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ORIGINAL ARTICLE

Survival benefit during zoledronic acid and docetaxel-based chemotherapy in metastatic hormone-refractory prostate cancer patients: an institutional report

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Summary

Purpose: *To assess the overall survival (OS) of metastatic hormone-refractory prostate cancer (mHRPC) patients when treated with zoledronic acid (ZOL) in combination with docetaxel-based chemotherapy (docetaxel combined with estramustine or oxaliplatin or gemcitabine).*

Methods: *A retrospective chart review of mHRPC patients in our clinic was performed. At the time of data collection, 23 patients with mHRPC were identified, of which 15 were still alive at data analysis. Survival data was analyzed through Kaplan-Meier methodology. OS stratification by prostatic specific antigen (PSA) response (50% and 80% decline) and multivariate analysis of prognostic variables were also conducted.*

Results: *182 cycles of chemotherapy (mean 8.27 cycles, range 1-23) were recorded. Median OS was 26 months (range 5-56; 95% CI: 4.0-48.0). No patient achieved complete response (CR), 5 (21.7%) showed partial response (PR), 2 (8.7%) minor response (MR), 7 (30.4%) stable disease (SD) and 9 (39.1%) progressive disease (PD). Twelve (52.2%) patients exhibited a decrease in PSA levels >50% (9 of 12 >80%). No association of age, PSA response, or tumor response with OS could be demonstrated. The most frequent toxicities were anaemia (52.1%) and neutropenia (26%).*

Conclusion: *In our clinical setting, ZOL and docetaxel-containing chemotherapy was a beneficial therapeutic scheme for the patients in terms of safety and survival.*

Key words: docetaxel, overall survival, prostate cancer, toxicity, zoledronic acid

Introduction

Prostate cancer is the most common non-cutaneous cancer among men [1]. More than 65% of all prostate cancers will be diagnosed in men 65 years of age and older, with 9% being 70 years of age or older. Unfortunately, 22% of men diagnosed with prostate cancer will initially present with metastatic disease [2]. Most will be diagnosed at an early stage, but a significant number will still progress and die from mHRPC [3]. While the initial response is favorable in most men, documented with improvement in pain, shrinkage of soft tissue metastases, and decreases in PSA, the median duration of response and OS ranges below 24 months. Testosterone-targeting therapy via surgery or hormonal therapy, leading to castration, is the mainstay of treatment for patients with metastatic disease [4].

Bone is the most common site for metastasis in prostate cancer and of particular clinical importance due to the prevalence of this disease. Tumor lesions in bones result in considerable morbidity and increased demands on health care resources, adversely affecting patients' quality of life (QoL). Treatment with biphosphonates is shown to reduce skeletal morbidity, complications and pain from malignant bone lesions [5]. Furthermore, preclinical evidence indicates that biphosphonates may also have direct anti-tumor effects [6].

ZOL is a biphosphonate approved for the treatment and prevention of skeletal complications related to primary bone lesions from multiple myeloma and secondary bone metastases from all solid tumors [7]. Results from clinical trials, as well as from clinical observations, strongly support that ZOL prevents bone loss in patients with prostate cancer receiving androgen deprivation therapy [8], decreases the incidence, delays

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the onset and reduces the risk of skeletal related events compared to placebo [7-11].

In terms of chemotherapeutic agents targeting mHRPC, to date, 3 chemotherapeutic drugs (mitoxantrone, estramustine and docetaxel) have been approved by the US Food and Drug Administration (FDA) for first-line treatment. Among these, docetaxel-based chemotherapy is the treatment of choice. Docetaxel is a semisynthetic, microtubule-targeting taxane, inhibiting mitosis and cell growth [12,13]. Docetaxel's approval was based upon data from two large randomized phase III trials in 2004 (TAX-327 and SWOG 9916), both showing significant improvement in OS compared with the referenced standard treatment (18.9 for docetaxel vs. 16.5 months for mitoxantrone and 17.5 months for docetaxel plus estramustine vs. 15.6 months for mitoxantrone plus prednisone) [14,15].

