Phase II study of oral bis (aceto) ammine dichloro (cyclohexamine) platinum (IV) (JM-216, BMS-182751) given daily x 5 in hormone refractory prostate cancer (HRPC)

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Summary

JM-216 is an orally bioavailable platinum compound with activity against many tumor models. The objective of this study was to determine the safety profile and anti-tumor activity of JM-216 in patients with hormone refractory prostate cancer (HRPC) when given orally daily × 5 days. In this open label phase II study JM-216 was administered orally at the dose of 120 mg/m²/d for 5 days every 4 weeks. Patients continued on the therapy until evidence of disease progression or intolerable toxicity developed. Dose escalation and de-escalation were allowed according to patient's tolerance. Thirty-nine patients were enrolled onto the study and received a total of 155 courses (median 2, range 1–16) of JM-216. Dose delays (77% of courses) and dose reductions (31% of courses) were common and were mainly due to myelosupression. Treatment was discontinued in 5 patients due to treatment related toxicities. One patient developed myelodysplastic syndrome 11 months after the start of treatment. The most frequent grade III or higher adverse events included thrombocytopenia (54%), neutropenia (52%), anemia (24%) nausea (13%), vomiting (16%) and diarrhea (28%). PSA response was assessed in 32 patients, 10 (26%) had partial response, 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. Although JM-216 had moderate activity in HRPC when given on daily basis for 5 days, it is associated with significant treatment related toxicities in this patient population.

Introduction

Metastatic prostate cancer remains the second leading cause of male cancer deaths in the United States of America with estimated 28, 900 deaths in the year 2003 [1]. Although androgen deprivation is the mainstay of treatment in metastatic prostate cancer it is generally considered palliative and all patients eventually become resistant to hormonal therapy. Once prostate cancer becomes hormone refractory, the prognosis is dismal with a median overall survival generally demonstrated to be less than one year [2]. To date none of the several clinical trails evaluating experimental chemotherapeutic and or hormonal regimens in hormone refractory prostate cancer (HRPC) patients had demonstrated a definite survival benefit [2]. Due to the use of differing response and entry criteria the comparison of objective advantage obtained from the use of these cytotoxic agents is difficult to assess [3, 4]. Nonetheless objective response rate (i.e. reduction in measurable disease including complete and partial response) remains less than 10% with most of these regimens [5]. Although no evidence was available in favor of chemotherapy improving the survival in HRPC recent trials have demonstrated encouraging results in symptom palliation, response rate and quality of life [6].

JM-216, (BMS-182751, Satraplatin), {bis (aceto) ammine dichloro (cyclohexamine) platinum (IV)}, is a novel platinum analog that can be administered orally on a daily basis [7]. JM-216 has shown antitumor activity comparable to that of cisplatin or carboplatin in human ovarian

carcinoma xenograft and murine sarcoma models [8]. It has also shown antitumor selectivity far superior to that observed for cisplatin or carboplatin against murine plasmacytoma in the in vivo preclinical studies [9]. Although phase I studies of JM-216 as a single agent have evaluated three administration schedules, daily dose for 5 consecutive days, every three weeks was the recommended schedule for further studies due to ease of administration and best tolerability [10]. Utilizing this schedule the dose-limiting toxicities included thrombocytopenia, and diarrhea and the maximum tolerated dose (MTD) was 100–140 mg/m^2/d. The most frequent reasons for treatment discontinuations due to an adverse effect were hematologic and/or gastrointestinal toxicities. The recommended phase II dose using the daily times 5 days schedule was 100–120 mg/m^2/d every three to four weeks [10, 11]. Multiple phase I/II trials have evaluated the role of cisplatin and carboplatin, either as single agent or in combination with other cytotoxic agents, in HRPC [12–18]. The objective response rate to single agent cisplatin ranged 0 to 19% in these trials and was comparable to that seen with other chemotherapeutic agents in HRPC [14–18]. Carboplatin in combination with pactlitaxel and estramustine phosphate (TEC) has shown significant antitumor activity (45% response rate in patients with measurable disease) [12, 13]. Based on these results, ease of daily oral administration and the need for improved therapy for HRPC a phase II study of JM-216 in the treatment of HRPC was undertaken. The objectives of the study were to determine the anti-tumor activity of JM-216 in the treatment of HRPC, and to evaluate the safety profile of this unique agent in this patient population and schedule proposed.

