic and anti-tumor activities comparable to cisplatin or carboplatin, as well as improved toxicity profiles with nephrotoxicity (as compared with cisplatin) and neurotoxicity (as compared with oxaliplatin), with myelosuppression as the major dose-limiting toxicity (Sternberg, 2005). Platinum agents, in general, has been studied in AIPC, but single-agent cisplatin response has been in the range of 0% - 19% (Rossof et al, 1979; Merrin, 1980; Qazi and Khandekar, 1983; Moore et al, 1986). However, single-agent carboplatin has shown some activity with 50% disease stabilization (Canobbio et al, 1993), and carboplatin in combination with paclitaxel and estramustine (TEC) has shown some antitumor activity with response rates up to 45% in patients with measurable disease (Kelly et al, 2001; Solit et al, 2003), or in previous taxane failures (Tay et al, 2004). Recently, carboplatin has been used for second-line treatment in patients who have failed prior docetaxel therapy (Oh et al, 2006). Updated results from a phase II trial that evaluated 34 patients using a combination regimen of docetaxel 60 mg/m^2 and carboplatin area under the curve of 4 (AUC 4 mg/ml/min) every 21 days showed PSA declines of ≥50% in 6 of 34 patients (18%, 95% C.I. 7-35%), with a median duration of PSA response of 7.4 months (95% C.I. 2.8-7.4 months) (Oh et al, 2007). There was also an observed partial response in 3 out of 21 patients who had measurable disease at baseline (14%; 95% C.I. 3-36%). These findings suggest that there may be synergism between carboplatin and docetaxel that warrants further investigation of its use in patients who have failed taxanes. These promising results using older generation platinum agents led to studies using the third generation satraplatin.

Preclinical studies in human AIPC cell lines exhibited sensitivity to satraplatin. Satraplatin entered clinical trials in 1992. Phase I trials of single-agent satraplatin have explored different dosing schedules with the recommended dosing schedule in chemonaïve patients of 80 – 120 mg/m^2 for 5 consecutive days every 4 – 5 weeks (McKeage et al, 1994; McKeage et al, 1995; McKeage et al, 1997; Beale et al, 1998; Sessa et al, 1998; Kurata et al, 2000). Based on promising preclinical and clinical efficacy in prostate cancer, several phase II and III trials have been conducted in AIPC (see Table 1). Satraplatin for first-line treatment of AIPC has been conducted in a Phase II trial CA142-013 and two Phase III trials (CA142-029 and EORTC 30972), while satraplatin for second-line treatment of AIPC has been studied in one Phase II trial CA142-026 and a Phase III trial (SPARC). However, much of these studies, except the phase II CA142-013 and recently concluded SPARC trial, were prematurely terminated as part of a commercial decision of the original pharmaceutical sponsor. Analyses of the data are discussed herein.

CA142-013 was a phase II trial conducted at multiple US sites which accrued 39 patients with AIPC. The starting dose was 120 mg/m^2/day for 5 days, but most patients had the dose reduced

to 100 mg/m^2/day for 5 days because of excessive toxicity (Latif et al, 2005). Patients received a total of 155 courses (median 2, range 1-16) of satraplatin. Dose delays (77% of courses) and dose reductions (31% of courses) were common and were mainly due to myelosupression. Response was assessed in 32 patients, 10 (26%) had partial response (PSA decline of at least 50 % without disease progression during or before response period), 14 (36%) had stable disease while PSA progression was seen in 8 (21%) patients. Of 20 (54%) patients with measurable disease two patients had a documented partial response. The median survival for the whole cohort is 16.7 months (95% CI, 9.3 – 19.2 months) and the median PSA response duration was 3.8 months with a median progression-free survival of 7.7 months in 32 assessable patients.