Taking under consideration that recent data support that ZOL and docetaxel exhibit synergistic activity in inhibiting proliferation of prostate carcinoma cells *in vitro* [16], the purpose of the present study was to present the clinical profile of patients with mHRPC when treated with ZOL in combination with docetaxel-based chemotherapy (docetaxel plus estramustine or oxaliplatin or gemcitabine) in our institution. We aimed also to assess the impact of various factors, among which the degree of PSA decline on the prognosis of longer OS.

Methods

Study design and endpoints

A retrospective chart review was carried out on patients having received ZOL and docetaxel-based chemotherapy for metastatic, hormone refractory prostate cancer from November 2003 to October 2009 in our clinic. Eligibility criteria for study inclusion were confirmation of mHRPC by 3 sequential rises in PSA with castrate levels of serum testosterone (<50 ng/dL), and metastatic disease detected by imaging methods (x-ray, computed tomography or bone scan).

The primary endpoint in the present study was OS. Secondary endpoints included objective response rate (ORR), stable disease rate (SDR), manifestation of haematologic and non-haematologic toxicities, as well as OS stratification by PSA response (50% and 80% decline) and univariate and multivariate analysis of prognostic variables.

Data collection

The data collected were: date of mHRPC diagnosis (defined as the date of the third consecutive PSA rise), prior therapy received, dates and total number of cycles of docetaxel-containing chemotherapy, concomitant or palliative therapy, percent of PSA decline (based on the last available value), tumor response, toxic reactions and death.

Study definitions

Tumor responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST), as CR, PR, MR, SD or PD [17,18], every 8 weeks. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria, version 3.0 [19]. OS was defined as the time elapsed from the first day of chemotherapy administration till death. The secondary efficacy variables, ORR and SDR, were calculated based on tumor response types. ORR was defined as the sum percentage of patients who showed CR, PR and MR. SDR was defined as the sum percentage of patients who showed CR, PR, MR and SD.

Statistical analysis

Kaplan-Meier curves were constructed to estimate OS time from the first administration of docetaxel. OS was also analysed after stratifying patients by PSA response (50% and 80% decline from baseline) using the log-rank (Mantel-Cox) test. Univariate Cox regression analysis (Cox proportional hazards model) was performed testing age, achievement of ORR and percentage PSA decline, as prognostic factors of OS. Statistical analysis was performed with the statistical package SPSS 17.0.

Results

Patient characteristics and treatment

A total of 23 patients had stage IV mHRPC, with mean age of 73.5 years at diagnosis (range 47-89). The demographic and related disease characteristics of the patients are shown in Table 1. Prior to the initiation of docetaxel-based chemotherapy the majority of the patients (76.2%) had received hormonal therapy, 19% radiotherapy and chemotherapy (estramustine, etoposide) and only one (4.8%) was subjected to surgery (radical prostatectomy) (Table 2).

Upon diagnosis of mHRPC, patients received ZOL (4 mg i.v. every 3 weeks) and first line docetaxel-containing chemotherapy (docetaxel 75 mg/m^2 i.v. every 3 weeks, along with estramustine 280 mg orally

Table 1. Baseline patient characteristics (n = 23)

Characteristics	*n*	*%*
Age, years (mean ± SD)	73.5 ± 6.0	
ECOG performance status		
0	3	13
1	10	43.4
2	10	43.4
Gleason score at initial cancer diagnosis		
≤6	1	4.3
7	0	0
8-10	6	26
NA	16	69.5
Metastasis		
Bone	23	100
Liver	3	13
Lungs	2	8.7
Lymph nodes	2	8.7
Bladder	1	4.3
NM	3	13

ECOG: Eastern Cooperative Oncology Group; NA: not applicable due to unresectable disease, NM: non measurable by any imaging technique

Table 2. Patient therapy prior to docetaxel-containing chemotherapy

Prior therapy	*n*	*%*
Hormonal therapy	16	69.5
GnRH agonists (goserelin, triptorelin or leuprolide)	14	60.9
Antiandrogens	11	47.8
Radiotherapy	4	17.3
Chemotherapy	4	17.3
Docetaxel	1	4.3
Estramustine	3	13
Etoposide	1	4.3
Surgery	1	4.3
Zoledronic acid	1	4.3
None	1	4.3
Not available	5	21.7

