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Original Article

Docetaxel in very elderly men with metastatic castration-resistant prostate cancer

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ABSTRACT

Purpose: To evaluate the use of docetaxel in very elderly men with metastatic castration-resistant prostate cancer (mCRPC) treated in routine clinical care.
Methods: A retrospective case series of men with mCRPC aged ≥80 years and treated with docetaxel between July 2006 and June 2012 at three community hospitals in Melbourne, Australia.
Results: Twenty patients were identified, with a median age of 83 years (range 80–93 years). Aside from one patient treated weekly, all patients were treated with a 3-weekly regimen of docetaxel with a median of six cycles (range 1–10 cycles) delivered. Eight patients (40%) had an initial dose reduction and 11 patients (55%) had subsequent dose delays or reductions. Eight patients (40%) completed planned treatment. Grade 3/4 hematologic toxicity was observed in nine patients (45%), and five patients (25%) were admitted to hospital with chemotherapy-related complications. Prostate-specific antigen (PSA) response was assessable for 16 patients, of whom nine (56%) had a PSA response of ≥50% and one (6%) had a PSA-complete response. The median overall survival in this cohort was 13.4 months.
Conclusions: Very elderly patients (80 + years) with mCRPC are infrequently included in clinical trials, yet the use of chemotherapy in this population is likely to increase. Our series demonstrates significant response rates to docetaxel chemotherapy, but that a substantial number of patients had treatment-related complications. This highlights the need for careful patient selection and optimization of chemotherapy dosing.

1. Introduction

Prostate cancer is the second most commonly diagnosed malignancy in men worldwide.[1] Approximately three-quarters of the registered cases occur in developed countries, with Australia and New Zealand recording the highest incidence rates. It is predominantly a disease of the elderly, with incidence and mortality increasing with age. In an analysis of men with prostate cancer from the Surveillance, Epidemiology, and End Results database, elderly patients were more likely to present with metastatic disease at diagnosis and those aged >75 years accounted for over half of prostate cancer-related deaths.[2]

Prostate cancer is typically hormone-responsive, however, once castration resistance sets in, median overall survival is generally <2 years.[3] Docetaxel was the first agent to offer a survival advantage in metastatic castration-resistant prostate cancer (mCRPC). It has been shown in two randomized phase III trials to improve survival and quality of life compared to mitoxantrone.[4,5] Subsequently, 3-weekly docetaxel at 75 mg/m^2 has become the current standard first-line treatment for mCRPC.

In elderly patients, a significant concern with this regimen is the risk of serious toxicity, in particular, myelosuppression and sepsis. In a subgroup analysis of the landmark TAX327 trial, men aged ≥75 years had significantly higher rates of infection and required more frequent dose reductions than younger patients.[6]

This retrospective study was performed to review the use of docetaxel in very elderly men (aged ≥ 80 years) with mCRPC treated in a community setting. In particular, the aims were to

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explore dosing practices in routine clinical care, and the tolerability and efficacy of docetaxel in this group of patients.

2. Methods

2.1. Patients

Men with mCRPC aged ≥80 years and treated with docetaxel between 1 July 2006 and 30 June 2012 were identified from the databases of three hospitals in Melbourne, Australia. Clinicopathologic, treatment, and response data were extracted from a retrospective review of hospital charts and pharmacy dispensing records.

2.2. Variables

Baseline patient characteristics of interest were Eastern Cooperative Oncology Group (ECOG) performance status, and the presence of the following comorbidities: ischemic heart disease, chronic pulmonary disease, diabetes, renal impairment (estimated glomerular filtration rate < 60 mL/min) and cognitive or mood disorders. Disease characteristics at baseline were obtained, including time to castration resistance, Gleason score, sites of metastatic disease, and the presence of pain requiring regular opioid analgesia.

Initial planned docetaxel doses and schedules were recorded, along with subsequent dose modifications and reasons for discontinuing treatment. Hematologic toxicities and treatment-related complications resulting in hospital admissions were noted. Serum prostate-specific antigen (PSA) was recorded pretreatment and post-treatment to calculate the best PSA response. Symptomatic response to treatment was recorded where applicable. Overall survival was calculated from the first dose of docetaxel to the date of death or last follow up.

