Cancer Chemother Pharmacol (2011) 67:1455–1461
DOI 10.1007/s00280-011-1594-z

CLINICAL TRIAL REPORT

Phase II trial of cisplatin plus prednisone in docetaxel-refractory castration-resistant prostate cancer patients

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Received: 26 December 2010 / Accepted: 27 January 2011 / Published online: 2 March 2011

Abstract
Background Docetaxel represents the first-line treatment for castration-resistant prostate cancer (CRPC). New therapeutic options are needed for subsequent lines of therapy in CRPC patients.
Methods Patients with progressive CRPC, pretreated with docetaxel, were enrolled at the Department of Molecular and Clinical Oncology and Endocrinology of University 'Federico II of Naples' from April 2007 to January 2010. Accrued patients received cisplatin at the dose of 75 mg/m^2 every 3 weeks with daily 10 mg prednisone. Measures of response and progression were defined according to the Prostate Cancer Working Group (PCWG1) criteria. Toxicity was graded according to the Common Toxicity Criteria of the National Cancer Institute, version 3.0.
Results Twenty-five patients were recruited. Median age was 65 years (interquartile range 55–74 years). All patients were evaluable for PSA response and toxicity and thirteen patients (52%) were evaluable for measurable disease. A total of 170 cycles of cisplatin chemotherapy were administered. Median dose intensity corresponded to 96% (range 83.8–98.3%) of the maximum dose intensity that could be delivered. Three patients (12%) presented grade 3–4 neuropathy and ten (40%) presented grade 3–4 neutropenia. Five patients (20%) showed a greater than 50% PSA decline, and three of thirteen patients with measurable disease presented a partial response. Median progression-free survival was 5.6 months (24 weeks; range 15–24). Median survival was 55 weeks (range 46–64; see Fig. 1).
Conclusions Cisplatin plus prednisone appears to represent an active regimen in docetaxel-refractory CRPC with an acceptable toxicity profile. Further investigations in this setting are warranted to confirm these early encouraging findings.

Keywords Castration-resistant prostate cancer · Cisplatin · Pretreated patients

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Introduction

About 32,050 men died of prostate cancer in 2010 in the United States [1]. Docetaxel has represented the sole efficacious treatment for castration-resistant prostate cancer (CRPC) for several years [2, 3] and is also a viable option for re-treatment of selected patients who received docetaxel but interrupted it for reasons other than disease progression [4]. Presently, a variety of novel drugs have great potential to become part of the therapeutic armamentarium for the management of this disease [3]. In particular, the expanding and diversifying treatment options for CRPC now include three agents, which have showed to prolong survival in large, well-designed phase III trials: immunotherapy agent Sipuleucel-T (Dendreon) [5] for metastatic, asymptomatic or minimally symptomatic CRPC patients, CYP 17A1 inhibitor abiraterone (Johnson and Johnson) [6] and cytotoxic agent cabazitaxel [7] (Sanofi-Aventis), which were both employed in docetaxel-refractory CRPC patients. These rapid and exciting discoveries have taken place in a context where the effects of the 'counter-revolution' brought by the PCWG2 criteria [8] cannot be fully captured yet. In fact, as suggested by the PCWG1 criteria [9],

PSA response rate has been used as primary end point and employed to calculate the sample numerosity in several recently published trials [10, 11].

Platinum agents showed modest/moderate activity in CRPC long before the introduction of PCWG1 criteria [12]. A phase III, placebo-controlled trial has recently failed to demonstrate an OS advantage for docetaxel-refractory patients treated with second-line satraplatin [3]. Combination treatment with picoplatin plus docetaxel in chemotherapy naïve patients [3] and with carboplatin plus etoposide in docetaxel-pretreated patients [13] has showed promising efficacy in phase II trials. Surprisingly, prospective data about cisplatin employed in a CRPC population previously exposed to docetaxel are currently lacking. We here present the results of the first phase II trial on second-line cisplatin in docetaxel-refractory CRPC patients.

