

Weekly high-dose calcitriol and docetaxel in patients with metastatic hormone-refractory prostate cancer previously exposed to docetaxel

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OBJECTIVE

To evaluate the activity and tolerability of weekly high-dose calcitriol and docetaxel in patients with metastatic hormone-refractory prostate cancer (HRPC) previously exposed to docetaxel, as patients who progress after docetaxel treatment might be considered for second-line chemotherapy, but with no standard salvage therapy available we hypothesised that high-dose calcitriol might restore sensitivity to chemotherapy.

PATIENTS AND METHODS

The study comprised 26 patients who had progressed after first-line treatment with

docetaxel-based chemotherapy had failed. Treatment cycles consisted of calcitriol (32 µg orally as 0.5 µg tablets) on day 1 and docetaxel (30 mg/m² intravenous) on day 2, administered for six consecutive weeks followed by a 2-week rest interval for a maximum of 24 cycles.

RESULTS

There was a response in prostate-specific antigen (PSA) level in eight patients (31%); seven (27%) had a stable PSA level for ≥12 weeks. The median time to PSA progression was 4.2 months and the median survival was 9.3 months. The regimen was generally well tolerated; there was grade 2 hypercalcaemia,

probably related to calcitriol, in one patient after six treatment cycles.

CONCLUSION

Weekly high-dose calcitriol and docetaxel seems to be an effective and well-tolerated treatment option for patients with metastatic HRPC previously exposed to docetaxel-based chemotherapy.

KEYWORDS

calcitriol, prostate cancer, docetaxel, hormone-refractory.

INTRODUCTION

The results of two large randomized trials recently provided substantial support in favour of the role of chemotherapy in the treatment of hormone-refractory prostate cancer (HRPC) by showing that the combinations of docetaxel with prednisone and docetaxel with estramustine improve survival compared with older regimens, and significantly improve the quality of life [1,2]. Therefore, docetaxel has become the first-line standard of care for metastatic HRPC, with PSA responses of ≈50% and median survivals of usually <20 months. The combination of docetaxel with other chemotherapeutic drugs or novel biological agents represents an active area of clinical investigation and, in this setting, interesting results in terms of decreases in PSA (up to 80%) were described with docetaxel plus high-dose calcitriol [3].

Calcitriol, the principle active metabolite of vitamin D, has significant antineoplastic activity in preclinical models of prostate cancer and many other tumour types. The principle mechanisms of activity include inhibition of proliferation and cell-cycle arrest, induction of apoptosis, and reduction of invasiveness and angiogenesis [4,5]. Preclinical data suggest that calcitriol acts in a synergistic and/or additive manner when combined with antineoplastic agents, including docetaxel [6]. The antineoplastic activity of calcitriol occurs at concentrations that exceed the normal physiological range and cannot be safely achieved with conventional daily dosing. Instead, intermittent administration of calcitriol has allowed significant dose escalation, and the large randomized trial (ASCENT) has been conducted to verify the possible advantage of the combination of high-dose calcitriol and docetaxel over docetaxel alone [7].

Patients with HRPC who progress after docetaxel treatment might be considered for second-line chemotherapy, especially if they have a reasonable performance status, have symptoms, and/or are likely to soon develop symptoms from their disease. As no standard salvage therapy is available for such patients, and with the hypothesis that calcitriol might restore sensitivity to chemotherapy, in the present clinical study we evaluated the activity and tolerability of weekly high-dose calcitriol and docetaxel in patients with metastatic HRPC previously exposed to docetaxel.

PATIENTS AND METHODS

The study included patients with histologically confirmed, measurable or evaluable advanced prostatic adenocarcinoma who had progressed after

failure of first-line chemotherapy including docetaxel. Patients were defined as docetaxel-resistant if there was progression during and within 60 days of docetaxel therapy. In all patients standard androgen-deprivation therapy had also failed, including antiandrogen withdrawal, before starting first-line chemotherapy. They were admitted to the chemotherapy protocol provided that they met at least one of the following criteria: a $\geq 50\%$ increase in PSA level from baseline on two successive occasions separated by at least 2 weeks; new metastatic lesions revealed by a bone scan; and a 25% increase in a bidimensionally measurable tumour mass. All of the patients had to have an Eastern Cooperative Oncology Group performance status of ≤ 2 , adequate haematological (leukocytes $\geq 3000/\text{mm}^3$; haemoglobin ≥ 10 g/dL, platelets $\geq 100\,000/\text{mm}^3$), renal (serum creatinine ≤ 2.0 mg/dL), and hepatic function (serum bilirubin ≤ 2.0 mg/dL).