Patients and methods

Patient eligibility and evaluation

From December 1995 to October 1998 patients with histologically confirmed metastatic prostatic adenocarcinoma, who had disease progression despite one or more hormonal therapies, and after anti-androgen withdrawal were enrolled in the study. Both measurable and evaluable patients were eligible for the study provided progression of disease could be objectively established. Progression was demonstrated by worsening disease on bone scan or other objective measures including bone X-ray, CAT scan and magnetic resonance imaging (MRI). Isolated increase in Prostate Specific Antigen (PSA) was not considered sufficient evidence of disease progression. Patients were required to have ECOG performance status of 0–2, and a life expectancy of at least 6 months. No prior cytotoxic chemotherapy (including suramin) or large field radiation (greater than 30% of marrow bearing area) was allowed.

Patients were required to have adequate bone marrow reserve, renal and hepatic function. Sexually active, fertile patients were required to use effective birth control methods while receiving study drug. Individuals were excluded if they were diagnosed with a serious concurrent uncontrolled medical disorder; a history of major gastrointestinal surgery or pathology likely to influence absorption; and a history or prior malignancy except appropriately treated localized epithelial skin cancer.

Pretreatment evaluation included a history and physical examination including height, weight, performance status, and symptom review. Pretreatment testing included an EKG, chest X-ray, pain assessment, and tumor assessment. Laboratory tests required within 14 days of initial treatment included the following: complete blood count (CBC), blood chemistry profile, urinalysis, PSA and creatinine clearance in case of abnormal serum creatinine. While receiving treatment, weekly CBC was obtained. History and physical examination, pain assessment, blood chemistry profile, urinalysis and PSA were required prior to each treatment cycle. Repeat creatinine clearance values were obtained if the serum creatinine rose to above the upper normal limit. Chest X-ray and EKG were repeated as clinically indicated. Toxicity assessment was performed at every clinic visit using National Cancer Institute common toxicity criteria (version 1). Tumor reassessment was required prior to every other course and as clinically indicated.

Treatment

JM-216 was provided by Bristol-Myers Squibb Pharmaceutical Research Institute in capsules of 10 mg, 50 mg, and 200 mg. JM-216 was initiated at 120 mg/m^2/d for five days, repeated every three weeks. The dose interval was amended to every four weeks after the first five patients experienced delayed hematologic recovery. Dose escalation or de-escalation was allowed according to preplanned dose adjustment schema that is shown in Table 1. Patients were allowed to continue treatment as long as clinical benefit was observed, in the absence of disease progression and/or intolerable toxicities. Reasons for termination

Table 1. Schema for planned dose adjustments

Toxicity	Dose adjustment[a]
≤Grade 1 hematological toxicity[b]	Escalate to next level
Equal to grade II hematological toxicity	No change
≥Grade II hematological toxicity or 25–50% reduction in creatinine clearance	Reduce one level

[a] Dose levels: − 2 = 80 mg/m^2/d, − 1 = 100 mg/m^2/d, 0 = 120 mg/m^2/d, + 1 = 140 mg/m^2/d, + 2 = Do not exceed 140 mg/m^2/d.
[b] According to CTC version 1.

included toxicity, disease progression, patient request, non-compliance, or physician decision.

Evaluation

Evaluation for progression of disease or response to chemotherapy was performed using physical examination, bone scans, bone X-rays, and other appropriate imaging techniques and PSA levels. Measurable disease was defined as lesions measurable in two perpendicular diameters. A complete response (CR) in patients with measurable disease consisted of complete disappearance of all tumor lesions and of all signs and symptoms of disease for at least four weeks from the date of documentation of the complete response. A partial response (PR) among patients with measurable disease consisted of a decrease by more than 50% in the sum of the products of the two largest perpendicular diameters of all measurable lesions as determined by two consecutive observations, at least four weeks apart. Stable disease was defined as failure to observe either a CR or PR, in the absence of progressive disease (PD), as determined by two consecutive observations at least four weeks apart. Progressive disease was determined by an increase in size by at least 25% of any measurable or evaluable lesion, and/or the appearance of new lesions or the occurrence of malignant pleural effusion or ascites.