Patients and methods

Patients

Eligibility criteria for the study are detailed in Table 1 and were mainly the following: adult age; histologically confirmed prostate adenocarcinoma; progressive disease, defined as either confirmed raise in PSA values, or at least one new osseous lesion at bone scan or enlargement of target measurable lesions on CT scan, according to the PCWG1 [9] and the RECIST criteria [14], after first-line treatment with docetaxel; adequate heart, bone marrow, renal and hepatic function; normal calcium levels. There was no restriction on previous hormonal manipulations; either surgical castration or pharmacological castration with *LHRH* luteinizing hormone-releasing hormone *agonists* was required. No prior chemotherapy agents, other than docetaxel or estramustine, were allowed. Androgen blockade had to be interrupted for at least 4 weeks with flutamide and for 6 weeks with bicalutamide. Previous treatment with bisphosphonates was permitted. The study, approved by the Institutional Ethics Committee of the participating center, was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. Written informed consent was obtained from all patients before study entry.

Table 1 Eligibility criteria

Age >18 years
ECOG PS 0–2
Life expectancy >3 months
Histologically confirmed adenocarcinoma of the prostate
Testosterone serum levels <50 ng/dL
Prior first-line chemotherapy with a docetaxel regimen
Biochemical or osseous progressive disease or progression of measurable lesions, according to RECIST and PCWG1 criteria
Written informed consent
Hemoglobin >9 g/dl
Absolute leukocyte count >3,500/μL
Absolute granulocyte count >1,500/μL
Absolute platelet count >100,000/μL
Creatinine clearance ≥60 ml/min according to the Cockroft–Gault formula
Transaminases <2 × ULN
Bilirubin <1.5 × ULN
Heart ejection fraction >50%
Corrected calcium levels >8.5 and <10.4 mg/dL
Absence of brain metastases
Absence of grade 3–4 peripheral neuropathy

ULN upper limit of normal, *ECOG PS* Eastern cooperative oncology group performance status

Treatment

Cisplatin was delivered intravenously with adequate pre- and posthydration at the dose of 75 mg/m^2 every 3 weeks. Only one dose reduction to 60 mg/m^2 was allowed. A dose of 5 mg prednisone was orally administered twice daily.

Patients were fit to receive full doses of cisplatin on the condition that hematologic, hepatic, and renal function was within the inclusion criteria, and no other nonhematologic toxicities more severe than grade 2 were reported. Patients were fit to receive reduced doses of cisplatin on the condition that hepatic and renal function was within the inclusion criteria, no other nonhematologic toxicities more severe than grade 2 were reported, platelet count was >75,000, and neutrophil count was >1,000.

Doses were reduced if patients presented a toxicity-related treatment delay of 2 weeks or experienced grade 4 neutropenia, grade 4 thrombocytopenia, or febrile neutropenia. Patients who developed grade 3–4 peripheral neuropathy or with a treatment delay longer than 2 weeks were excluded from the trial.

Patients on LHRH agonists continued to receive this medication; patients who received a bisphosphonate drug at study entry continued to receive it throughout the trial. Patients who required palliation of bone metastasis with radiotherapy were removed from the trial. Treatment continued until disease progression or unacceptable toxicity.

Assessments

All patients had a complete medical history, a physical examination, and a PSA measurement within 1 week before study entry. Cardiac ecography for estimation of heart ejection fraction and other laboratory tests (complete blood count, creatinine, serum calcium, aspartate

aminotransferase, alanine aminotransferase, total bilirubin, and biochemical markers of neuroendocrine differentiation) were performed within 2 weeks before study entry. Neuron-specific enolase (NSE) was determined by ELISA (Intermedical, Italy), while chromogranin A was measured by immunoradiometric assay (Cis Bio International, France). Patient on proton-pump inhibitors was advised to suspend the treatment for at least 2 weeks before evaluation of chromogranin A [15]. All radiologic examinations (bone scan, chest–abdomen–pelvis computed tomography scan) were performed within 4 weeks before study entry.

Every week, a complete blood count analysis was performed, while PSA, hepatic, kidney, and serum calcium laboratory tests were performed every 3 weeks. Pain intensity and analgesic consumption were evaluated every week. All adverse events were graded according to the Common Toxicity Criteria of the National Cancer Institute, version 3.0. Bone scan and chest–abdomen–pelvis computed tomography scan were repeated every 12 weeks.

According to PSWG1 criteria [9], PSA response was defined as a more than 50% reduction from baseline values confirmed on two consecutive measurements taken at least 4 weeks apart. Progressive disease was defined as either PSA or osseous progression or progressive measurable target lesions. PSA progression was defined as a confirmed 25% increase in PSA from either baseline or nadir, respectively, in patients who showed either no decline in PSA or a less than 50% decline in PSA and as a confirmed 50% increase in PSA from nadir in patients who showed a PSA response. Osseous progression was defined as the appearance of one new lesion on bone scan, while progressive measurable disease was defined according to the RECIST criteria [14].