The first phase III trial using satraplatin and prednisone for first-line treatment of AIPC was led by the European Organization for Research and Treatment of Cancer (EORTC) trial 30972 (Sternberg et al, 2005). Although the target accrual was 380 patients, only 50 patients were enrolled when the study was terminated early by the sponsoring company. Patients with symptomatic AIPC were randomized to treatment with satraplatin (100 mg/m^2/day for 5 days every 5 weeks) plus prednisone (10 mg bid daily) (N = 27) or prednisone alone (N=23). All patients have been followed until progression or death. Forty-two patients have died, most due to prostate cancer. A > 50% decrease in PSA was observed in 2/23 (8.7%) on the prednisone alone arm versus 9/27 (33.3%) in the satraplatin + prednisone arm (P=0.046). Toxicity was minimal in both arms; one patient on each arm died due to stomach perforation, most likely related to prednisone. Compliance to treatment was excellent. The median progression-free survival (PFS) was twice as long in the satraplatin + prednisone arm versus the prednisone alone arm (5.2 versus 2.6 months, p=0.023). Median overall survival (OS) also favored the satraplatin arm, 14.9 versus 11.9 months. This difference was not statistically significant, probably due to the small patient numbers. The second trial (CA142-029) was a randomized, double blind, placebo-controlled study initiated in December 1998. Fourteen patients with symptomatic AIPC were enrolled and randomized to treatment with either 100 mg/m^2/day satraplatin for 5 days plus BID administration of 10 mg prednisone for 5 days (N = 7), or placebo plus BID administration of 10 mg prednisone alone for 5 days (N = 7) every 5 weeks. The primary end-point was pain response and at the time of study termination, only 14 patients were enrolled, and therefore, no formal analysis was conducted.

CA142-026 was the first trial using satraplatin and prednisone for second-line treatment of AIPC, using a regimen of 80 – 100mg/m^2/day for 5 days, every 3 weeks. Again, the study was terminated with only 10 subjects enrolled.

SPARC (SatraPlatin Against Refractory Cancers) is a Phase III pivotal trial that opened in 2003. It is a multicenter, double-blind, placebo-controlled, randomized Phase III trial assessing satraplatin plus prednisone versus placebo plus prednisone as 2nd line chemotherapy treatment of AIPC. Satraplatin 80 mg/m^2 or placebo was administered daily on days 1-5 of a 35-day cycle, and prednisone 5 mg was given twice daily on days 1-35 (Petrylak et al, 2007). A total of 950 patients were accrued at more than 200 clinical sites in fifteen countries on four continents. Results from this study showed a 40% reduction in the risk of progression, p<0.00001, Hazard Ratio of 0.6 (95% Confidence Interval: 0.5-0.7). The improvement seen in progression-free survival by patients treated with satraplatin increased over time. Progression-free survival at the median (50th percentile) demonstrated a 13% improvement in patients who received satraplatin plus prednisone (11 weeks) compared to patients who received prednisone plus placebo (9.7 weeks). At 6 months, 30% of patients in the satraplatin arm had not progressed, compared to 17% of patients in the control arm. At 12 months, 16% of patients who received satraplatin had not progressed, compared to 7% of patients in the control arm. Pain response was 24.2% for satraplatin and prednisone versus 13.8% for

prednisone and placebo ($p<0.005$) and PSA response was 25.4% for the combination versus 12.4% for prednisone ($p<0.01$).

In summary, satraplatin with prednisone is emerging as an active treatment regimen for AIPC patients in the second-line setting, especially for those patients who have progressed on taxane-based regimens. Final results of the SPARC trial are being awaited to determine whether satraplatin and prednisone would have an impact in overall survival. For the first line setting, current available studies on satraplatin have insufficient statistical power to conclude equivalence with standard therapy. Therefore, additional studies are needed to confirm the promising results seen thus far with the use of satraplatin and prednisone in the upfront treatment of metastatic AIPC.

C. Epothilones

The class of antineoplastic agents called epothilones function in a manner similar to taxanes in microtubule stabilization. Microtubules are essential for normal mitosis and cell division. Polymerization of heterodimeric α/β tubulin subunits, with multiple isoforms of both α and β tubulin present in proliferating human cells, is regulated by several microtubule-associated proteins (Jordan et al, 1993). Differences in the individual binding result in differences in tubulin function between epothilones and taxanes (Bode et al, 2002). Preclinical studies suggest that tumor cells resistant to taxanes will retain sensitivity to epothilones and hence provide a role for these class of compounds in the setting of clinical progression after taxane therapy (Bhandari and Hussain, 2005). Of the four known drugs in the epothilone class forms A-D, Aza-epothilone B (BMS-247550; Ixabepilone) and epothilone B (EPO906; patupilone) have been most widely studied for AIPC.