Patients were excluded if they had not received previous docetaxel-based chemotherapy or if they had congestive heart failure, a recent myocardial infarction, nephrolithiasis within 5 years, or any other previous malignant diseases except basal cell carcinoma of the skin. Bisphosphonates were allowed in all of patients who presented with bone metastases. All of the patients gave their informed consent, and the protocol was approved by the Ethics Review Board of Siena University.

The treatment consisted of calcitriol (32 μg as 0.5 μg tablets) given orally in three divided doses on day 1. Docetaxel (30 mg/m^2) was given i.v. on day 2 with corticosteroid premedication (dexamethasone 8 mg orally 12 h before, at the time of, and 12 h after docetaxel administration). Calcitriol and docetaxel were given based on a schedule of six consecutive weekly administrations followed by a 2-week rest interval.

Cycles were administered if the serum white blood cell levels were $>3000/\text{mm}^3$, granulocytes $>1500/\text{mm}^3$ and platelets $>100\,000/\text{mm}^3$. Ondansetron 8 mg was administered at the beginning of each treatment cycle as anti-emetic medication. The patients continued to take analgesic medication at doses adjusted to provide optimum pain control. The chemotherapy was administered for a maximum of 24 cycles, or until disease progression or dose limiting toxicity.

The tumour response in patients with measurable lesions was evaluated using the RECIST criteria [8]. The serum PSA level was measured every 3 weeks; a PSA response was defined as a reduction from baseline of at least half for at least 3 weeks, whereas PSA progression was defined as an increase from nadir of $\geq 25\%$ in the men with no PSA response or $\geq 50\%$ for the others. The duration of PSA response, and duration of palliative response were defined as the interval between the time of starting chemotherapy and the last evaluations at which the response criteria were met. Time to progression was defined as the time from starting chemotherapy to the first occurrence of objective or PSA progression, or death from any cause.

The laboratory variables (blood and platelet counts, and a comprehensive screening profile) were assessed at baseline and every 3 weeks, and the patients had a weekly complete blood cell count and electrolyte profile, including corrected serum calcium, before chemotherapy.

The imaging studies included abdominal and pelvic CT or MRI, a bone scan, and chest radiography. All measurable disease was re-evaluated at 8-week intervals. Radionuclide bone scans were repeated as clinically indicated. In all cases, a baseline electrocardiogram was obtained, and a further cardiac evaluation used if indicated.

Toxicity was defined using the National Cancer Institute Common Toxicity Criteria, version 2.0. The treatment was delayed at the first occurrence of grade II haematological toxicity, and administered at the same dose after it returned to grade I or better. In the case of grade III or IV toxicity, the treatment was interrupted and a maximum of 3 weeks was allowed for recovery, after which the patients were withdrawn from the study. If there was a second episode of grade III or IV toxicity in the same patient, treatment was resumed after recovery and the subsequent administration of docetaxel was reduced to 20 mg/m^2 . Calcitriol was withheld for grade 2 or 3 hypercalcaemia until the return of normocalcaemia, with a maximum of delay of 2 weeks. Calcitriol was discontinued for grade 4 hypercalcaemia and for persistent grade 2 or 3 hypercalcaemia. Anaemia was treated as clinically indicated, and nausea and vomiting were treated symptomatically. Haematopoietic growth factors were only

given when neutrophil counts were $<1000/\text{mm}^3$, and continued until complete haematological recovery.

In accordance with Simon's 'minimax design', a sample size of 25 patients was planned, assuming a response rate of $\approx 10\%$ for other second-line chemotherapy, and a target level of interest of 30%, with an α of 0.05 and a β of 0.80.

RESULTS

From April 2003 to June 2006, 26 patients were enrolled (median age 68 years, range 54–79); 24 had bone metastases (92%). As first-line chemotherapy, 18 patients had been previously treated with a combination of weekly epirubicin 30 mg/m^2 and docetaxel 30 mg/m^2 , six with weekly docetaxel 30 mg/m^2 and two with 3-weekly docetaxel 75 mg/m^2 . Progression had occurred within 30, 45 and 60 days of previous docetaxel-based chemotherapy in eight, 13 and five patients, respectively. Patients continued to receive bisphosphonates, which had been started after failure of first-line chemotherapy in all patients with bone metastases. The median (range) interval between the end of first-line chemotherapy and the start of high-dose calcitriol and docetaxel was 13 (2–72) weeks (Table 1).

In all, 404 cycles of high-dose calcitriol and docetaxel were administered, with a median of 16 (3–23) cycles per patient. Two patients received only three cycles before being lost to follow-up, and were considered evaluable for response and toxicity. One patient was lost to follow-up after the ninth cycle, showing no severe toxicity or signs of progressive disease.