2.3. Statistical analysis

Individual patient data were tabulated and summarized using descriptive statistics. Overall survival was calculated using the Kaplan–Meier method. All statistics were calculated using Graphpad Prism V6.01 (GraphPad Software, Inc., La Jolla, CA, USA).

2.4. Ethics approval

Approval for this study was obtained from the research and ethics committees of the participating institutions. Patient consent was not obtained due to the retrospective nature of the study, and no identifying or sensitive information is presented.

3. Results

3.1. Patient characteristics

Twenty men were identified with a median age of 83 years (range 80–93 years). Patient and disease characteristics are presented in Table 1. ECOG performance status was documented for 13 (65%) patients, who were all of a good performance status of ECOG 0 or 1. Fifteen (75%) patients had at least one comorbid condition, with renal impairment ($n = 11$) and ischemic heart disease ($n = 10$) the most commonly observed.

Eleven (55%) patients had bone-only disease, two (10%) patients had visceral metastases, and one (5%) patient had local recurrence only. Pretreatment serum PSA was available for all but one patient, with a median of 140 ng/mL (range 13–1810 ng/mL). Three (15%) patients had pain requiring daily opioid analgesia.

3.2. Treatment delivery

Treatment details are presented in Table 2. Aside from one patient treated weekly, all received the standard 3-weekly regimen of docetaxel 75 mg/m^2, with a median of six cycles received (range 1–10). All patients also received prednisolone 10 mg/day. Eight (40%) patients commenced treatment with an initial dose reduction and 11 (55%) patients required subsequent dose modifications, including three patients who had commenced treatment at a reduced dose.

Eight (40%) patients completed their planned treatment, with six and two patients receiving six and 10 cycles, respectively. Two (10%) patients discontinued treatment early for toxicity, five (25%) patients due to other medical problems, and four (20%) patients stopped due to disease progression.

Table 1
Baseline characteristics of 20 patients aged ≥80 years who received docetaxel for metastatic castrate-resistant prostate cancer.

Patient	Age (y)	ECOG	Number of comorbidities	Time to castration resistance (y)	Gleason score	Baseline PSA (ng/mL)	Metastatic disease sites	Pain requiring daily opioid analgesia
1	85	1	2	10	10	113	Bone	Yes
2	80	N/A	2	1	10	869	Bone and lymph nodes	N/A
3	93	1	0	8	N/A	1760	Bone	No
4	83	1	2	13	N/A	524	Bone and lymph nodes	No
5	87	1	2	5	8	61	Bone	Yes
6	80	1	2	4	7	22	Bone	No
7	80	1	1	6	8	13	Lymph nodes	No
8	82	1	1	17	N/A	112	Bone	No
9	83	1	1	11	N/A	N/A	Bone	No
10	88	1	1	3	N/A	18	Visceral	Yes
11	82	1	0	3	9	125	Bone	No
12	83	1	0	4	N/A	1810	Bone and visceral	No
13	81	N/A	2	7	7	71	Lymph nodes	No
14	82	N/A	0	4	6	372	Bone	No
15	80	N/A	2	9	8	107	Local recurrence	No
16	80	0	2	16	7	233	Bone	N/A
17	80	N/A	2	2	9	437	Bone and lymph nodes	No
18	83	N/A	1	4	7	339	Bone and lymph nodes	No
19	85	0	0	12	7	161	Bone	No
20	87	N/A	1	3	7	140	Bone	No

ECOG, Eastern Cooperative Oncology Group performance status; N/A, data not available; PSA, prostate specific antigen.

Table 2
Treatment delivery, toxicities, and prostate specific antigen (PSA) response of 20 patients aged ≥ 80 years who received docetaxel for metastatic castrate-resistant prostate cancer.