Pain was weekly measured as the 'average pain' experienced in the previous week by using a numeric rating scale from 0 to 100 (0 being no pain and 100 representing the most intense pain ever experienced). Analgesic use was weekly self-recorded. Pain medications were prescribed by the treating oncologist and dosages were monitored at least weekly. Pain medications were classified as nonopioids (antiinflammatories, paracetamol, etc.) and opioids. Opioids intake was converted into oral morphine equivalents before analysis. As previously done [16], we defined 'pain response' as a >50% reduction in analgesic consumption, coupled with a >50% decrease of pain since baseline evaluation or maximum pain measurement.

Statistical analyses

Descriptive statistics and frequency counts were used to summarize characteristics of the study population. Median numbers were presented with interquartile ranges. As this study was designed before the publication of PCWG2 criteria [8], PSA response was chosen as primary end point and employed to calculate the study sample. Pain response, radiographic response rate, time to progression, and toxicity were secondary end points. The sample size was based on a Simon two-stage minimax design [17] to evaluate the null hypothesis that the true PSA response rate was less than 10% and the alternative hypothesis that the true PSA response was more than 30%, with both a type I and II errors equal to 10%. The PSA response rate of the null hypothesis was based on the PSA response rate of 12% reported with second-line mitoxantrone after first-line docetaxel, considering that mitoxantrone was the standard second-line treatment at the time this study was designed [18]. Sixteen patients had to be recruited for the first stage. If at least one patient showed a PSA response, accrual was continued for a total of 25 patients enrolled. Treatment was considered active if at least 5 PSA responses were recorded. Univariate analysis with the Fisher's exact test and the log-rank test were used for testing the hypothesis of a relationship between PSA response rate, progression-free survival, and survival and pretreatment biochemical neuroendocrine markers levels, as previously done [13].

Results

Patients' characteristics

Twenty-five patients were recruited at the Department of Molecular and Clinical Oncology and Endocrinology of University 'Federico II of Naples' from April 2007 to January 2010. Median age was 65 years (range 55–74 years). Bone was the most common site of metastasis, with twenty patients presenting osseous lesions. Thirteen patients (52%) had measurable. Median PSA was 170 ng/ml (range 80–1,000). The majority of the patients had received prior three-weekly docetaxel, while the remaining had received docetaxel according to a weekly/biweekly schedule. Fifteen patients were assuming opioids at the time of recruitment, with a median dosage equivalent to 60 mg of oral morphine (range 40–80). Patients' characteristics are detailed in Table 2.

Treatment and tolerance

A total of 170 cycles of cisplatin chemotherapy were administered to patients. The three-weekly schedule of cisplatin resulted in a median dose intensity of 24.5 mg/m^2/week, which corresponds to 96% (range 83.8–98.3%) of the maximum dose intensity that could be delivered. All of the patients were evaluable for toxicity.

Dose reduction and treatment delays were infrequent (see Table 3). Side effects were generally manageable, and

Table 2 Patients' characteristics

Characteristics	No. of patients (total, $n = 25$)
WHO performance status	
0	12
1	12
2	1
Gleason score[a]	
<7	10
≥7	15
Prior local therapy	
Surgery	18
Radiotherapy	12
Prior hormonal treatment	
LHRHa	25
Antiandrogens	25
Bicalutamide	25
Flutamide	10
Estramustine	1
Cyproterone acetate	8
Estrogen	2
Prior chemotherapy	
Docetaxel	25
Standard schedule (q21)	20
Adapted schedule (weekly/biweekly)	5
Current site of metastases	
Any site	23
Bone	20
Measurable visceral	13
Lung	6
Liver	7
Lymph nodes	10
Adrenal glands	1
Best biochemical response to docetaxel first-line	
Partial response	16
Time since last docetaxel administration to progression	
<3 months	22
≥3 months	3
Previous docetaxel cycles	
6	5
8	3
10	16
12	1
Prior bisphosphonates	
Zoledronic acid	21
Ibandronate	2
Clodronate	2
Analgesic intake	
Opioids	15
Nonopioids (corticosteroids excluded)	24
Serum NSE before second-line chemotherapy	
<12.5 ng/ml	19
>12.5 ng/ml	6
Serum chromogranin A before second-line chemotherapy	
<100 ng/ml	17
>100 ng/ml	8
PSA doubling time	
<3 months	10
≥3 months	15

[a] At radical prostatectomy or at biopsy if no prostatectomy was performed

severe toxicity was mainly constituted by neutropenia, nausea/vomiting, and peripheral neuropathy. Of note, only three patients presented grade 3–4 neuropathy, respectively, after 4, 4, and 6 cycles and were removed from the trial and censored from the PFS analysis. One patient experienced a vertebral fracture and was removed from the trial after receiving 4 cycles for progressive osseous disease. Eleven patients presented a PSA progression only, while five patients presented bone and/or measurable progressive disease without PSA progression. The rest of the patients with progressive disease presented both conditions. Main toxicity is reported in Table 4.