GnRH: gonadotropin-releasing hormone

twice a day, days 1-5 of a 3-week cycle) for 182 cycles (mean 8.27, range 1-23; Table 3). During this treatment 8 patients died and 15 progressed or manifested toxic reactions and were thus switched to second-line chemotherapy (oxaliplatin plus estramustine or gemcitabine plus paclitaxel). However, 10 out of the 15 (66.7%) patients were still administered docetaxel in 3-week cycles (115 cycles in total, mean 8.21, range 1-34). Differentiations in treatment characteristics involved the combination of chemotherapeutic and palliative agent used. After 15 second-line chemotherapy cycles, one patient proceeded to third-line treatment with paclitaxel-containing chemotherapy. All second- and third-line treated patients were still alive at the time of analysis.

Table 3. Therapy administered after diagnosis of mHRPC

Therapy administered	*n*	*%*
First line		
Number of patients (n, %)	23	100
Number of cycles (mean, range)	8.27	1-23
Chemotherapy agents		
Docetaxel	21	91.3
Estramustine	15	65.2
Oxaliplatin	2	8.7
Paclitaxel	2	8.7
Supportive/palliative agents		
Zoledronic acid	23	100
Goserelin	1	4.3
Second line		
Number of patients	15	100
Number of cycles (mean, range)	8.21	1-34
Chemotherapy agents		
Docetaxel	10	66.6
Estramustine	4	26.6
Oxaliplatin	6	40
Paclitaxel	2	13.3
Gemcitabine	1	6.7
Supportive/palliative agents		
Zoledronic acid	11	73.3
Vinorelbine tartrate	7	46.7
Calcitriol	1	6.7
Third line		
Number of patients	1	100
Number of cycles (range)	13	(1-13)
Chemotherapy agents		
Paclitaxel	1	100
Supportive/palliative agents		
Zoledronic acid	1	100
Vinorelbine tartrate	1	100

Survival analysis

During the follow-up period, 8 (34.8%) patients died and disease monitoring was continued in the remaining 15 (65.2%) patients. The median OS from initiation of ZOL and docetaxel was 26 months (range 5-59; 95% CI: 4.0-48.0) for the entire group (Figure 1). Since not all patients had died from mHRPC, the exact calculation of the primary endpoint was ongoing. Log-rank test comparing distribution of survival curves according to presentation of SDR or ORR did not reveal significant differences in patient OS. Stratifying patients by those having no, 50% or 80% PSA decline, 42 days after docetaxel initiation also did not correlate with OS (Figures 2 and 3).

Tumor response

CR was not documented by imaging methods in any patient. Five patients (21.7%) achieved PR, 2 (8.7%) MR, 7 (30.4%) SD, while 9 (39.1%) patients

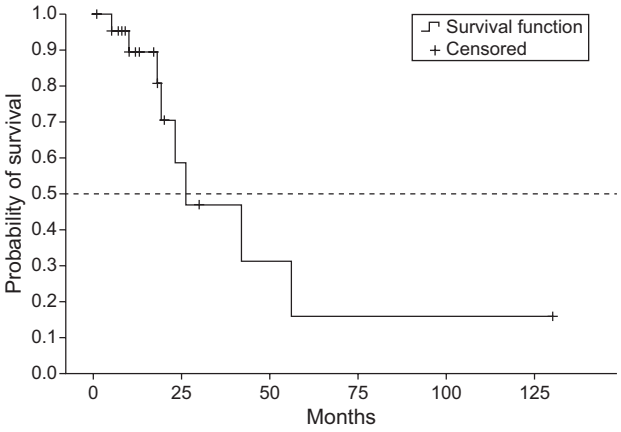

Figure 1. Kaplan-Meier overall survival curve of patients. Crosses in the graph line represent patients living at the time of data analysis (censored data).