There was a decrease in PSA level by half or more in eight patients (31%, 95% CI 16.5–50.1); of these, seven had shown a PSA response and one had shown stable disease during the previous first-line therapy. The median (95% CI) duration of the PSA response was 3.8 (2.2–5.4) months.

There were responses in five of 18 patients previously treated with weekly epirubicin and docetaxel, and in three of six previously treated with weekly docetaxel alone. Seven patients (27%) had a stable PSA level for ≥ 12 weeks. There was stable disease in the two patients with measurable disease. The median time to PSA progression was 4.2 (2.6–5.8)

Variable	Value	TABLE 1 <i>The main patient characteristics</i>
Median (range) age, years	68 (54–79)	
ECOG performance status, n		
0	2	
1	17	
2	7	
Sites of metastases, n		
bone	21	
bone + prostate cancer	2	
bone + lymph nodes	1	
lymph nodes + prostate cancer	1	
lymph nodes + liver	1	
Median (range) PSA level, ng/mL	184 (58–812)	
Previous treatments, n		
prostatectomy	23	
radiotherapy	3	
estramustine	7	
Hormone therapies		
1	3	
2	21	
>2	2	
Previous first-line chemotherapy		
epirubicin + docetaxel	18	
docetaxel alone	8	
Previous second-line chemotherapy		
oral etoposide	12	ECOG, Eastern Cooperative Oncology Group.
epirubicin	2	

Adverse event	Grade			TABLE 2 <i>The number (%) of patients having the most frequent treatment-related adverse events</i>
	1	2	3	
Haematological				
neutropenia	17 (65)	4 (15)	2 (8)	
anaemia	15 (58)	8 (31)	2 (8)	
thrombocytopenia	13 (50)	6 (23)	1 (4)	
Non-haematological				
nausea/vomiting	7 (27)	3 (11)	1 (4)	
diarrhoea	3 (11)	1 (4)	0	
constipation	5 (19)	3 (11)	0	
nail changes	5 (19)	3 (11)	0	
dry eye/tears	8 (31)	2 (8)	0	
myalgia/arthralgia	7 (27)	3 (11)	0	
fatigue	12 (46)	9 (35)	1 (4)	
sensory neuropathy	8 (31)	1 (4)	0	
peripheral oedema	4 (15)	1 (4)	0	
epistaxis	5 (19)	2 (8)	0	
dyspnoea	7 (27)	1 (4)	0	
hypercalcaemia	16 (61)	1 (4)	0	
hypophosphataemia	13 (50)	11 (42)	0	

months; after a median follow-up of 19.6 months, 14 patients had died; the median (95% CI) survival was 9.3 (2–21) months.

The regimen was generally well tolerated, and there were no unexpected toxic effects (Table 2). There was no grade 4 toxicity or congestive heart failure, and all of the cycles

were administered on an outpatient basis. The most frequent side-effects were neutropenia, anaemia, thrombocytopenia, and fatigue, which were grade I or II in most cases; grade III neutropenia occurred in two patients, grade III anaemia in two and grade III thrombocytopenia in one. There was grade 3 vomiting in one patient after eight cycles, and the treatment was resumed after a 2-week interval. Grade III fatigue was reported one patient after 11 cycles; despite reducing the docetaxel dose and discontinuing calcitriol, treatment was then interrupted because of the persistence of this side-effect. There was grade 2 hypercalcaemia, probably related to calcitriol, in one patient after six treatment cycles; calcitriol was delayed for 2 weeks and then resumed after return to normocalcaemia. Most patients showed hypophosphataemia; the dose of docetaxel was reduced in three.

DISCUSSION

To date there is no standard second-line treatment for patients with metastatic HRPc previously exposed to docetaxel. The results of the present study suggest that the combination of weekly high-dose calcitriol with docetaxel is effective and tolerable for treating patients with metastatic HRPc who have progressed after docetaxel-based chemotherapy; the 31% PSA response compares favourably with the results observed in other phase II studies of second-line chemotherapy [9]. Other chemotherapeutic agents might be used after initial treatment with docetaxel, including those with first-line activity against the disease, a different mechanism of action from docetaxel, and that are well tolerated. In this setting, mitoxantrone and prednisone are treatments with manageable toxicity that can provide relief of symptoms in ≈30% of patients as first-line therapy [10]. However, the studies that evaluated the cross-over from docetaxel to mitoxantrone achieved disappointing results [11,12]. Although a clinical benefit was reported with the use of the anthracyclines, doxorubicin and epirubicin, as first-line chemotherapy in HRPc, no information exists about their use as second-line treatment [13,14]. Other older drugs e.g. vinorelbine, oral cyclophosphamide and etoposide, might be options for patients with progression after treatment with docetaxel, but these agents are mostly used in combination with other drugs as first-line

chemotherapy [15,16]. A retrospective analysis of the results obtained in HRPC with second-line chemotherapy including docetaxel plus cisplatin, or mitoxantrone, or vinblastine, doxorubicin or etoposide, reported no objective response and a 14% laboratory response [17]. Another recent study described modest activity for the combination of carboplatin and vinblastine as second-line therapy in 23 patients with HRPC that progressed during or after first-line chemotherapy [18].