Patient	Docetaxel regimen[a)]	Initial dose reduction	Number of cycles received	Subsequent dose reduction or treatment delay	Reason for discontinuing treatment	Hospital admission for chemotherapy-related complication	Grade ≥3 hematologic toxicity	Best PSA response
1	3-weekly	No	6	Yes	Treatment completed	Yes	Yes	<50% decline
2	3-weekly	Yes	3	Yes	Other medical problem	Yes	No	≥50% decline
3	3-weekly	Yes	6	Yes	Treatment completed	No	Yes	<50% decline
4	3-weekly	Yes	1	N/A	Other medical problem	No	No	≥50% decline
5	3-weekly	Yes	6	No	Treatment completed	No	No	≥50% decline
6	3-weekly	Yes	10	Yes	Treatment completed	No	No	N/A
7	3-weekly	No	8	Yes	Progressive disease	Yes	Yes	≥50% decline
8	3-weekly	No	9	Yes	Progressive disease	Yes	Yes	≥50% decline
9	3-weekly	Yes	3	No	Unclear	No	No	N/A
10	3-weekly	Yes	2	No	Other medical problem	No	No	Progression
11	3-weekly	No	8	Yes	Progressive disease	No	Yes	N/A
12	3-weekly	Yes	2	No	Other medical problem	No	Yes	N/A
13	3-weekly	No	6	No	Toxicity	No	No	≥50% decline
14	3-weekly	No	6	Yes	Treatment completed	No	Yes	<50% decline
15	Weekly	No	1	N/A	Other medical problem	Yes	No	<50% decline
16	3-weekly	No	8	No	Toxicity	No	No	≥50% decline
17	3-weekly	No	6	Yes	Progressive disease	No	No	Progression
18	3-weekly	No	6	Yes	Treatment completed	No	Yes	≥50% decline
19	3-weekly	No	10	No	Treatment completed	No	No	<50% decline
20	3-weekly	No	6	Yes	Treatment completed	No	Yes	≥50% decline

N/A, data not available; PSA, prostate specific antigen.
[a)] Docetaxel regimens: 3-weekly, 75 mg/m^2 every 21 days; weekly, 35 mg/m^2 on Days 1 and 8 every 21 days.

3.3. Toxicities

Grade 3 or 4 hematologic toxicity was observed in nine (45%) patients, including six patients with Grade 3 or 4 neutropenia. Five (25%) patients were admitted to hospital with chemotherapy-related complications, with three of these due to infections.

3.4. Efficacy

PSA response was assessable for 16 patients (Table 2). Of these, nine (56%) patients had a PSA response of ≥50% and one (6%) patient had a PSA-complete response. All three patients who had pain requiring opioid analgesia had improvement in their pain after commencing treatment.

Summary data for initial dose reduction, toxicity, and PSA response for patients stratified by number of comorbidities and number of chemotherapy cycles are presented in Fig. 1.

Follow up was recorded up to 30 June 2014, where two patients were lost to follow up and all remaining patients had died. The median overall survival was 13.4 months and 1-year survival was 64.6%. One-year survival in patients with ≥50% PSA response was 89%, compared to 43% in patients with <50% PSA response ($P = 0.081$; Fig. 2).

4. Discussion

The management of elderly patients with mCRPC remains challenging due to a paucity of prospective randomized trial data to guide clinical decision-making. Subgroup analyses of clinical trial participants[6] and retrospective studies[7] suggest that older patients treated with docetaxel derive similar benefits to younger patients, although at a cost of potentially increased toxicity.

In the landmark TAX327 study in which approximately 20% of patients were at least 75 years of age, the overall survival benefit from 3-weekly docetaxel was equivalent across age groups, with hazard ratios of 0.81 and 0.77 for men aged ≤68 years and >68 years, respectively.[5] Even with an older age cutoff of 75 years, the hazard ratio was maintained at 0.80. Measures of clinical benefit, such as improvements in quality of life and pain responses, were also comparable among the under 65 years, 65–74 years, and ≥75 years age groups.[6]

However, older patients appear to be more susceptible to treatment-related adverse events, with those aged ≥75 years having significantly higher rates of infection of any grade and requiring dose reductions more frequently than those in the <65 years and 65–74 years age groups.[6] Similar trends were seen in a small retrospective study of 51 Japanese patients treated with docetaxel 70 mg/m^2 every 3 weeks, with higher rates of Grade 3–4 neutropenia in the 20 patients aged ≥75 years (70% vs. 48% of patients <75 years, $P = 0.16$).[7]

In our series, 40% of very elderly (age ≥ 80 years) patients were able to complete planned treatment; however, a substantial proportion required dose modifications, highlighting the difficulties in determining optimal dosing in patients of advanced age. Similar findings have been reported in a retrospective series of 159 Japanese patients aged ≥75 years who received docetaxel in the community setting, in which 87% of patients required dose modifications.[8]

