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Phase III Trial of Satraplatin, an Oral Platinum plus Prednisone vs. Prednisone alone in Patients with Hormone-Refractory Prostate Cancer

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Key Words

Satraplatin · Oral platinum · Hormone-refractory prostate cancer (HRPC) · Phase III · Randomized trial

Abstract

Satraplatin is a novel oral platinum (IV) complex that shows activity against hormone-refractory prostate cancer (HRPC) in cisplatin-resistant human tumor lines in phase I and phase II trials [1]. A randomized multicenter phase III trial with a target sample size of 380 patients was initiated in men with HRPC. After 50 randomized patients, the trial was closed to further accrual by the sponsoring company. An ad hoc analysis of all available data is reported here. Eligibility criteria included pathological proof of prostate cancer, documented progression despite prior hormonal manipulation, WHO PS 0–2, and no daily intake of narcotic analgesics. Patients were randomized between satraplatin 100 mg/m^2 for 5 days plus prednisone 10 mg orally BID or prednisone alone. Compliance was excellent. 48/50 patients have progressed and 42 have died, mostly due to prostate cancer. Median overall survival was 14.9 months (95% CI: 13.7–28.4) on the satraplatin plus prednisone arm and 11.9 months (95% CI: 8.4–23.1) on prednisone alone (hazard ratio, HR = 0.84, 95% CI: 0.46–1.55). A >50% decrease in prostrate specific antigen (PSA) was seen in 9/27 (33.3%) in the satraplatin plus prednisone arm vs. 2/23 (8.7%) on the prednisone alone arm. Progression-free survival was 5.2 months (95% CI: 2.8–13.7) on the satraplatin plus prednisone arm as compared to 2.5 months (95% CI: 2.1– 4.7) on the prednisone alone arm (HR = 0.50, 95% CI: 0.28–0.92). This difference is statistically significant (p = 0.023). Toxicity was generally minimal in both arms. This randomized comparison of a combination of satraplatin and prednisone versus prednisone alone supports the antitumor activity of the combination. Its role in the treatment of HPRC remains to be elucidated in an appropriate phase III setting.

Introduction

The incidence of prostate cancer has increased dramatically over the past few years as a result of heightened public awareness, screening programs, more widespread use of prostate specific antigen (PSA) measurement, and advances in imaging techniques. Approximately 30–35% of patients with prostate cancer will have regional or metastatic tumors. An additional 25% will develop metastases

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during the course of the disease, commonly to the bone. In patients with metastatic disease who are receiving androgen ablation, median overall survival is 2.5 years [2].

The development of hormonal resistance predictably occurs after androgen deprivation treatment. Hormone-refractory prostate cancer (HRPC) is defined as progressive disease despite castrate levels of serum testosterone. Responses to current second-line therapies are temporary, and the median overall survival after developing HRPC is approximately 12–18 months [3, 4].

The current FDA approved treatments for HRPC in the United States are mitoxantrone plus prednisone and taxotere plus prednisone. Bone is the primary site of metastases in 65% of patients with metastatic prostate cancer. For this reason, objective measurable or evaluable criteria for response evaluation are often lacking. In many patients, bone pain and decreased performance status are predominant. Relief from these symptoms is as important as prolongation of survival. As a result, assessment of these symptoms has become a fundamental part of many prostate cancer studies, and has provided an important endpoint for clinical trials in this disease.

Prednisone therapy has been shown to produce palliation of pain symptoms for patients with advanced prostate cancer [2, 5–7]. Prednisone alone produces palliative responses in 12–56% of patients [6, 7].

The combination of mitoxantrone plus prednisone was approved by the FDA in the United States for patients with symptomatic HRPC following two randomized studies [6, 8]. The combination produced palliative responses, using pain response criteria in symptomatic patients, in 29% vs. 12% of patients using prednisone alone ($p = 0.01$). Despite the improvement in painful symptoms, no improvement in overall survival was observed.

Since their original discovery, platinum compounds (cisplatin, carboplatin) have emerged as important agents for the therapy of several human tumors including testicular, bladder, lung, head and neck, ovarian, and cervical cancer.

Satraplatin, bis(acetato)amminedichloro(cyclohexylamine) platinum (IV), is a novel platinum (IV) complex synthesized by Johnson Matthey (JM-216). Satraplatin exhibits in vitro cytotoxicity comparable to cisplatin. This platinum analog is of particular interest for two reasons: it has activity in platinum-resistant tumor models in vitro, and unlike other platinum compounds, it is absorbed when administered orally. In studies using murine tumors and human ovarian carcinoma xenografts, orally administered satraplatin demonstrated meaningful antitumor activity, which was generally comparable to that of cisplatin or carboplatin administered parenterally.