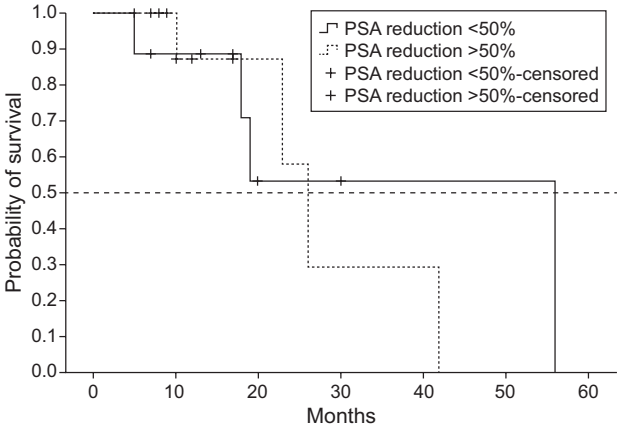

Figure 2. Kaplan-Meier survival curve of patients showing PSA decline >50% (dotted line) and PSA decline <50% (solid line). Crosses in the graph line represent patients living at the time of data analysis (censored data). Log-rank, p =0.748.

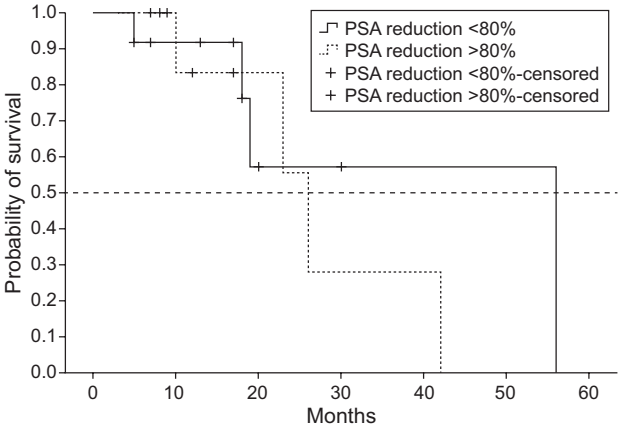

Figure 3. Kaplan-Meier survival curve of patients showing PSA decline >80% (dotted line) and PSA decline <80% (solid line). Crosses in the graph line represent patients living at the time of data analysis (censored data). Log-rank, p=0.534.

progressed during the observational period. ORR was estimated at 30.4% (95% CI: 11.9-54.7%), and SDR at 60.9% (95% CI: 34.7-79.6%).

PSA response

The mean PSA decline was 15.04% (range -99.9 to +640.7; Table 4). The PSA decline was >50% of the baseline value for 12 (52.1%) of the patients, out of whom 9 (39.1%) presented with decrease >80% of the baseline value.

Cox regression analysis

Age, ORR, SDR, and PSA response were tested and not identified as predictors of patients' OS in the univariate analysis (Table 5).

Safety analysis

The major haematological and non-haematological toxicities reported are tabulated in Table 6. Neither WHO grade IV toxicities nor deaths related to toxic reactions were observed. Nine patients (39.1%) did not exhibit any adverse event. Out of 25 adverse events in total, the most frequent were grade I anaemia and neu-

Table 4. Decline in PSA levels after docetaxel-based chemotherapy

PSA levels (mean, range)		
Prior to docetaxel administration	181.9 μg/L	(0.03-1156)
After docetaxel administration	63.7 μg/L	(0.02-628.2)
PSA change (mean change %, range)	+15.04	(-99.9, +640.7)
50% PSA decline (PSA_{50}), patients, n (%)		
Yes		12 (52.2)
No		11 (47.8)
Total		23 (100)
80% PSA decline (PSA_{80}), patients, n (%)		
Yes		9 (39.1)
No		14 (60.9)
Total		23 (100)

PSA: prostate specific antigen

Table 5. Univariate analysis for the association of age, ORR achievement and PSA decline with patients' OS

Variable	*Score*	*p-value*
Age	0.372	0.542
ORR achievement	0.094	0.760
SDR achievement	0.211	0.646
50% PSA decline	0.001	0.980
80% PSA decline	0.237	0.627

ORR: objective response rate, SDR: stable disease rate, PSA: prostate specific antigen

