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ORIGINAL ARTICLE

**Gianfilippo Bertelli · Abdelhamid Heouaine
Giuseppe Arena · Ambrogio Botto · Ornella Garrone
Ida Colantonio · Marcella Occelli · Elena Fea
Silvia Giubergia · Marco Merlano**

Weekly docetaxel and zoledronic acid every 4 weeks in hormone-refractory prostate cancer patients

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Abstract *Objectives*: To investigate the safety and efficacy of docetaxel and zoledronic acid in patients with hormone-refractory prostate cancer (HRPC), based on preclinical evidence of synergism between taxanes and bisphosphonates. *Methods*: Twenty-five patients with advanced HRPC received weekly docetaxel 30 mg/m^2: in 18 patients with symptomatic bone metastases and normal renal function, docetaxel was combined with zoledronic acid, 4 mg i.v. every 4 weeks. Premedication consisted of intravenous dexamethasone before docetaxel. No oral steroids were given. *Results*: Overall, 12 patients (48%) had a PSA response (reduction of 50% or more compared to baseline). A PSA response was achieved in 8/18 patients (44%) receiving concomitant docetaxel and zoledronic acid, and in 7/12 patients (58%) receiving docetaxel and zoledronic acid as first-line therapy. The weekly schedule of docetaxel resulted in a mean received dose intensity of 26 mg/m^2/week, or 87% of the planned dose intensity. Toxicity was mild and as expected for docetaxel. The median time to progression was 7 months, and the median overall survival was 16 months. *Conclusions*: Concomitant treatment with docetaxel and zoledronic acid is safe and has encouraging activity in HRPC. The combination should be evaluated in randomised clinical trials.

Keywords Hormone-refractory, prostate cancer · Docetaxel · Zoledronic acid · PSA

G. Bertelli (✉)
Singleton Hospital, South West Wales Cancer Institute,
Sketty, Swansea, SA2 8QA UK
E-mail: gianfilippo.bertelli@swansea-tr.wales.nhs.uk

A. Heouaine · O. Garrone · I. Colantonio · M. Occelli
E. Fea · S. Giubergia · M. Merlano
Department of Medical Oncology, S.Croce General Hospital,
Cuneo, Italy

G. Arena · A. Botto
Department of Urology, S.Croce General Hospital,
Cuneo, Italy

Introduction

Although androgen deprivation, the standard initial treatment of metastatic prostate cancer, results in effective disease control in the majority of patients, progression to an androgen independent status is almost universal. Secondary hormone manipulations such as the addition or withdrawal of oral antiandrogens, or the use of estrogens, have a low response rate and no impact on survival, which is usually <12 months. Until recently, chemotherapy was considered to have a minor role in hormone-refractory prostate cancer (HRPC), due to the lack of agents with sufficient activity [1]. The regimen of mitoxantrone plus low-dose steroids was proven to have palliative efficacy superior to steroids only, without however improving survival [2, 3].

Docetaxel—an inhibitor of tubulin depolymerization—has emerged in the last years as a promising new treatment in HRPC. Phase II studies have shown encouraging results in terms of prostate-specific antigen (PSA) reduction and survival with docetaxel at doses of 70–75 mg/m^2 every 3 weeks as a single-agent [4, 5]. Weekly administration of docetaxel has been shown in other tumor types to have similar efficacy with less neutropaenia than 3-weekly schedules [6]. Several phase II studies in HRPC have investigated weekly docetaxel, given at doses ranging between 25 mg/m^2 and 40 mg/m^2 in a variety of schedules (most commonly 6 weeks out of 8 weeks) [7–13].

Bone metastases are common in HRPC and contribute substantially to morbidity and decreased quality of life in this phase of the disease. Bisphosphonates have become the standard of care in patients with malignant bone disease: in HRPC, zoledronic acid (4 mg i.v. every 4 weeks) has been shown to significantly reduce bone pain and the incidence of skeletal complications compared to placebo [14]. The main action of zoledronic acid consists in inhibition of osteoclasts, but there is an expanding body of preclinical evidence suggesting direct

antitumor effects as well, with a possible synergism with taxanes [15–18].

We have investigated docetaxel, given in a 'dose dense' schedule of 30 mg/m^2 once a week without routinely scheduled treatment interruptions, in a group of patients with HRPC. Docetaxel was combined with zoledronic acid, 4 mg i.v every 4 weeks, in patients with symptomatic bone metastases and normal renal function. The primary endpoint of the study was the proportion of patients obtaining a PSA response (≥50% reduction of PSA level on two consecutive evaluations, at least 4 weeks apart).