Satraplatin has been investigated in a number of clinical studies, and over 600 patients have participated in satraplatin clinical trials. Three previous phase II or III trials were initiated evaluating satraplatin for prostate cancer. Two were terminated early by the sponsor for business reasons, but the third one, a multicenter phase II trial for patients with progressive HRPC, was completed [9]. The study was small, with 39 patients. One partial response was observed in a patient with measurable liver lesions, and there were 10 PSA responses (>50% decrease), including 2 complete responses. With these encouraging results, EORTC GU Protocol 30972 was designed as a randomized phase III trial, to determine the comparative efficacy of satraplatin plus prednisone to that of prednisone alone. The primary objectives of this study were to compare the two treatment arms in terms of overall survival and time to pain progression as primary endpoints. Secondary endpoints were: present pain intensity (PPI), response rate, time to overall progression, PSA response rate, complete and objective tumor response rates, duration of response, quality of life and safety (National Cancer Institute of Canada – Common Toxicity Criteria, NCI-CTC). Prednisone alone was felt to be an appropriate control arm since it does provide palliation of symptoms.

Materials and Methods

Patient Population

Eligibility criteria included: pathological or cytological diagnosis of adenocarcinoma of the prostate, documented evidence of progression (worsening disease-related pain, increasing PSA, new painful bone lesions, or increase in measurable disease) despite sustained previous hormonal treatment, WHO performance status of 0–2, analgesic pain score of 0–3 (table 1) (patients without pain had to have rising PSA >10 ng/ml). All patients had to have had antiandrogen withdrawal for at least 6 weeks before entry into the study. An adequate bone marrow, liver function and renal function were required. All patients had a life expectancy of at least 6 months and gave written informed consent after the protocol was reviewed by their individual human subjects committees.

Patients could not have had large-field radiotherapy (>30% of marrow-bearing area) within the previous 8 weeks of protocol entry. They could have received radiotherapy to the prostate, as long as the field did not include >30% of bone marrow-bearing area.

Treatments

Patients were randomized between satraplatin 100 mg/m^2 on days 1–5 every 35 days plus prednisone 10 mg twice daily per os (continuously) and prednisone 10 mg alone twice daily. Satraplatin was administered orally once daily between 9:00 and 11:00 a.m. on an empty stomach. A light breakfast was allowed 1 h before dosing

Table 1. Analgesic pain score

0	Analgesics not required
1	Non-narcotic analgesics required, less than daily
2	Non-narcotic analgesics required daily
3	Oral or parenteral narcotic analgesics required, less than daily
4	Oral or parenteral narcotic analgesics required daily

and patients were not allowed to eat for 1 h after treatment. Fluid intake was unrestricted.

Prophylactic antiemetics were to be given during satraplatin therapy. Treatment with prednisone was given in both arms until overall progression or excessive toxicity. According to the protocol, the patients were to receive a maximum of 8 cycles of satraplatin plus prednisone and were supposed to continue with prednisone alone after cycle 8 in the absence of progression.

Dose reductions and interruptions for satraplatin plus prednisone were made for hematological toxicities based upon nadir counts and nonhematological toxicities (grade II) such as a decrease of 25–50% in creatinine clearance from baseline in the preceding course using the Common Toxicity Criteria (CTC) grades.

Patients did not receive other drugs, with the exception of luteinizing hormone-releasing hormone (LHRH) agonists, while in the study. Palliative and supportive care for disease-related symptoms was allowed.

Follow-Up

In both treatment groups, clinical examinations, biochemistry, PSA tests and toxicity (NCI-CTC) assessment were performed at baseline and every 5 weeks until the end of the treatment, then every 3 months until death. Weekly blood cell counts were performed every week on treatment in the combination arm only. Tumor assessment via physical exam, nuclear medicine scans, CT scans of abdomen and pelvis and other imaging techniques as clinically indicated were performed at baseline and every 10 weeks until progression in both treatment groups.

Endpoints

Overall progression had to be defined as either an increase in analgesic pain score (table 1) of 1 point compared to baseline, confirmed by history exceeding 2 weeks or the requirement for radiation therapy for disease-related pain symptoms, a 2-point worsening in WHO performance status compared to baseline confirmed by a history exceeding 2 weeks, progression of measurable or nonmeasurable disease, or confirmed doubling of PSA to >20 ng/ml as compared to baseline.

Pain progression was defined as either: (1) an increase in analgesic pain score of 1 point over baseline level and lasting 2 weeks or more; or (2) the requirement of radiation therapy for disease-related pain symptoms; or (3) an increase in PPI score of 1 point over baseline PPI score or of 2 points over the nadir level, lasting at least 2 weeks; or (4) a decrease of performance status by 2 scores or more from the baseline level, lasting 2 weeks or more.