A complete PSA response was defined as PSA values within institutional normal range provided there was no disease progression during or before the response period. Partial PSA response consisted of PSA values that had decreased by at least 50% of their baseline values, without disease progression during or before the response period. A stable PSA response was defined as PSA values that are less than 50% from the baseline value, provided there is no CR, PR or PD, during or before the response period. PSA progression was determined by PSA values with atleast a 50% increase from the nadir value. Assessment of PSA response required two consecutive PSA values at least 28 days apart for each of the circumstances (CR, PR, and PD)

Statistical methods

The original study incorporated a two-stage accrual design to allow early termination should preliminary results indicates that treatment has minimal activity or unacceptable toxicity in this population. Objective response rate was the primary endpoint of the study. However, the decision to continue the trial was based on overall evidence of response including both objective response and PSA response. Fifteen evaluable patients were to enter into the study initially; if 2–4 responses were observed, then stage two would begin with the accrual of 15 additional patients to estimate the effectiveness of JM-216 in this patient population. If more than 7 responses were observed, the regimen was concluded to be promising. Tabulations and descriptive statistics were used to analyze patient characteristics, drug efficacy, drug safety and laboratory observations.

Results

The pretreatment characteristics of patients entered into this trial are listed in Table 1. Thirty-nine patients were registered from December 1995 to October 1998. All patients initiated treatment at a dose of 120 mg/m^2/day and received a total of 155 courses of JM-216 (median 2, range 1–16). The original protocol required that the chemotherapy be given for five consecutive days every 21 days. The protocol was amended in July 1996, to reflect the discovery of late hematologic nadirs occurring at approximately day 21 of each course. The cycle length was then changed to every 28 days. Dose delays were common and occurred in 88 (77%) of 116 courses delivered subsequent to the first course and the median number of days between courses was 38 (range 21–72 days). The majority of courses were delayed due to the late recovery from hematologic toxicity. Dose reductions occurred frequently and reasons for dose reduction included cytopenia in 23 patients and an increase in creatinine in 2 patients. Of 37 patients who received a minimum of two courses, 22 (59%) patients required at least one dose reduction during their treatment. Dose reductions occurred in 36 (31%) of 116 courses administered subsequent to the first course. However, 10 (26%) patients who received a minimum of two courses, were dose escalated to 140 mg/m^2/day at some point in time during their therapy. Permanent dose discontinuation occurred in 5 patients. Three had elevated liver function tests and one each had leukopenia and thrombocytopenia.

Hematologic toxicities are summarized in Table 2. Median time to hematologic nadir during evaluation of all courses was day 27 for hemoglobin (range 2–154); day 22 for absolute neutrophil count (range 2–45) and day 24 for platelet count (range 2–108). Fourteen patients required transfusions for anemia or thrombocytopenia at some time during their course of treatment. Approximately 88% of patients had abnormal lymphocyte values at the initiation of the study with 95% of patients developing grade 3 lymphopenia during the treatment phase. One patient developed a latent myelodysplastic syndrome (MDS) with complex karyotype (including 7q-) on cytogenetic analysis approximately eleven months after his treatment.

Non-hematological toxicities were mostly grade I or II and included nausea (95%), asthenia (90%), diarrhea

Table 2. Patient characteristics

Characteristics	N = 39
Age	
Median (years)	69
Range	47–82
Performance status	
0	16 (41%)
1	22 (56%)
Not Reported	1 (3%)
PSA	
Median (ng/L)	117.7
Range	4.3–1497.8
Time from diagnosis	
Median (months)	55
Range	<1–116
Bone metastases	
Present	33 (85%)
Absent	6 (15%)
Prior therapy	
Radiation	24 (61%)
Hormone therapy	39 (100%)
Orchiectomy	12
LHRH agonist	29
Anti-androgen	35
Estrogen	6

Table 3. Grade 3 or higher toxicities according to CTC version 1

Toxicity	% of Patients, N = 39
Hematologic	
Anemia	24
Leukopenia	41
Neutropenia	52
Lymphopenia	95
Thrombocytopenia	54
Gastrointestinal	
Diarrhea	28
Vomiting	13
Nausea	16
Elevated Liver enzymes	10
Renal	0

(87%), anorexia (69%), vomiting (51%) constipation (44%), chills (38%), myalgia (36%), dysgeusia (33%), dizziness (33%), and headache (31%). As summarized in Table 2 Gastrointestinal toxicities were significant, with Grade 3 or higher nausea, vomiting and diarrhea noted in 13, 16 and 28% of the patients respectively. Approximately one-third of patients had an elevation of ALT, AST, or total bilirubin from baseline at some point during treatment. Most elevations were grade 1or II, transient, tended to occur soon after the course of treatment and recurred in some cases upon re-challenge with JM-216. Grade 3 or higher abnormalities of liver related enzymes occurred in 4 patients and treatment was discontinued in three patients. Abnormalities of liver enzymes were uniformly reversible in all cases on discontinuation of therapy. Renal toxicities were mild and infrequent with only two patients requiring dose delays and reductions secondary to renal function abnormalities. Seventeen patients reported a total of 35 hospitalizations during the course of this study. Twelve of these hospitalizations were believed related to study drug toxicity. Treatment were discontinued due to progressive disease in 19 (49%) patients, treatment related toxicity in 13 (33%) patients and upon patient's request in 5 (13%) cases.