Ixabepilone has been used predominantly in chemotherapy-naïve metastatic patients. (See Table 2). Initial phase I study in solid tumors showed promising anti-tumor activities (Goodin et al, 2004), which led to several phase II studies that was used in AIPC. Single agent phase II trial was conducted by South-West Oncology Group (SWOG, 0111) using ixabepilone 40 mg/m^2 intravenously (IV) over 3 hours every 3 weeks (Hussain et al, 2004). The primary objective of this study was PSA response and patients were given upfront first-line chemotherapy with ixabepilone. Of the 41 patients enrolled, 16 patients (39%) had a ≥ 50% PSA decline, and 14 of the responding patients (34%) had a confirmed PSA decrease. The median progression-free survival (PFS) was 6 months. These results were published in 2005 with 42 eligible patients, 14/42 (33%; 95% CI, 20% to 50%) PSA responses, with 72% of patients achieving ≥ 80% declines in PSA. The PFS was 6 months (95% CI, 4 to 8 months), and the median survival is 18 months (95% CI, 13 to 24 months) (Hussain et al, 2005). Adverse effects from ixabepilone were mainly hematological and neurological with 17% occurrence of grade 3 or 4 neutropenia, while 12% of grade 3 sensory neuropathy occurred.

Ixabepilone in combination with estramustine (EMP), a nornitrogen mustard linked to estradiol via a carbamate bond, was also studied in another phase II trial (Smaletz et al, 2003). Thirteen patients were treated at 2 dose levels of 35 mg/m^2 and 40 mg/m^2 in combination with EMP 280 mg three times daily for 5 days. The phase II dose of ixabepilone combined with EMP was determined to be 35 mg/m^2 every 3 weeks, and a decline in PSA of ≥ 50% was found in 11 of 12 patients (92%). A subsequent study enrolling a total of 92 patients with 45 patients treated with ixabepilone and EMP versus 47 patients treated with ixabepilone alone was done (Kelly et al, 2004). Objective response was seen in 8 of 25 patients (32%) in the ixabepilone alone arm and 11 of 23 patients (48%) in the combination arm, but days to PSA progression was similar in both arms. Despite low-dose warfarin prophylaxis, the combination arm had a 9% incidence of grade 3 or 4 thrombotic event.

Since preclinical studies have shown no cross-resistance between epothilones and taxanes, the second-line use of epothilones after taxanes may hold some promise. Although most of the studies that have been reported for ixabepilone have been for front-line treatment of AIPC, the activity of second-line ixabepilone after initial taxane treatment has been described in a 2-arm, non-comparative randomized phase II study (Lin et al, 2006). Forty-one evaluable patients were assigned to receive either: Mitoxantrone 14 mg/m^2 IV every 3 weeks with 5 mg twice daily of prednisone (MP) or Ixabepilone 35 mg/m^2 IV every 3 weeks. The study's primary endpoint was to detect a ≥ 50% PSA decline by Consensus Criteria in at least 25% of 2nd-line patients for each arm. The median follow-up was 5.0 months at the time of data presentation with a median number of 3 cycles administered to each 2nd-line arm. Median survival from protocol entry was equivalent, with 13.0 months for the ixabepilone arm and 12.5 months with MP. Confirmed 2nd-line post-therapy response of ≥50% PSA declines were observed in 17% of ixabepilone patients (95% CI = 7-32) and 20% of MP patients (95% CI = 9-35). Partial responses in patients with measurable disease were observed in only 1 out of 18 patients on 2nd-line ixabepilone (6%; 95% CI = 0.1-27.3) and in 1 out of 15 patients on 2nd-line MP (7%; 95% CI = 0.2-31.9). The median duration on 2nd-line treatment was similar in both ixabepilone and MP arms, at 2.2 months and 2.3 months, respectively. Crossover to 3rd-line treatment seemed to occur more with MP, in 68% of MP patients versus 39% of ixabepilone patients. Again, the confirmed 3rd-line post-treatment ≥50% PSA declines were similar in both arms, occurring in 3 out of 24 ixabepilone treated patients and in 4 out of 13 MP patients. The most common grade 3/4 toxicity associated with 2nd-line treatment was neutropenia with occurrence of 41% for ixabepilone patients and 54% of MP patients. Conversely, there is some activity with second-line taxane therapy in patients who were previously treated with ixabepilone with a median time to PSA progression of 4.6 months (Rosenberg et al, 2005). Patupilone (EPO906; Epothilone B), a more potent microtubule stabilizer than paclitaxel formulated in polyethylene glycol-300 (Wartmann et al, 2000), has been studied in previous taxane-failure patients. In a phase II study of 3 out of 4 weekly 2.5 mg/m^2 patupilone in AIPC patients, 7 of 28 patients (25%) had a response of 50% PSA decline (Hussain et al, 2004). Three of these 7 patients had received previous taxane-based chemotherapy, although the median duration of the PSA response was short, at 2.2 months.