Patients and methods

Eligibility criteria

Patients were required to have histopathologically proven adenocarcinoma of the prostate with documented metastases, or locally advanced or recurrent disease not suitable for surgery or radiotherapy, with evidence of disease progression (new metastatic lesions, or increasing serum levels of PSA documented on three measurements obtained at least a week apart) despite optimal androgen suppression (either by bilateral orchidectomy or LHRH analogues). Patients who were receiving combined androgen blockade (LHRH analogues or orchidectomy plus an antiandrogen) discontinued the antiandrogen and were observed for 4 weeks (6 weeks for bicalutamide) before starting chemotherapy to exclude antiandrogen withdrawal response. Testosterone levels were not routinely assessed, but LHRH analogues were continued during chemotherapy if well tolerated. Additional inclusion criteria were: PSA levels more than 10 ng/mL, ECOG performance status ≥2, and life expectancy ≥3 months. Patients were allowed to have had previous radiotherapy or chemotherapy if these had been discontinued for more than 1 month. Exclusion criteria were: WBC3, neutrophil count $<1{,}500/\ mm^3$, platelet count $<100{,}000/\ mm^3$, bilirubin > upper limit of normal (ULN). All patients gave written informed consent to treatment according to local ethical regulations.

Evaluations

Before starting the treatment, patients were evaluated with history, physical examination, full blood count, serum biochemistry, and serum PSA. Full blood count, serum biochemistry and toxicity assessment were repeated weekly before docetaxel administration; serum PSA and physical examination were repeated every 4 weeks. In patients with measurable disease, measurements were repeated every 8 weeks. PSA response was defined according to the recommendations of the Prostate Specific Antigen Working Group as a 50% or more decrease in PSA maintained on two consecutive evaluations at least 4 weeks apart [19]. PSA nadir was defined as the lowest value achieved that was confirmed by a second, equal or lower measurement. Response in measurable disease was assessed by RECIST criteria [20]. Progression was defined as a confirmed increase of PSA of 50% above nadir, or appearance of new lesions on bone scan, or progression in measurable disease as defined by RECIST criteria. Toxicity was graded according to the National Cancer Institute common toxicity criteria.

Treatment

Docetaxel was administered weekly at a dose of 30 mg/m^2 intravenously over 30 min. Premedication consisted of dexamethasone 20 mg intravenously before docetaxel, reduced to 8 mg after the first month of treatment if the patient did not develop hypersensitivity reactions or fluid retention. No oral steroids were given. Treatment was withheld in the following cases: neutrophil count $<1{,}000/mm^3$, platelet count $<75{,}000/mm^3$, bilirubin > ULN, and any other toxicity > grade 1 apart from alopecia or anaemia. Patients experiencing anaemia were treated with packed red cells transfusions and offered erithropoietin when appropriate, but treatment was not interrupted. Weekly docetaxel was resumed when toxicity was resolved or reduced to grade 1: patients who failed to recover within 4 weeks discontinued the treatment permanently, otherwise docetaxel was continued until progression or for a maximum of 6 months. The received dose intensity (mg/m^2/week) of docetaxel in each patient was calculated as the total dose per square meter administered to the patient, divided by the total treatment duration.

At the same time as starting of weekly docetaxel, patients with symptomatic bone metastases and normal serum creatinine were commenced on zoledronic acid, 4 mg intravenously over 15 min infused immediately before docetaxel. Zoledronic acid infusions were repeated every 4 weeks, on the same day of docetaxel, and continued after the completion of chemotherapy, provided that renal function remained normal.

Statistical considerations

The sample size was chosen based on the two-stage minimax design [21], with alpha = 0.05 and beta = 20%, aimed at rejecting the regimen if less than 2 of 15 patients respond in the first stage, and recommending it for further study if at least 6 of 25 patients respond in the second stage. Time to progression was calculated by the Kaplan-Meyer method from the date of the first docetaxel dose to the date of objective progression, or biochemical progression (PSA increase > 50% compared to nadir levels), or death in the absence of progression, whichever occurred first. Overall survival was calculated by the Kaplan-Meyer method from the date of the first

docetaxel dose to the date of death, or to the last date the patients was seen alive.

Results

Twenty-five patients were recruited between August 2001 and December 2003. Table 1 summarizes pretreatment characteristics of the patients. Briefly, median age at study entry was 71 years (range: 56–75), median performance status was one, median PSA was 141 ng/mL (range: 15–1,404). Twenty-three patients (92%) had bone metastases and eight (32%) had measurable disease. Eight patients (32%) had received prior chemotherapy with mitoxantrone plus prednisone.