PSA response was evaluated according to the Bubley criteria [10]. Overall survival was measured from the date of randomization until the date of death (any cause) or the date of most recent information (censored observation).

Statistical Design

The trial was planned to be a randomized phase III trial of 380 patients with two primary endpoints: overall survival and time to pain progression. To correct for the presence of 2 primary endpoints, a significance level of 0.025 was to be used in the statistical analysis of each primary endpoint, so as to ensure an overall 5% risk of erroneously claiming statistical significance for either endpoint. The sample size was determined to provide 80% power to detect an increase of 4 months in median overall survival (from 9 months on prednisone alone to 13 months for the combination) and 90% power to detect a difference of 3 months in time to pain progression (from 6 to 9 months).

Early Trial Closure and ad hoc Analysis Plan

After a few months of recruitment and a total of only 50 randomized patients, the trial was closed due to a decision of the sponsor (Bristol-Myers-Squibb, BMS) not to study the experimental treatment further. This was apparently based upon the low commercial priority for this drug by BMS at the time.

With only 50 patients entered, the objectives of the phase III trial were not met. However, the EORTC followed all patients until progression and most until death. In the present report, we attempt an ad hoc analysis of all available data. The endpoint of 'time to overall progression' was assessed and is available with the maximum potential power as 49 of 50 patients have progressed and all have finished treatment. The endpoint 'overall survival' was also analyzed as 42 of 50 patients have died (84%).

At the time the trial was stopped, the assessment of the PPI scores was stopped. Therefore, the endpoints time to pain progression and pain response could not be assessed. Quality of life was also not assessed due to the limited sample size.

Results

Eighteen institutions participated in this trial and entered 50 patients until the development of satraplatin was stopped by the sponsoring company. We present below all available information concerning the toxicity and activity of the experimental and reference treatments.

Recruitment and Patient Characteristics

Eligibility of the patients and compliance to the treatment was evaluated by the study coordinator and the EORTC medical advisor.

Of the 50 randomized patients, 27 patients were assigned to the prednisone plus satraplatin arm and 23 to the prednisone alone arm. Patient characteristics are detailed in table 2.

Treatment Compliance and Toxicity

Treatment compliance is detailed in table 3. Dose reductions due to hematological or other toxicities were rare. The median dose of satraplatin administered was 3,150 mg (range 900–15,250 mg). The median dose of

Table 2. Baseline characteristics

	Prednisone (n = 23)		Prednisone + satraplatin (n = 27)	
	n	%	n	%
Median age, years (range)	72.5 (53.3–81.4)		70.4 (42.2–79.9)	
Baseline Hb (NCIC-CTC)				
0	1	4.3	1	3.7
1	19	82.6	26	96.3
2	3	13.0	0	0.0
Analgesic pain score				
0 No analgesics (with PSA >10 ng/ml)	8	34.8	10	37.0
1 Non-narcotics, < daily	4	17.4	4	14.8
2 Non-narcotics, daily	10	43.5	8	29.6
3 Narcotics, < daily	1	4.3	4	14.8
4 Narcotics, daily	0	0.0	1	3.7
WHO performance status				
WHO 0	7	30.4	12	44.4
WHO 1	9	39.1	10	37.0
WHO 2	7	30.4	5	18.5
Bone scan result				
Normal	2	8.7	2	7.4
1–5 hot spots	5	21.7	3	11.1
6–15 hot spots	4	17.3	10	27.0
>15 hot spots	7	30.4	6	22.2
Superscan	4	17.4	2	7.4
Unknown	1	4.3	4	14.8

Table 3. Treatment compliance

	Prednisone (n = 23)		Prednisone + satraplatin (n = 27)	
	median	range	median	range
Total duration of treatment, weeks	15	5–15	20	1–103
Average cycle duration, weeks	5.0	4.4–6.1	5.0	0.9–5.8
Number of cycles of prednisone	3	1–12	4	1–20
Dose intensity prednisone, mg/day	20.2	16.4–20.6	20.1	14.4–23.3
Dose reduction due to hyperglycemia grade 3	2 (8.7%)		0	
Number of cycles of satraplatin	–	–	4	1–15*
Dose intensity satraplatin, mg/m^2/day	–	–	100.0	39.4–103.1
Dose reduction due to hematological toxicity	–	–	6 (22.2%)	
Cycle delayed due to toxicity	–	–	9 (33.3%)	
Satraplatin discontinued due to toxicity or refusal	–	–	4 (14.8%)	

* One patient received 9 cycles and 1 patient 15 cycles, all patients have now finished treatment.

prednisone administered was 2,090 mg (range 700–7,020 mg) in the prednisone alone arm as compared to 2,800 mg (140–14,440 mg) in the satraplatin plus prednisone arm.