One strategy when administering docetaxel to older patients is to use weekly scheduling, which is generally perceived to be better tolerated due to lower rates of hematologic toxicity compared to the standard 3-weekly regimen. In a *post hoc* analysis of the patients aged ≥75 years in the TAX327 study, there was no difference in the type or frequency of toxicities between the weekly and 3-weekly docetaxel arms, although significantly more dose reductions were required in patients receiving 3-weekly treatment.[6] By contrast, a retrospective multicenter French study of 175 patients aged ≥75 years, including 57 (32.6%) patients aged ≥ 80 years, showed significantly higher rates of febrile neutropenia among those who received standard 3-weekly docetaxel, whereas those who received weekly treatment experienced more Grade 3–4 fatigue and were more likely to stop chemotherapy because of toxicity (30% vs. 8%), possibly due to a higher proportion of older and poor performance status patients in this group.[9]

A fortnightly treatment schedule has also been prospectively explored in a European multicenter trial of 361 patients (median

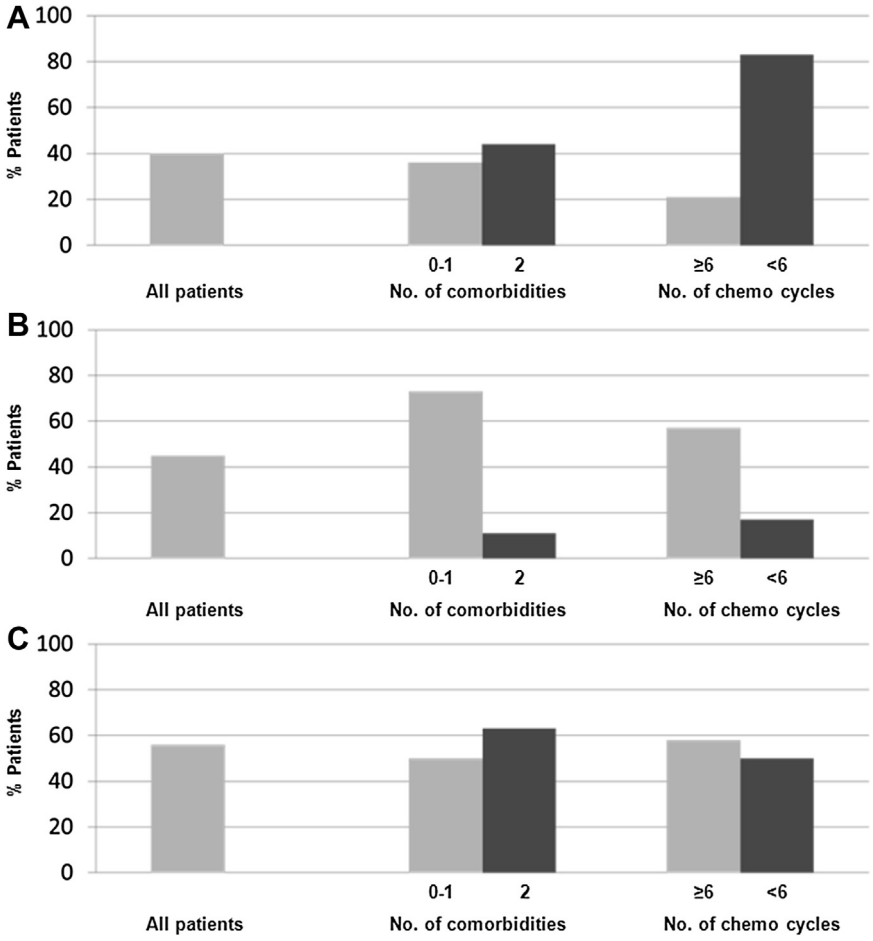

Fig. 1. Summary data for patients stratified by number of comorbidities and number of chemotherapy cycles. Proportion of patients: (A) requiring initial dose reduction, (B) with ≥ Grade 3 hematologic toxicities; and (C) with ≥50% prostate-specific antigen (PSA) response.

age 68 years) randomized to receive 50 mg/m^2 docetaxel every 2 weeks or 75 mg/m^2 every 3 weeks.[10] Patients receiving fortnightly treatment had significantly fewer neutropenic infections (6% vs. 24%, $P = 0.002$), with no difference observed in nonhematological toxicities or quality of life. In addition, 2-weekly treatment was associated with longer time to treatment failure (hazard ratio 1.3, 95% confidence interval 1.1–1.6) and longer overall survival (median 19.5 months vs. 17 months, $P = 0.021$).