D. Other agents

Vinorelbine is a semi-synthetic vinca alkaloid that has shown some activity in AIPC. The vinca alkaloids, similar to taxanes and epothilones, work by perturbing the dynamic equilibrium of microtubule polymerization and depolymerization (Horwitz, 1992). Single-agent studies showed a ≥50% decrease in PSA levels sustained for 3–4 weeks in 13% to 17% of evaluable patients (Fields-Jones et al, 1999; Morant et al, 2002). Vinorelbine and hydrocortisone has been used for palliative benefit in a phase III study compared to hydrocortisone alone (Abratt et al, 2004), although this study excluded patients who have had prior chemotherapy. This study included 414 patients, a regimen using vinorelbine given 30 mg/m^2 on days 1 and 8 every 3 weeks and hydrocortisone 40 mg/day versus hydrocortisone alone was used. The PSA response rate (≥50% decline of PSA sustained for at least 6 weeks) was 30.1% (95% CI 24% to 36%) in the combination arm and was 19.2% (95% CI 14% to 25%) in the hydrocortisone alone arm. The 6-month progression-free survival (PFS) rates were 33.2% versus 22.8%, and the median durations of PFS were 3.7 versus 2.8 months. The combination regimen was relatively well tolerated with the majority of patients receiving a median relative dose intensity of 90%.

Another vinca alkaloid, vincristine, has shown anti-tumor activity in conjunction with cyclophosphamide and dexamethesone (CVD regimen) in AIPC (Daliani et al, 2003). The patients received oral cyclophosphamide, 250 mg daily on Days 1-14; intravenous vincristine, 1 mg daily on Days 1, 8, and 15; and oral dexamethasone, 0.75 mg twice daily on Days 1-14.

Cycles were repeated every 28 days. Fifteen of 52 patients (29%; 95% CI 18-42%) had a >50% decrease in serum PSA level, the median overall PFS duration was 10.11 weeks (95% CI 8.91-14.87), and median OS duration was 10.6 months (95% CI 7.24-14.1). Toxicity, which was mainly hematologic, was also acceptable in this study.

Capecitabine has also been investigated in AIPC. In a small study of 25 patients, response was observed in 25% of patients, but because of toxicity (3 deaths in the study), further investigation in phase III trials was not pursued (Morant et al, 2004). This trial utilized capecitabine at 1250 mg/m^2 BID on days 1-14, every 3 weeks. However, a recent phase II study using a combination of 3 out of 4 weekly docetaxel (35 mg/m^2/week) and capecitabine (625 mg/m^2 twice daily on days 5 – 18) in 46 patients was shown to be well tolerated and showed a 68.2% response defined as PSA reduction of ≥50% (Ferrero et al, 2006). The median overall survival was 17.7 months (95% CI, 15.8 months to not reached).

III. Future Directions

There is an urgent need for newer agents or varying combinations of chemotherapeutic drugs that will improve upon the responses seen with docetaxel and prednisone. However, most of these studies are conducted as first-line regimens for the treatment of AIPC. Previous studies using varying combinations of docetaxel with agents using different mechanisms of action show promise in synergistic combinations (Dahut et al, 2004; Beer et al, 2007). Synergism with other agents including anti-angiogenic drugs like thalidomide and bevacizumab is quickly emerging as one of the most promising therapies. In a phase II trial of bevacizumab, thalidomide, docetaxel, and prednisone (Ning et al, 2007), treatment consisted of docetaxel 75 mg/m^2 plus bevacizumab 15 mg/kg on day 1, every 21 days as a cycle, plus thalidomide 200 mg and prednisone 10 mg daily. Enoxaparin was used for thrombosis prevention and pegfilgrastim initiated after detection of grade ≥3 neutropenia. Twenty-three of 33 patients (70%) had >80% PSA declines and objective response rates (ORR) of 64%, and was well tolerated with significant toxicities involving the following: febrile neutropenia (4/33 patients), syncope (3/33 patients), colon perforation or fistula (2/33 patients), grade 3 bleeding (2/33 patients), thrombosis (2/33 patients). This trial is the first study to combine antiangiogenic agents of different mechanisms with docetaxel in metastatic AIPC. Most of the accrued patients have unfavorable characteristics as evidenced by a high Gleason score (median Gleason score of 8) and a rapid PSA doubling time (median of 1.6 months). This trial is currently ongoing at the NCI and may pave the way for a future CALGB trial to determine the benefits of combined anti-angiogenic therapy with standard chemotherapeutic agents. Other agents in combination with docetaxel have shown promising activity, including calcitriol (Beer et al, 2007), estramustine and bevacizumab (Picus et al, 2003), lenalidomide (Moss et al, 2007), and several of these combinations are currently being investigated in cooperative trials.

