Satraplatin in the treatment of hormone-refractory metastatic prostate cancer

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Abstract: Satraplatin is an orally bioavailable platinum chemotherapeutic agent under development for several cancer types, including hormone-refractory prostate cancer (HRPC). Satraplatin is being developed for the treatment of men with chemorefractory HRPC for several reasons: 1) relative ease of administration, 2) potential lack of cross-resistance with other platinum agents, 3) clinical benefits seen in early studies of HRPC, and 4) an unmet need in this patient population after docetaxel failure. As men who have progressed after docetaxel and prednisone have an expected median survival of approximately 12 months, there is great opportunity for improved palliation in this disease. Satraplatin may provide a palliative benefit for these men in terms of progression-free survival according to the most recent analyses of the phase III SPARC trial comparing satraplatin and prednisone to prednisone alone in the second-line setting for HRPC, and is currently under USFDA review for this indication. Whether satraplatin and prednisone offer an advantage over docetaxel retreatment or other cytotoxic agents in this setting is an unanswered question and worthy of study. Investigation of predictors of platinum sensitivity and the use of satraplatin in patients with neuroendocrine subsets of metastatic prostate cancer may be warranted given the advances in biomarker and genomic technology and the known sensitivity of small cell cancers to platinum agents. Further study of satraplatin alone or in combination with docetaxel or other molecular and chemotherapeutic agents seems warranted to improve on current outcomes.

Keywords: hormone-refractory prostate cancer, satraplatin, metastatic prostate cancer, SPARC trial, progression-free survival

Background

The regimen of docetaxel and prednisone is the preferred systemic treatment in patients with progressive metastatic hormone-refractory prostate cancer (HRPC), based on improved palliation of disease symptoms, overall survival, and disease response rates as compared to mitoxantrone and prednisone, the previous standard of care (Tannock et al 2004). Currently, however, there are no approved agents for second-line therapy in HRPC patients after docetaxel failure. The goals of therapy in this setting are palliation and quality of life improvement, with strict attention to pain control, treatment of fatigue and depression, prevention of spinal cord compression and pathologic fractures, and relief of bladder outlet obstruction. These measures may be accomplished through multidisciplinary pain management, anti-depressants and psychosocial support, radiotherapy to painful or high risk bony metastatic sites, the use of bisphosphonates, and surgical therapy to relieve urethral obstruction (Saad et al 2002).

Current options for these advanced metastatic HRPC patients, who form a relatively common subgroup with a 12 month median survival, include clinical trials of novel agents, docetaxel retreatment, other cytotoxic agents, additional hormonal manipulations, and best supportive care (Berthold et al 2006). The regimen of mitoxantrone and prednisone is currently approved for the palliative care of metastatic HRPC patients

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but has minimal activity in the second-line setting (Lin et al 2006). Estramustine is also US FDA approved for HRPC, but is not well studied in the second line setting. Additional cytotoxic agents with modest first or second line palliative benefit include vinorelbine, paclitaxel, etoposide, cyclophosphamide, capecitabine, cisplatin, and carboplatin, and gemcitabine, alone or in combination regimens (Armstrong et al 2007; Berthold et al 2006). However, these agents have not been studied in adequately controlled or powered trials in this setting, and use is limited by toxicity, particularly neurotoxicity for vinorelbine and paclitaxel in patients who have progressed on docetaxel. Thus, these agents are of unclear benefit in the second-line setting and second-line therapy remains an unfilled need in the management of HRPC.

Satraplatin [bis-(acetato)-ammine dichloro (cyclohexylamine) platinum IV, also known as JM-216, GPC Biotech AG and Pharmion; Munich, Germany and Waltham, Massachusetts] is a novel orally formulated platinum analog that is currently under study in HRPC among other malignancies (Sternberg 2005). As platinums have typically not demonstrated a clinically significant tumor response rate in men with HRPC, satraplatin's novelty may reside in its putative lack of cross-resistance with other platinums compounds (Moore et al 1986; McKeage et al 1997; Fokkema et al 1999). While an oral formulation is attractive, efficacy remains the ideal endpoint over convenience in this palliative setting. Its lack of cross-resistance to date remains theoretical and based on cell culture studies demonstrating activity in cisplatin-resistant models of various tumor types, with the potential ability to create DNA adducts that are more resistant to DNA nucleotide excision repair enzymes (Sternberg 2005; Fokkema et al 2002).