Table 3 Treatment and response to treatment

Treatment	No. of cycles
Median cycles administered (range)	7 (4–8)
Total cycles administered	170
Total cycles administered at reduced doses	30
Total cycles delayed	13
Response	**No. of patients (%)**
Biochemical (25 evaluable patients)	
≥50% PSA decline	5 (20)
≥30% PSA decline	9 (36)
Best objective response (13 evaluable patients)	
Complete response	0
Partial response	3 (23)
Stable disease	4 (30)
Progressive disease	6 (47)
Pain response (25 evaluable patients)	
>50% decline in pain score coupled with >50% decline in analgesic intake	8 (32)

Table 4 Toxicity data experienced per patient ($n = 25$)

Toxicity	All grades (%)	Grade 3–4 (%)
Neutropenia	17 (68)	10 (40)
Anemia	8 (32)	3 (12)
Thrombocytopenia	6 (24)	2 (8)
Nausea/vomiting	14 (56)	3 (12)
Peripheral neuropathy	11 (44)	3 (12)
Constipation	15 (60)	2 (8)
Fatigue	7 (28)	2 (8)

Efficacy

All of the patients were evaluable for biochemical response. The primary end point of the study was met, with 20% of 25 evaluable patients experiencing a greater than 50% PSA decline and 36% experiencing a greater than 30% PSA decline. Three of thirteen patients evaluable for measurable disease presented a partial response, for an overall disease control rate (partial responses plus stable diseases) of 53%. Median progression-free survival was 5.6 months (24 weeks; range 15–24). All patients were dead at the time of the analysis. Median survival was 55 weeks (range 46–64; see Fig. 1). Three patients were censored from the PFS analysis due to neurologic toxicity, while no patient was censored from the OS analysis. Fifteen patients failed to report their pain levels or analgesic consumptions on a few occasions, but this did not interfere with evaluation of pain response. Overall, eight patients presented a pain response, according to the criteria employed (see Table 3). No association was identified between markers of neuroendocrine differentiation and outcome measurements (see Table 5).

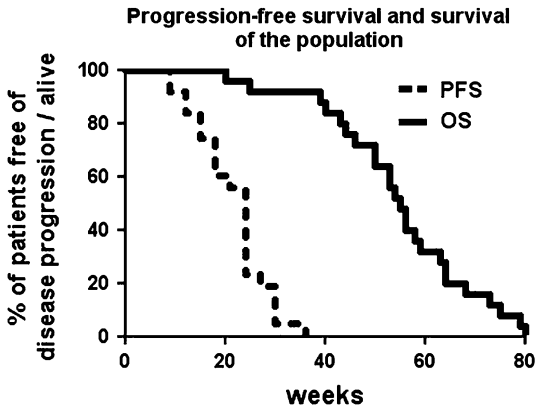

Fig. 1 Progression-free survival and overall survival of the study population

Discussion

The issue of the best second-line treatment in docetaxel-refractory CRPC patients has remained unresolved for several years [2]. The quest for novel agents for CRPC paralleled that for adequate criteria for the evaluation of their efficacy. In 2008, new consensus recommendations about the design of clinical trials in prostate cancer patients were published by an international group of experts, namely the PCWG2 [8]. The role attributed by the PCWG1 to a biochemical marker such as PSA, which has no corresponding counterpart in any other solid malignancy, was rejected by the PCWG2, which advised *against* the use of PSA and emphasized the importance of assessing measurable disease, bone disease, pain and quality of life to determine response to treatment, and progressive disease. Several new drugs have recently proven to provide a survival prolongation in CRPC patients [3]. The novel agent abiraterone, which selectively inhibits both intratumoral and adrenal androgen biosynthesis by blocking the CYP17 enzyme, provided a consistent advantage in OS with respect to placebo in a large phase III trial in 1,195 mCRPC patients (14.8 vs. 10.9 months, $P < 0.0001$) [6]. Cabazitaxel is another novel agent, which belongs to the pharmaceutical class of taxanes. A phase III trial recruited 755 docetaxel-pretreated, CRPC patients, who were randomized to receive 10 mg/day of prednisone with either three-weekly mitoxantrone (12 mg/m^2) or cabazitaxel (25 mg/m^2). Treatment caused a high rate of grade 3–4 neutropenia, which was observed in 81.7% of patients in the cabazitaxel arm and in 58.0% of patients in the mitoxantrone arm, with an incidence of febrile neutropenia of 7.5 and 1.3%, respectively. Median progression-free survival was 2.8 months (95% CI 2.4–3.0) in the cabazitaxel group and 1.4 months (1.4–1.7) in the mitoxantrone