Apart from strategies combining multi-agent chemotherapy, understanding of pharmacogenomics will also help determine which patients would ultimately benefit from chemotherapy agents. For instance, patients with DNA repair gene polymorphisms have been shown to exhibit platinum sensitivity in a variety of cancers (Kang et al, 2006; Olaussen et al, 2006). Presence of variant gene polymorphisms may help predict response to platinum agents in prostate cancer and forms the basis of a planned clinical trial at NCI using satraplatin in patients with different nucleotide excision repair (NER) gene polymorphisms.

IV. Conclusions

Chemotherapy currently has a well defined role in the treatment of prostate cancer. Although improvements in OS have been demonstrated using taxanes, responses are short with current standard therapy, and improvements in clinical endpoints by using combination chemotherapy,

along with the use of synergistic cytostatic agents such as angiogenic inhibitors (i.e., bevacizumab, thalidomide), can be obtained. Second-line chemotherapeutic agents for prostate cancer patients who have progressed after taxanes remain very limited. Perhaps a better understanding of the mechanisms of drug resistance, discovery of new agents, and targeting of new pathways in the emergence of AIPC, would ultimately lend better survival with the use of standard, and evolving combination therapies.

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Abbreviations

AIPC
androgen-independent prostate cancer

NCI
National Cancer Institute

OS
overall survival

PFS
progression-free survival

PSA
prostate-specific antigen

Table 1

Satraplatin studies in androgen-independent prostate cancer

Trial	Phase	Number of patients	Regimen	Results
CA142-013 (Latif et al, 2005)	II	39	S 120 mg/m^2/day × 5 d q 4 wks	PR:26%; SD:36%; OS:16.7 mos (95% CI, 9.3 – 19.2 mos)
CA142-029	III	14	S 100 mg/m^2/day x 5 d q 5 wks + P 10 mg BID (n=7 pts) x 5 d q 5 wks vs P 10 mg BID (n=7) x 5 d q 5 wks	No formal analysis; terminated prematurely
EORTC 30972 (Sternberg et al, 2005)	III	50	S 100 mg/m^2/day x 5 d q 5 wks + P 10 mg BID (n=27 pts) vs. P 10 mg BID (n=23)	PSA response: 33.3% (S+P) vs. 8.7% (P); PFS: 5.2 vs. 2.6 mos, p=0.023; OS:, 14.9 versus 11.9 months (NS)
CA142-026	II	10	S 80 - 100 mg/m^2/day x 5 d q 3 wks + P 10 mg BID	No formal analysis; terminated prematurely
SPARC (Petrylak et al, 2007)	III	950	S 80 mg/m^2/day × 5 d q 5 wks + P 5 mg BID vs. P 5 mg BID	40% RR; PFS: 11.7 (S+P) vs. 9 wks (P); at 12 mos, 16% (S+P) and 7% (P) had not progressed

Legends: SPARC: SatraPlatin Against Refractory Cancers; PFS: Progression-free survival; OS: overall survival; RR: risk reduction; SD: stable disease; CI: confidence interval; S: Satraplatin; P: Prednisone;mos: months; wks: weeks; d:days; PR: Partial response; NS: Not significant

Table 2

Selected Ixabepilone studies in prostate cancer

Investigator	Phase of study	Number of patients	Regimen	Results
Smaletz et. al.(2003)	II	13	Ixabepilone at 2 dose levels: 35 mg/m^2 and 40 mg/m^2 and oral EMP (280 mg TID × 5 days) every 3 weeks	11/12 (92%) with PSA decline of ≥ 50%; Objective response in soft tissue (57%) and bone metastasis (40%)
Hussain et. al.(2005)	II	42	Ixabepilone at 40 mg/m^2 every 3 weeks	33% PSA response; PFS of 6 mos (95% CI, 4 - 8 mos), OS of 18 mos (95% CI, 13 - 24 mos)
Kelly et. al.(2004)	II	92	Arm 1: 45 pts on ixabepilone 35 mg/m^2 and EMP 280 mg TID × 5 days q 3 wks vs. Arm 2: 47 pts treated with ixabepilone 35 mg/m^2	≥ 50% PSA decline: 31/45 (69%) pts in combination arm vs. 21/44 (48%) pts in ixabepilone alone; days to progression: 141 in combination arm vs. 145 in ixabepilone arm

Legends: EMP: Estramustine phosphate; pts: patients; mos: months; TID: Three times a day; PFS: progression-free survival; OS: Overall survival;