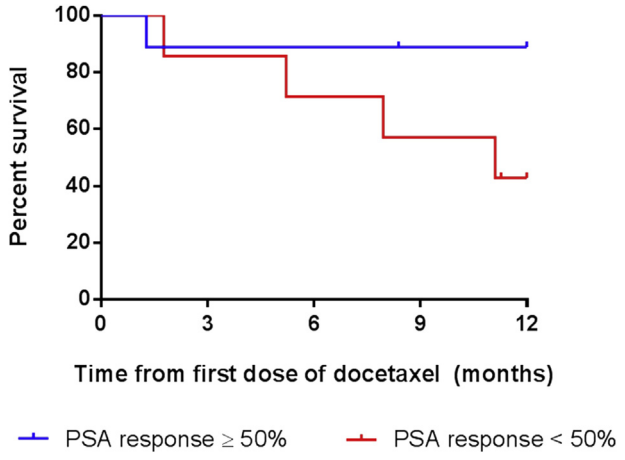

Fig. 2. One-year overall survival for patients with prostate-specific antigen (PSA) response ≥ 50% versus < 50%. One-year overall survival proportions: patients with ≥50% PSA response = 89%, Patients with <50% PSA response = 43%, $P = 0.081$.

Treatment efficacy in our patient series is difficult to determine due to the retrospective nature of this study and the absence of a control group. However, just over half of the patients derived clinical benefit from treatment in terms of ≥50% PSA response or improvement in pain. We also observed that patients who had a PSA response of ≥50% had longer overall survival than those who did not, consistent with previous reports.[11]

In recent years, multiple new agents have been shown to improve survival in patients with mCRPC. These include chemotherapy (cabazitaxel),[12] hormonal agents targeting androgen biosynthesis (abiraterone)[13,14] or the androgen receptor (enzalutamide),[15,16] and radium-223, an alpha emitter.[17] Although optimal treatment sequencing is not known, hormonal agents are an attractive alternative to chemotherapy in elderly patients due to the lower rates of myelosuppression and sepsis. In *post hoc* subgroup analyses of the phase III studies of abiraterone[18] and enzalutamide,[19] both agents were well tolerated in patients aged ≥75 years, although older patients treated with abiraterone experienced higher rates of cardiac arrhythmias and peripheral edema than those aged <75 years.[17]

It is well recognized that the elderly are a particularly heterogeneous population and patients enrolled in clinical trials are not always representative of real world practice. This is reflected in the International Society of Geriatric Oncology guidelines,

which highlight the importance of adapting treatment to individual health status independently of chronological age.[20] The consensus recommendation is that patients undergo screening for comorbidities, dependence, and malnutrition in order to be classified as “healthy”, “vulnerable”, or “frail”, where vulnerable and frail patients may be considered for treatment after medical intervention. This concept has been embraced in novel clinical trials designed specifically for older patients, such as the GERICO10-GETUG P03 trial which randomized mCRPC patients aged ≥75 years and classified as “vulnerable” or “frail” after comprehensive geriatric assessment to weekly or 3-weekly docetaxel, with the primary objective to examine the feasibility of either regimen.[21]

There are several limitations to our case series. As with all retrospective studies, data for some patients were incomplete and nonhematologic toxicities were difficult to capture. In addition, we did not record data on postdocetaxel treatment. However, this small series highlights the complexities of treating very elderly patients with mCRPC in routine practice.

In conclusion, selected fit elderly patients appear to tolerate docetaxel and derive clinical benefits from treatment, however, optimal dosing remains unclear, because pharmacokinetic changes with aging could potentially alter drug exposure and metabolism. New hormonal agents such as abiraterone and enzalutamide are attractive alternatives in elderly patients due to lower rates of myelosuppression, although optimal treatment sequencing is not yet known. Comprehensive geriatric assessment is likely to be helpful in identifying patients at risk of increased toxicity, however, it is time-consuming and difficult to implement in a busy oncology practice.

Conflicts of interest

P.P. and M.R. received honoraria for Sanofi-Aventis board membership. All other authors have no disclosures to declare.

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