In total, 377 weekly doses of docetaxel were administered: the median number of doses per patient was 14 (range: 3–32). Treatment was interrupted because of progression in seven patients, toxicity in 10, patient or physician's preference in one. In the remaining patients, a maximum of 6 months of treatment was administered: one patient with an objective response elected to continue the treatment up to 8 months. Eighteen patients (72%) received concomitant zoledronic acid: of the seven patients who did not receive it, two were without bone metastases, and five with bone metastases but mildly impaired renal function or lack of bone pain.

Dose intensity

Fifteen patients (60%) had docetaxel withheld on one or more weeks because of toxicity or patient request. The median received dose intensity of docetaxel in the whole group of patients was 26 mg/m^2/week, representing 87% of the planned dose intensity of 30 mg/m^2/week.

Table 1 Patient characteristics

No. of patients	25
Age (years)	
Median (range)	71 (55–75)
ECOG performance status	
0	11(44%)
1	(48%)
2	(8%)
Gleason score	
Median (range)	7 (4–10)
PSA (ng/mL)	
Median (range)	141 (15–1,404)
Site of metastases	
Bone	14 (56%)
Bone and soft tissues	5 (20%)
Bone and viscera	4 (16%)
Soft tissues	2 (8%)
Prior treatments for primary tumor	
Radical prostatectomy	5 (20%)
Radical radiotherapy	9 (36%)
Hormone therapy only	11 (44%)
Prior chemotherapy	
No	17 (68%)
Yes	8 (32%)

Toxicity

Table 2 summarizes toxicity results. There were no treatment-related deaths. Ten patients (40%) interrupted docetaxel because of toxicity: four had onycholysis with subungueal infection, two had pleural effusions, and four had grade III asthenia. No significant side effects were attributed to zoledronic acid infusions and no patient had to discontinue it because of renal toxicity.

Response

Biochemical and objective response results are summarized in Table 3. Overall, 12 patients (48%: 95% confidence interval [CI] 28% to 66%) had a PSA reduction of 50% or more compared to baseline, with a median duration of 8 months. PSA response rate was higher (64%: 11/17) among chemotherapy-naïve patients. An explorative analysis of the subgroup of 18 patients treated with concomitant docetaxel and zoledronic acid showed that 8 patients (44%) obtained a PSA response; also in this subgroup, PSA response rate was higher among chemotherapy-naïve patients (7/12, 58%).

Since PSA response was the main endpoint of the trial, quality of life and pain intensity were not formally assessed, although it was noted that most patients with a PSA response were able to reduce their analgesic use.

Among eight patients with measurable disease, four (50%) obtained a partial response (of lymph node and skin metastases) and one (12.5%) had stable disease.

Time to progression and survival

Overall, the median time to progression was 7 months, and the median overall survival was 16 months.

Discussion

In 2004, the results of a landmark randomised trial (TAX 327) [22] have demonstrated for the first time a survival benefit from single agent docetaxel in HRPC. In TAX 327, 1,006 men with metastatic HRPC were randomised to three arms: (a) docetaxel 75 mg/m^2 every 3 weeks; (b) docetaxel 30 mg/m^2 weekly for 5 weeks every 6; (c) mitoxantrone 12 mg/m^2 every 3 weeks. All patients also received prednisone 5 mg twice daily. The PSA response rates were 45% with 3-weekly docetaxel, 48% with weekly docetaxel, and 32% with mitoxantrone ($P = 0.0005$ and $P = 0.0001$, respectively, for 3-weekly and weekly docetaxel vs. mitoxantrone). The 3-weekly docetaxel arm had the longest median overall survival at 18.9 months, compared to 17.3 months for weekly docetaxel and 16.4 months for mitoxantrone ($P = 0.009$ and $P = 0.3$, respectively, for 3-weekly and weekly

Table 2 Toxicity

	Grade 1		Grade 2		Grade 3	
	n	Percent	n	Percent	n	Percent
Neutropaenia	8	32	2	8	0	0
Anaemia	8	32	5	20	3	12
Thrombocytopaenia	1	4	1	4	1	4
Nausea and vomiting	11	44	3	12	0	0
Asthenia	11	44	7	28	6	24
Fluid retention	5	23	3	12	0	0
Mucositis	7	28	2	8	2	8
Onycholysis	1	4	1	4	4	16
Alopecia	6	24	8	32	–	–
Other	7	28	6	24	4	16

Table 3 Results

	n	Percent
Biochemical response (n = 25)		
PSA response (≥50% reduction)	12	(48%)
PSA reduction ≥90%	6	(24%)
PSA reduction between 25–50%	7	(28%)
PSA reduction < 25% or increase	6	(24%)
Objective response in patients with measurable disease (n = 8)		
Partial response	4	(50%)
Stable disease	1	(12.5%)
Progression	3	(37.5%)

docetaxel vs. mitoxantrone). Another phase III trial published at the same time of TAX 327, SWOG 99-16 [23], investigated docetaxel combined with estramustine and provides further evidence for a survival advantage of docetaxel over mitoxantrone.