Rationale for use in HRPC

The most compelling argument for an oral non cross-resistant platinum analog in HRPC is the potential ability to improve the palliative outcomes in this poor-risk group, in terms of pain, quality-of-life, and duration of progression-free and overall survival. The median survival of patients who have progressed despite first-line docetaxel is approximately 12 months, and as many of these patients have progressive symptoms of disease, palliative therapies are vitally needed (Lin et al 2006). Biologically, some prostate cancers are known to acquire neuroendocrine features, and indeed chromogranin A levels may correlate independently with an adverse prognosis in HRPC (Taplin et al 2005). As small cell tumors and poorly differentiated neuroendocrine tumors may respond to platinum-based therapies, it is rational to explore

platinum-based therapy in this setting. Indeed, satraplatin had clinical activity and was well tolerated in a trial of patients with small cell lung cancer (Fokkema et al 1999). However, is unclear what the prevalence of neuroendocrine differentiation is in the second-line HRPC setting or if platinum-based therapy confers a greater benefit than other cytotoxics in this subset of patients. Given the paucity of controlled data in the second-line setting in HRPC, an oral agent that meets criteria for improved palliation would be a welcome addition to the chemotherapeutic armamentarium at a clinician's disposal.

Phase I trials

To date, the dose-limiting toxicity of satraplatin, like other platinum analogs, is myelosuppression (McKeage et al 1997; Sternberg 2005). Satraplatin has been studied using several oral schedules, including a daily for 5 days regimen every 4–5 weeks at 80–120 mg/m^2 and a single dose every 3 weeks (McKeage et al 1997). Currently, the daily $\times$ 5 regimen has emerged as the preferred regimen and for phase III clinical trials. Other toxicities (grade 3–4) have included gastrointestinal side effects in 7%–10% (predominantly nausea and vomiting), hyperglycemia (7.4%), and increases in alkaline phosphatase (11%) which may not necessarily be attributable to satraplatin (Latif et al 2005; Sternberg 2005; Sternberg et al 2005; Vouillamoz-Lopez et al 2005). Vomiting (grade $\geq$1) has been noted in 50%–60% of the cycles in phase I trials at the maximal tolerated dose (McKeage et al 1997). To date, there have not been major reports of nephrotoxicity, ototoxicity, or peripheral neuropathy in over 1500 patients studied to date, and therapy has generally been administered as an outpatient. However, there have been some concerns about the degree of myelosuppression and overall toxicity profile of satraplatin at the 120 mg/m^2 daily $\times$ 5 schedule based on a phase II study in HRPC patients, which led to the selection of a lower dose in the second-line population (Latif et al 2005).

Satraplatin pharmacokinetics are linear, with peak concentrations occurring at a median of 2 hours, but exhibit a high degree of inter-patient variability based on creatinine clearance (Vouillamoz-Lopez 2003). Approximately 10% of satraplatin is excreted unchanged in the urine, and renal excretion seems to be the predominant mode of clearance. Satraplatin has not been studied in patients with impaired renal clearance, and thus its use in these patients should be with caution due to potential increased toxicity. Fortunately, the pharmacokinetics of patients who vomited during the first five days of administration was not statistically different than those patients who did not (Vouillamoz-Lopez 2003).

Satraplatin is highly protein bound and little appears as free drug in the plasma. Figure 1 shows the structure of satraplatin as compared to the other commonly used platinums in the clinic, notably cisplatin, carboplatin, and oxaliplatin; a full structure-function discussion of these compounds can be found elsewhere (Wong and Giandomenico 1999).