Table 5 Association of PSA response rate and PFS and OS with neuroendocrine features and PSA doubling time ($n = 25$)

<vs.> cutoff value	PSA response rate	PFS	OS
Chromogranin A	15.7 vs. 33.3% $P = 0.56$	24 vs. 19.5 ws, $P = 0.27$	55 vs. 55 ws, $P = 1$
Neuron-specific enolase	17.6 vs. 25%, $P = 1$	24 vs. 21 ws, $P = 0.31$	56 vs. 51.5 ws, $P = 1$
PSA doubling time	20 vs. 20%, $P = 1$	24 vs. 21 ws, $P = 0.62$	51.5 vs. 58 ws, $P = 1$

Cutoff values were 12.5 mg/ml for neuron-specific enolase, 100 mg/ml for chromogranin A and 3 months for PSA doubling time

PFS progression-free survival, *OS* overall survival, *ws* weeks

group (HR 0.74, 0.64–0.86, $P < 0.0001$). The 2.4-month advantage in survival that emerged in favor of the cabazitaxel group was statistically significant (15.1 months vs. 12.7 months, HR 0.70; 95% CI: 0.59, 0.83; $P < 0.0001$) [7].

In view of the results obtained with these novel agents, the findings of our small study might not appear of utmost interest. Nevertheless, we believe that several important results obtained in this phase II trial are worthy of attention.

First, cisplatin proved to have an acceptable tolerance in docetaxel-pretreated patients. Severe neutropenia occurred in 40% of patients and the incidence of grade 3–4 peripheral neuropathy was comparable to that obtained with the cisplatin–gemcitabine combination therapy [19].

Second, although the PSA response rate was similar to that reported for the carboplatin–etoposide combination [13], the PFS of more than 5 months is more than double the PFS of 2.1 months obtained with carboplatin–etoposide. Carboplatin is less toxic and more easily manageable than cisplatin and can be a substitute for cisplatin in specific settings, but it is wrong to assume their equal efficacy not the basis of experimental evidence [20]. Thanks to the new available agents, platinum compounds will likely be employed as third or fourth line of therapy. On the basis of the positive findings of this trial, cisplatin, which had showed modest/moderate activity in the 'pre-docetaxel era' [12], might be a better option than carboplatin in patients fit to receive it.

Third, the lack of association between neuroendocrine biochemical markers and response to platinum agents, for which conflicting evidence was previously reported [13], was confirmed by our analyses.

The major limitations of our study are the limited sample size, the lack of a control arm, and the use of the PCWG1, instead of the PCWG2 criteria, as it has occurred for other recently published trials [10, 11].

Of note, since eleven patients presented a PSA progression only, an even better PFS might have been achieved, should the PCWG2 criteria have been applied to the design of the trial.

One feature of cisplatin of great interest is its low cost. An increasing attention has been recently paid to the economic burden for society of cancer treatments [21]. Should a phase III trial prove noninferiority of cisplatin with respect to the only effective, presently available second-line chemotherapy agent cabazitaxel, it is highly likely that a cost-utility analysis would greatly favor cisplatin.

Conclusions

This trial is the first phase II trial ever published on cisplatin plus prednisone in a population of docetaxel-pretreated patients. Cisplatin showed an acceptable tolerance profile and moderate activity in terms of PSA response rate, and was associated to an extremely promising median PFS. Further clinical trials are required to investigate the effectiveness of cisplatin plus prednisone in this setting.

Acknowledgments CB wishes to dedicate this work to his loving mother, the late prof. Mariarosaria Napoletano, who kept encouraging him to complete the writing of this paper during the last weeks of her life.

Conflict of interest None to declare.

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