After the publication of these studies, 3-weekly docetaxel plus prednisone is likely to be considered the standard of care in HRPC. Weekly docetaxel, however, may still be regarded as an alternative regimen for some patients, especially when the avoidance of neutropaenia is seen as a priority (e.g. patients with impaired bone marrow reserve as a result of extensive metastatic involvement or prior radiotherapy). In this context, our study of weekly docetaxel in HRPC demonstrated a PSA response rate of 48% overall, and 64% in the subgroup of chemotherapy-naïve patients. This compares favourably with the response rate observed in other published studies of single-agent weekly docetaxel, including the weekly arm of the TAX 327 trial (table 4).

Two characteristics of our study deserve to be underlined. First, our regimen did not allow for scheduled treatment breaks: thus, the planned dose intensity of docetaxel was 30 mg/m^2/week. As expected, some of the weekly doses were eventually omitted for toxicity or patients' request: thus, the median received dose intensity (RDI) was 26 mg/m^2/week, or 87% of the planned dose intensity. The importance of dose intensity, and in particular of RDI, of docetaxel in HRPC has not been sufficiently investigated. As shown in Table 4, the majority of studies of weekly docetaxel in HRPC (including the present study) have used a higher planned dose intensity than in the weekly arm of the TAX 327 trial, i.e. > 25 mg/m^2/week. The weekly arm of TAX 327 was designed to deliver the same total dose and dose intensity of the 3-weekly arm, but it could be argued that in this way one of the advantages of a weekly scheduling—i.e. the possibility to increase dose intensity without excessive toxicity—was lost. In our opinion, this could help explain why weekly docetaxel was not as effective as 3-weekly docetaxel in TAX 327, in contrast with the results of phase III trials in metastatic breast cancer [24] and in advanced non-small cell lung cancer [25], where weekly and 3-weekly docetaxel show similar efficacy.

Secondly, a subgroup of 18 patients in our study received the powerful bisphosphonate zoledronic acid in combination with docetaxel. Zoledronic acid is currently employed to reduce the incidence of skeletal-related events in HRPC[14] and is not known to have any clinical antitumor effect: in vitro, however, it has shown direct antitumor effects, and a potential synergism with taxanes [15–18]. Only one other small clinical trial [26] has so far addressed the concomitant use of docetaxel and zoledronic acid in patients with HRPC: 14 patients with HRPC (five of whom had received previous chemotherapy) were treated with docetaxel 75 mg/m^2 and zoledronic acid 4 mg i.v., both every 4 weeks, obtaining a PSA response in 8/14 patients (57%). In our study, 8/18 patients (44%) treated with weekly docetaxel and 4-weekly zoledronic acid had a PSA response: considering only chemotherapy-naïve patients, the PSA response rate was 7 of 12 (58%). Due to the uncontrolled design of these reports, the contribution of zoledronic acid to the results is difficult to assess, but the observation that zoledronic acid did not add to the toxicity of the treatment is encouraging. Both docetaxel and zoledronic acid are part of the current armamentarium in the treatment of HRPC, therefore the concomitant use of the two agents is not unlikely in clinical practice. The combination of docetaxel and zoledronic acid deserves to be

Table 4 Phase II and III results of weekly single-agent docetaxel

Author	No. of patients	Percentage of patients with prior chemotherapy	Docetaxel dose (mg/m^2)	Routinely scheduled off-weeks	Planned dose intensity/RDI (mg/m^2/week)	PSA response (percent)
Berry[7]	60	26.7	36	2 out of 8	27/NR	41
Beer[8]	25	0	36	2 out of 8	27/24	46
Gravis[9]	30	50	35	2 out of 8	26/NR	48
Karavasilis[10]	16	18.7	30	1 out of 2	15/NR	38
Petrioli[11]	27	100	25	None	25/NR	33
Kojima[12]	10	30	30	2 out of 8	22.5/NR	50
Ferrero[13]	64	0	40	2 out of 8	30/27	64
Tannock[22]	334	0	30	1 out of 6	25/NR	48
Present study	25	32	30	None	30/26	48

RDI Received dose intensity (median) *NR* not reported

rigorously tested in phase III studies to elucidate its role in prostate cancer.

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