Prostate-specific trials

In 2005, Sternberg et al published the results of an aborted phase III EORTC study of satraplatin and prednisone compared to prednisone alone in the first-line setting in HRPC (Sternberg et al 2005). Fifty subjects out of an intended 380 were analyzed before the study was terminated by the sponsoring company (Bristol-Myers-Squibb) due to a variety of reasons. The dose of satraplatin was 100 mg/m^2 day 1–5, repeated every 5 weeks along with prednisone 10 mg twice daily, with up to 8 cycles administered with prophylactic anti-emetics. Despite the small numbers, a greater proportion of satraplatin-treated subjects experienced prostrate-specific antigen (PSA) declines over 50% (33.3% vs 8.7%), and progression-free survival favored satraplatin (5.2 vs 2.7 months, HR 0.50 and 95% CI 0.28–0.92, see Figure 2). Additionally, overall survival favored satraplatin by 3 months (14.9 vs 11.9 months, p = 0.58) but did not meet statistical significance
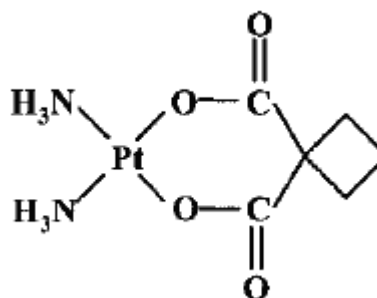
A. Satraplatin
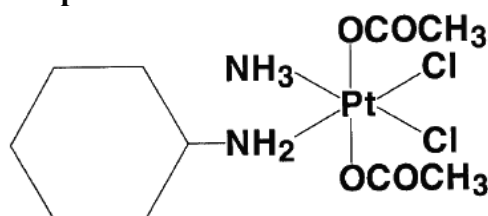
B. Cisplatin
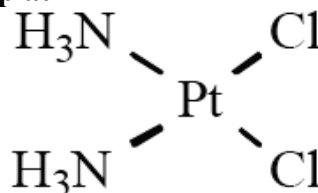
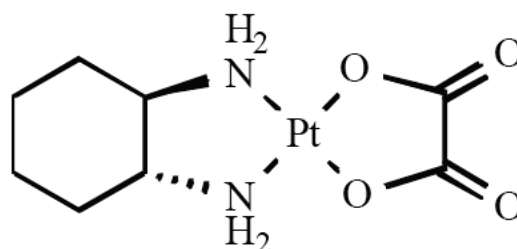**C. Carboplatin**

D. Oxaliplatin

Figure 1 Structures of satraplatin, cisplatin, carboplatin, and oxaliplatin. Satraplatin is a prodrug in which the acetato-based sidechains are released by reduction in the intestines and bioavailability is much higher than older platinum agents. Satraplatin is the only class IV platinum analog shown while the others are class II based on the oxidation state of the platinum. Reviewed extensively by Wong and Giandomenico (1999).
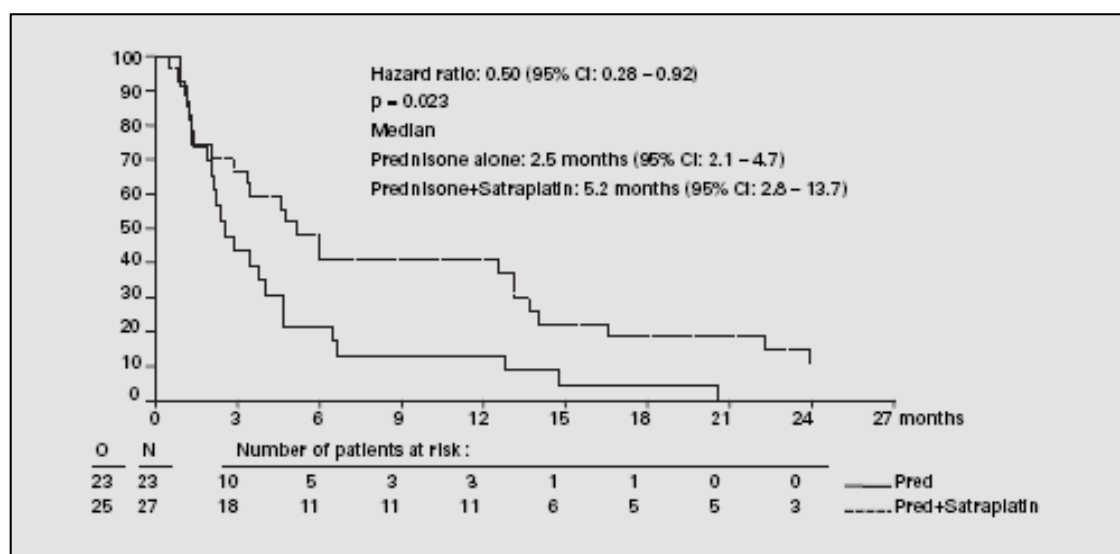
Figure 2 Progression-free survival in phase III trial of satraplatin and prednisone vs. prednisone alone in HRPC, terminated early after 50 patients. Reproduced with permission from Sternberg CN, Whelan P, Hetherington P, et al. 2005. Phase III trial of satraplatin, an oral platinum plus prednisone vs. prednisone alone in patients with hormone-refractory prostate cancer. *Oncology*, 68:2–9. Copyright © 2005 S. Karger AG.