In the prednisone alone arm, a median of 3 cycles (range 1–20) were delivered and in the satraplatin arm, a median of 4 cycles (range 1–15) were given. The median cycle duration was 35 days. Antiemetics were given on

Table 4. Toxicity

	Prednisone (n = 23)		Prednisone + satraplatin (n = 27)	
	n	%	n	%
Hematological toxicity				
WBC grade 3°	–		7	25.9
Platelets grade 3°	–		8	29.6
ANC grade 3–4	–		4	14.8
Hb grade 3–4	–		0	
Biochemical toxicity				
Serum creatinine grade 4*	1	4.3	0	
SGOT grade 3°	2	8.7	0	
Alkaline phosphatase grade 3–4	7	30.4	3	11.1
Nonhematological toxicity				
Diarrhea grade 3°	0	0.0	2	7.4
Vomiting grade 3°	0		2	7.4
Infection grade 3°	1	4.3	2	7.4
Cardiovascular grade 3°	2	8.7	2	7.4
Renal grade 3°	1	4.3	0	
Hyperglycemia grade 3°	4	17	2	7.4

° No grade 4 was observed; * no grade 3 was observed.

Table 5. PSA response

PSA response (Bubley)	Prednisone (n = 23)		Prednisone + satraplatin (n = 27)	
	n	%	n	%
Response	2	8.7	9	33.3
Stable disease	3	13.0	5	18.5
Progression	17	73.9	12	44.4
Not evaluable	1	4.3	1	3.7

days 1–5 in 26/27 (96.3%) of patients on the satraplatin arm.

Toxicity was generally minimal in both arms and is described in table 4. No grade 3–4 toxicity was observed for hemoglobin, nausea, fever, or pulmonary toxicity. In the combination arm, 2 patients experienced grade 3 vomiting and 2 had grade 3 diarrhea. In the prednisone alone arm, prednisone was reduced for grade 3 hyperglycemia in 2 (8.7%) patients or for other reasons in another 2 (8.7%) patients; it was discontinued in a further 2 (8.7%) patients. In the satraplatin arm, the chemotherapy was reduced at any time in only 6 (22.2 %) out of all the patients. One patient on each arm may have died due to stomach perforation, most likely related to prednisone.

For complete discontinuation of the protocol treatment: all but 3 patients stopped the treatment due to progression of disease. One on prednisone refused treatment, and 2 on the prednisone plus or minus satraplatin arm discontinued the treatment due to toxicity.

Efficacy

PSA response was observed in 9 (33.3%) patients on the satraplatin plus prednisone arm and 2 (8.7%) patients on the prednisone alone arm (odds ratio of response = 5.26, 95% CI: 1.00–2.78). Stable disease was seen in 5 (18.5%) patients in the satraplatin arm and in 3 (13%) on the prednisone arm. Progression was observed in 17 (73.9%) patients on the prednisone alone arm and 12 (44.4%) on the satraplatin plus prednisone arm. Responses are detailed in table 5.

The progression-free survival (fig. 1) was 5.2 months (95% CI: 2.8–13.7) on the satraplatin plus prednisone arm compared to 2.5 months (95% CI: 2.1–4.7) on the prednisone alone arm. The hazard ratio (HR) was 0.50 (95% CI: 0.28–0.92). This difference is statistically significant (p = 0.023). Table 6 presents the type of first failure in the patients who had progression as the first event. One patient on prednisone alone died of stomach perforation in the absence of progression.

Overall survival (fig. 2) was 14.9 months (95% CI: 13.7–28.4) on the satraplatin plus prednisone arm compared to 11.9 months (95% CI: 8.4–23.1) on the prednisone alone arm. The HR was 0.84 (95% CI: 0.46–1.55). This difference was not statistically significant (p = 0.579).

Discussion

Patients with metastatic prostate cancer are initially treated with hormone therapy, but hormonal resistance develops in most patients after androgen deprivation. The current FDA-approved treatments for HRPC in the United States are mitoxantrone plus prednisone and taxotere plus prednisone [11, 12]. These combinations are also approved in the EU. Mitoxantrone plus prednisone produces a palliative response in patients with pain, but there is no improvement in survival. Two recent studies comparing a docetaxel-containing arm to a mitoxantrone-containing arm demonstrated a survival advantage for the docetaxel arms. Thus, cytotoxic chemotherapy can improve survival in this disease, however, there continues to be a medical need for chemotherapeutic agents that may

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