Table 6. Haematologic and non-haematologic toxicities observed in this study

Toxicities	*Patients, n*	*%*
Hematologic		
Anaemia		
Total	12	52.1
Grade I	8	34.8
Grade II	4	17.3
Neutropenia		
Total	6	26
Grade I	5	21.7
Grade III	1	4.3
Thrombocytopenia		
Total	2	8.7
Grade II	2	8.7
Non-hematologic/other		
Nausea/vomiting		
Total	1	4.3
Grade II	1	4.3
Haemorrhage (gingival bleeding)		
Total	2	8.7
Grade II	2	8.7
Neurotoxicity		
Total	1	4.3
Grade II	1	4.3
Osteonecrosis of the jaw		
Total	1	4.3

tropenia occurring in 7 (30.4%) and 5 (21.7%) patients, respectively. The only grade III toxicity recorded was neutropenia in one (4.3%) patient. Non-haematologic toxicities observed included, nausea/vomiting, haemorrhage, neurotoxicity and osteonecrosis.

Discussion

Treatment of patients with mHRPC is currently acknowledged to involve the administration of docetaxel, estramustine, prednisone/hydrocortisone and/or mitoxantrone; This scheme, initially proposed by the Cancer Care Ontario (CCO) guideline and, subsequently endorsed by the American Society of Clinical Oncology [20], has shown to be both effective and safe in two phase II trials in our institution [21,22]. However, the short life expectancy after diagnosis of hormone-resistant disease raises other issues, aside to prolonging survival, as equally essential for the treatment of mHRPC patients. Given the increased age of such patient population, their unwillingness to endure disease and treatment-related morbidities and most importantly the increased pain index due to bone metastases, administration of palliative treatments in combination with effective chemotherapeutic agents, personally adapted to each patient health status, aims at ameliorating the patients' QoL [23].

In patients with mHRPC, pathologic fracture is an example of skeletal complication associated with increased pain, deterioration of the patient's QoL and reduced survival [24,25]. In this context, ZOL is a third-generation biphosphonate approved for prevention and treatment of skeletal events related to malignant bone metastasis [26], and the only biphosphonate shown to significantly reduce the occurrence of skeletal morbidity in patients with bone metastases from prostate cancer [27]. Furthermore, recent developments propose that ZOL should be considered for administration throughout the treatment continuum of all prostate cancer patients, regardless of their hormonal status or the evidence of bone metastases [28].

In our institutional setting, ZOL was administered in combination with docetaxel-based chemotherapy to all mHRPC patients retrieved from our medical records, presenting median OS of 26 months and stable or responding disease in 14 cases (60.8% of the patients), thereby indicating that this therapy scheme was beneficial in terms of survival compared to results from previous clinical studies (median OS ranging between 14 and 18 months [14,15,21,22,29]. Furthermore, survival benefit in this study coincided with marked decrease in PSA levels; 57.1% of patients showed a PSA decline >50% and 42.9% >80%, after administration of ZOL and docetaxel-based chemotherapy. Due to the small number of patients in our study we were not able to show statistically significant correlation of survival with known predictors such as PSA response [30]. Whether our findings arise from synergy between docetaxel and ZOL, already shown in *in vitro* studies [16,31], herein reported for the first time *in vivo,* remains to be explored.

No significant safety issues were met in patients administered ZOL and docetaxel-based chemotherapy. No grade IV toxicities were recorded. Among ZOL known toxicities (renal function impairment, osteonecrosis, hypercalcemia, fatigue, anaemia, flu-like symptoms, fever, swelling, myalgia) [32], only 12 cases of anaemia were recorded. A single case of osteonecrosis of the jaw was encountered in the ZOL treatment which was treated conservatively with antibiotics under the supervision of a dentist and a jaw surgeon. After resolution, the patient resumed his therapy cycles with ZOL given every other cycle.

In our study, ZOL and docetaxel-containing chemotherapy, supplemented according to each patient's profile, were beneficial for the patients in terms of safety and survival. In the future, more large multicentric clinical studies are needed to verify our results and complete the present findings.

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