(Sternberg et al 2005). Based on these results, satraplatin was revived by GPC Biotech and its development continued.

Another trial of satraplatin in patients with HRPC was performed as a phase II study (Latif et al 2005). This was a multicenter study involving 39 patients in the first-line setting, using 120 mg/m^2 on a daily × 5 schedule. Toxicity led to the discontinuation of treatment in 13% of patients, treatment delay in 77% of the courses, and dose reduction in 31% of the courses. Despite this toxicity and clear need for a lower initial dose, a PSA decline >50% was observed in 26% (95% CI 10%–50%), and measurable disease response in 10% (95% CI 1%–32%). These responses are similar to those seen with many other cytotoxics, but suggest a lower level of activity in the first-line setting than docetaxel-based chemotherapy (Tannock et al 2004).

A major question for the development of satraplatin is its position with other standard agents as treatment for patients with HRPC. With the recent approval of docetaxel-based therapy by the FDA and European agencies in 2004 for treatment of patients with metastatic HRPC, second-line therapy is a rational choice with no proven standard-of-care (Tannock et al 2004; Lin et al 2006; Berthold et al 2006). With this in mind, a phase III, multicenter, randomized, placebo-controlled trial of satraplatin and prednisone vs prednisone alone in patients with HRPC treated with one prior chemotherapy was initiated in 2003 and accrual completed in 2006 (Sternberg 2005). The SPARC trial (Satraplatin and Prednisolone Against Refractory Cancer) enrolled patients in a 2:1 fashion to satraplatin 80 mg/m^2 days 1–5 every 5 weeks with prednisone 5 mg twice daily, or to prednisone alone (see Figure 3 for schema). This trial accrued 950 patients over 24 months and had 90% power to detect a 30% improvement in progression-free survival (PFS), the primary endpoint. The use of a progression endpoint rather than overall survival in this setting is controversial, given the unclear surrogacy or validation of this measure in this setting, but the decision to use this endpoint was made with concordance by the FDA. In this study, PFS was defined as a composite of death, tumor progression, new skeletal event, or symptomatic disease progression. Tumor progression was defined by RECIST criteria or by two new bone scan lesions rather than through PSA criteria, and was evaluated by a blinded independent review committee, with assessments every 2 cycles (10 weeks). Skeletal events were defined as the clinical need for radiotherapy or surgery to the bone, new fracture, or initiation of bisphosphonate therapy. Symptomatic disease progression was defined by the Present Pain Inventory, an increase in analgesic consumption, a decline in performance status, or by weight loss ≥10% (Melzack 1975). PSA was not included in definitions of progression.