Twenty patients (54%) had measurable disease. Two patients, one with liver metastasis had a documented partial response. The remaining 18 patients did not have any measurable response to treatment, in 7 patients the disease remained stable for the duration of treatment. PSA values were measured at the time of each chemotherapy administration. Thirty-two patients had all PSA values available for response assessment. A complete PSA response or a partial PSA response was measured in 10 (26%) patients, stable disease was noted in 14 (36%) patients while PSA progression occurred in 8 (20%) patients. PSA response could not be evaluated in 7 (18%) patients due to the missing values. Treatment was discontinued in many patients before the documentation of PSA progression due to toxicity and other reasons, 14 (35%) patients enrolled in the study had documented PSA progression during the treatment period. The median survival for the whole cohort is 16.7 months (95% confidence interval 9.3–19.2 months). The median PSA response duration was 3.8 months while median progression-free survival was 7.7 months in 32 assessable patients.

Discussion

JM-216 (BMS-182751, Satraplatin) is a novel orally bioavalible platinum analog that had demonstrated antitumor activity comparable with parentrally administered cisplatin or carboplatin in both in vitro and in vivo studies. Although phase II studies in small cell lung cancer JM-216 has shown considerable promise as first line therapy [19], its antitumor activity in refractory cervical and non-small cell lung cancers is at best modest [20, 21]. Its role as a radiation sensitizer and in combination with other drugs has been evaluated in small studies [22, 23]. The overall response rate including objective and PSA response (excluding stable disease) was 26% in this study. Stable disease was observed in another 36% of the patients demonstrating modest anti-tumor activity of JM-216 in HRPC comparable to that observed for other cytotoxic agents in this setting.

Despite JM-216 showing modest activity within this patient group, frequent dose modification and delays secondary to treatment-related toxicity complicated management considerably. The most common and significant grade 3 or higher toxicities were myelosupression (54%) and gastrointestinal (28%) as noted in previous studies. The unexpected finding noted in this study was the unusually late recovery of neutropenia and thrombocytopenia as reflected by prolonged cycle interval (median 38 days) between subsequent courses. This result could be explained partly by older age of the patients and the fact that 61% of patients had received prior radiation therapy that can potentially damage bone marrow reserves [24]. It is more likely that the late nadir represents toxicity to stem cells, which has become evident in this patient population. Development of MDS in one patient eleven months after the therapy, the first noted case of possible treatment related leukemia following JM-216 therapy, supports the hypothesis of stem cell damage. Presence of complex karyotype (including 7q-, an abnormality typically associated with prior chemotherapy related leukemia/MDS) in our patient and existence of reports describing higher incidence of secondary leukemia following cisplatin and carboplatin therapy in ovarian cancer favors this conclusion [25, 26]. The cause and significance of lymphopenia in majority of patients during the treatment phase is also not clear even though it has been reported in other studies evaluating estrogen, corticosteroids, suramin and mitoxantrone in HRPC [27–29].

Non hematological toxicities were mainly gastrointestinal with grade 3 or higher nausea, vomiting and diarrhea occurring in 13–28% of patients. Three patients were hospitalized due to refractory gastrointestinal toxicities. Elevation of the liver enzymes and bilirubin was noted in approximately one third of the patients treated with JM-216 at some point during their treatment. Although these abnormalities were mild and transient in majority of patients, contrary to previous studies treatment had to be discontinued in three patients a finding that could also be related to older age and higher dose of JM-216 in our patients.

In conclusion although this study had demonstrated a modest antitumor activity of JM-216, comparable to other currently available chemotherapeutic agents for HRPC, we believe that toxicities associated with this dose and schedule significantly complicate the management of these patients. As evident by frequent dose delays and dose reductions starting dose in this trial seems to be too high for prostate cancer patients. Future studies should design to evaluate lower starting doses with longer cycle duration especially if used in combination with any other myelotoxic chemotherapeutic agents.

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