Interesting results as salvage chemotherapy in HRPC might be obtained with the new drugs satraplatin, a third-generation platinum analogue, and ixabepilone, an epothilone, which acts, like taxanes, by stabilizing the polymerized microtubules [19,20].

In addition, a few patients stop the first-line treatment with docetaxel while still responding to the drug because they have completed a planned course of therapy or desire a break due to adverse effects. Thus there is an important distinction between patients who have truly docetaxel-resistant disease and those who have been exposed to docetaxel and now have progression, but might still have docetaxel-sensitive disease. In this group of patients a repeated treatment with docetaxel might be appropriate if progression occurs after a reasonably long interval. In the present study all of the patients discontinued first-line treatment with docetaxel because of progressive disease, which occurred during and within 60 days of docetaxel therapy. Therefore the characteristics of the patients seem to support an effective role of high-dose calcitriol in restoring sensitivity to the drug. However, seven of eight responses were in patients who had shown an initial response to previous docetaxel as first-line treatment. This finding suggests that the apparent restoration of sensitivity to the drug by using high-dose calcitriol might develop almost exclusively in those patients who previously had a response to first-line treatment with docetaxel-based chemotherapy.

A recent study investigated weekly high-dose calcitriol, estramustine and docetaxel in advanced HRPC, including patients who had previously been treated with docetaxel; only one of 11 patients previously treated with docetaxel met the PSA response criteria [21]. Despite these results appearing to be less

encouraging than ours, the comparison of these two small clinical studies is difficult because of the interpatient variability and the different treatment schedules.

Another point to consider is that commercially available formulations of calcitriol required patients to consume >60 capsules at a time, which is inconvenient and might impair adherence to therapy. This limitation led to the development of a high-dose formulation of calcitriol (DN-101, Novacea, Inc, South San Francisco, USA), which was used specifically for the ASCENT study; this large randomized trial showed a trend for a better PSA response for DN-101 calcitriol plus docetaxel over placebo plus docetaxel in patients with HRPC (63% vs 52%; $P=0.07$), and an improvement in estimated median survival (24.5 vs 16.4 months) [22].

All of the present patients who had bone metastases continued to receive bisphosphonate therapy, because it was shown recently that long-term treatment with zoledronic acid is safe and provides sustained clinical benefits for men with bone metastases from prostate cancer [23]. Bisphosphonates had been started after the failed first-line chemotherapy in all of the patients with bone metastases, and therefore it is unlikely that they contributed to the rate of response and palliation of salvage chemotherapy with calcitriol and docetaxel.

Although all of the present patients had been previously exposed to chemotherapy (mainly docetaxel plus anthracyclines), toxicity was very mild; there was grade 3 neutropenia in only two patients, and hypercalcaemia, probably related to calcitriol, in only one. Although the simultaneous use of bisphosphonates might have contributed to the low level of hypercalcaemia, there were no dose-limiting toxicities in other studies when oral calcitriol was administered at doses up to 38 µg for 3 consecutive days every 7 days [24,25].

The low toxicity of docetaxel was mainly due to the weekly schedule. The efficacy of weekly docetaxel seems to be similar to that of the usual 3-weekly schedule, but their comparative toxicities differ markedly, with moderate to severe myelosuppression being common when the drug is administered once every 3 weeks [26]. An attenuated docetaxel dose of 30 mg/m² for 6 of 8 weeks was chosen because patients with HRPC

previously exposed to chemotherapy are usually elderly, with a poor performance status and a limited bone marrow reserve. Interesting results were previously reported with docetaxel and oral calcitriol 0.5 µg/kg [3], which is equivalent to about 30–38 µg as a total dose in most patients. In the absence of a relationship between weight and calcitriol pharmacokinetics, we chose an intermediate and fixed dose of 32 µg for calcitriol, which might be safely added to docetaxel in a second- or third-line chemotherapy.

In conclusion, the present results suggest that weekly high-dose calcitriol and docetaxel seems to be an effective and well-tolerated treatment option for patients with metastatic HRPC previously exposed to docetaxel. High-dose calcitriol seems to restore the sensitivity to the drug in patients who had progressed after an initial response to docetaxel-based chemotherapy.

CONFLICT OF INTEREST

None declared.

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