The SPARC trial was closed in September 2006, after reaching the primary endpoint of PFS. Results were presented in abstract form in February 2007 based on these early data (Petrylak et al 2007). In this trial, over 50% of subjects had received prior docetaxel therapy and nearly 50% had received another form of chemotherapy. Approximately 35%
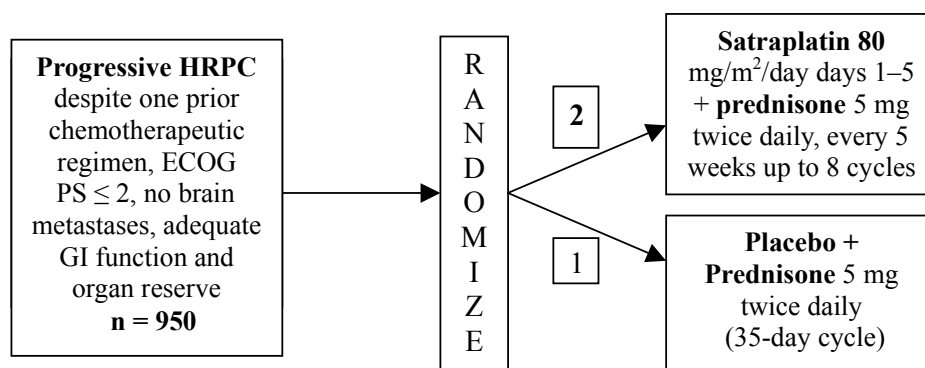
Figure 3 Trial schema for the randomized phase III SPARC trial which was recently completed in second-line HRPC. Anti-emetics are standard in the satraplatin arm, while an anti-emetic placebo is used in the standard prednisone alone placebo controlled arm (two placebos used).

of subjects had pain scores of 2 or higher on a 5 point scale, and baseline characteristics were well balanced, including type of progression at entry, use of bisphosphonates, age, and performance status. In the satraplatin arm, 19.7% of subjects required a dose reduction, 39.4% of subjects required at least a one week dose delay, and 15.3% of subjects required dose delays in 2 or more cycles. In the satraplatin arm, 40% of subjects completed 5 cycles, while only 20% of the predni-sone treated patients completed 5 cycles, which was attrib-utable to early progression in the prednisone arm (Petrylak et al 2007; Sternberg et al 2007). Toxicity was manageable, with 0.6% of subjects on satraplatin therapy developing neutropenic fever, 3.8% requiring platelet transfusions, and 15.9% requiring RBC transfusions. This compares to a rate of 0%, 0.3%, and 8% in the prednisone-alone arm. Neu-ropathy was seen in 0.3% and did not differ from placebo. Renal insufficiency developed in 0.8% of satraplatin treated subjects compared with 0.3% of prednisone-treated sub-jects. Vomiting was observed in 1.6% of satraplatin treated subjects, while no subjects on prednisone alone vomited. Other grade 3–4 adverse events that occurred with a higher frequency in satraplatin treated subjects included deep vein thrombosis (1.6% vs 0%), elevated bilirubin (0.5% vs 0%), severe fatigue (4.9% vs 2.6%), and diarrhea (2.1% vs 0%) (Petrylak et al 2007).

A hazard ratio of 0.67 (95% CI 0.57–0.77, $p < 0.0001$) for PFS was noted with a median PFS of 11.1 weeks in the combination arm, compared to 9.7 weeks in the prednisone alone arm, according to independent review (Petrylak et al 2007). This represents an improvement in median PFS of 1.3 weeks, or 9 days. Among subjects who had prior docetaxel therapy and progressed, the HR for PFS was 0.67 (95% CI 0.54–0.83, $p = 0.0006$), with a median sur-vival favoring satraplatin and prednisone by 1 week (10.1

vs 9.1 weeks). At 6 months, the proportion with PFS was 30% vs 17%, favoring satraplatin, and at 12 months, this rate was 17% vs 7% (Sternberg et al 2007). While the median difference in PFS is clinically modest, the 6- and 12-month rates of PFS compared with prednisone alone may be regarded as significant. These endpoints were met due to delays in the time to pain and/or radiologic progression, which are clinically significant. However, as PFS has not yet been validated as a surrogate for overall survival in men with HRPC, the use of a composite PFS endpoint should be interpreted with caution (Scher et al 2007). Finally, prednisone alone is unlikely to be used in the second-line setting in the majority of patients, and is not regarded as the community standard-of-care, and without a comparison to alternative and widely available cytotoxic agents such as mitoxantrone, the exact clini-cal impact of this agent in the oncology community is unclear. Overall survival and palliative endpoint results are anticipated by late 2007.

Future directions for research and development

If satraplatin is FDA approved for use in men with HRPC, where will it be used in relation to current therapeutic choices for patients with HRPC? The SPARC trial represents the first phase III trial in the second-line setting in HRPC, and should be examined closely for its impact on palliation and quality-of-life (QoL) as well as PFS. If palliative endpoints are met with overall survival endpoints, then this likely represents a treatment advance however modest the absolute differences are, and the issues will be those of risk-benefit profiles, cost effectiveness, and therapeutic niche including future combinatorial directions. The lack of a true control group with mitoxantone and prednisone, a proven palliative

combination in HRPC, limits the interpretability of the activity of satraplatin as a palliative agent. In our opinion, PFS may be considered a reasonable measure of clinical benefit if the results are substantially improved over the existing standard-of-care. However, if overall survival is not met despite a statistical improvement in PFS, there may be reason to question the value of intermediate outcomes such as PFS as a surrogate primary endpoint for overall survival in phase III trials in men with HRPC. Given the potential for a clinically relevant palliative benefit for men in the second-line setting and the lack of available proven therapies, satraplatin may represent a significant treatment advance.

Moving forward, what role will satraplatin play in the clinic? Clearly, the SPARC trial leaves open many questions, including 1) the degree of pain palliation, 2) the utility of satraplatin combination regimens in the first- and second-line setting, 3) the use of biomarkers to predict the subgroup that demonstrate satraplatin sensitivity (ie, serum chromogranin A, genomic markers), and 4) the benefits of satraplatin compared with already approved and less expensive cytotoxic agents, such as mitoxantrone and prednisone, docetaxel retreatment, low-dose cyclophosphamide, and other regimens. Mature data on specific palliative and overall survival endpoints for this trial are anticipated in late 2007 and will shed light on the prospects for this agent in the future. Satraplatin is currently under FDA review based on the SPARC trial data. If the FDA review of the palliative and primary endpoints of the SPARC trial is favorable, the likely indication for satraplatin would be for the palliative management of men with HRPC who have progressed despite first-line chemotherapy.

Conclusion

The development of satraplatin as an anti-cancer agent has progressed to phase III trials in HRPC, which have demonstrated improvements in PFS, which may indicate a clinically relevant benefit. Further data on specific elements of clinical benefit, including pain control, quality of life, and overall survival, are awaited in 2007 as this agent is reviewed for FDA approval. The benefits seen in progression may be of clinical significance, given the lack of approved therapies in the second-line setting; however, progression as an endpoint is not yet a proven surrogate for overall survival or clinical benefit in HRPC. This trial does demonstrate the need for hard clinical outcomes in HRPC, and for rigorously defined definitions of progression that meet surrogacy criteria for overall survival (Armstrong et al 2007). The utility of satraplatin will likely reside in combination therapy in the first- or second-line

setting, using docetaxel, other taxane-based strategies, or novel biologic agents, and as single-agent palliation in those patients who have progressed after docetaxel and who prefer an oral regimen (Jones et al 2002). It is also essential to further define subgroups of HRPC that are likely to exhibit platinum sensitivity, as exemplified by the histologic or genomic approaches taken in lung cancer (Olaussen et al 2006; Potti et al 2006).

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