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Research Article

Efficacy and safety of cabazitaxel therapy in elderly (≥75 years) patients with castration-resistant prostate cancer: A multiinstitutional study

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ABSTRACT

Background: There is little data on the outcome of cabazitaxel (CBZ) treatment of elderly patients with castration-resistant prostate cancer (CRPC). This study assessed the efficacy and safety of CBZ chemotherapy in patients with CRPC aged 75 years or older in a multiinstitutional study.
Methods: We retrospectively reviewed the 74 patients with CRPC treated with CBZ enrolled in 10 institutions. Clinicopathological backgrounds, prognosis including prostate-specific antigen decline, time to treatment failure, progression-free survival, overall survival, and safety profiles were compared between younger (<75 years) and elder (≥75 years) patients.
Results: In total, 74 patients were enrolled; 50 patients were younger than 75 years and 24 were ≥75 years. Clinicopathological characteristics were comparable between younger and elder patients, with the exception of serum albumin values at the time of CBZ treatment. The median prostate-specific antigen decline in younger and elder men was −8.8% and −32.3% from baseline, respectively. The median time to treatment failure, progression-free survival, and overall survival for younger and elder men were 0.24 and 0.33 years, 0.23 and 0.43 years, and 0.69 and 1.17 years, respectively. In addition, safety profiles were comparable between younger and elder patients.
Conclusions: This multiinstitutional study suggests that patients with CRPC aged 75 years or older eligible for CBZ treatment can be treated safely and with noninferior efficacy compared with those younger than 75 years.

1. Introduction

For years, androgen deprivation therapy (ADT) has been an essential treatment for metastatic prostate cancer.[1,2] Specifically, docetaxel (DTX), the first synthetic taxane, is the first-line treatment for metastatic prostate cancer. DTX treatment every three weeks is associated with better survival outcomes for metastatic castration-resistant prostate cancer(CRPC) (mCRPC) in patients

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aged 75 years or older compared with the younger patients in a TAX327 subgroup analysis.[3] In terms of DTX safety in elderly patients, TAX327 showed that DTX is associated with similar tolerance compared with younger patients, while the patients aged 75 years or older needed dose reductions.[3] A prospective international registry study suggests that first-line taxane therapy for mCRPC might benefit patients aged 70 years or older more than those who do not receive taxane treatment.[4] Recent concomitant treatment with ADT plus DTX for metastatic hormone-sensitive prostate cancer resulted in significantly longer overall survival (OS) than with ADT alone in the CHAARTED study.[5] Furthermore, the subgroup analysis in CHAARTED reported that the patients aged 70 years or older had increased benefit from ADT plus DTX treatment compared with those younger than 70 years.[5] Upfront treatment with DTX as the first-line chemotherapy for metastatic prostate cancer would incur a paradigm shift in primary chemotherapy for metastatic prostate cancer.

Cabazitaxel (CBZ) is a novel tubulin-binding taxane and a second-generation drug for mCRPC.[6] The phase 3 TROPIC trial showed increased survival inpatients with mCRPC after DTX administration receiving CBZ treatment compared with mitoxantrone. Furthermore, the safety profile of CBZ treatment was acceptable, but febrile neutropenia incidence was frequent.[6] Elderly and Asian population are known to be at higher risk for febrile neutropenia incidents, as well as severe febrile neutropenia in taxane chemotherapy.[7,8] However, less than 20% of patients included were aged 75 years or older and less than 10% of the enrolled patients were Asian. Furthermore, the efficacy and safety profiles in Asian patients aged 75 years or older were not assessed in the TROPIC trial. Recently, noninferior prostate-specific antigen (PSA) response and OS and safety profile of CBZ treatment in patients with CRPC aged 80 years or older were reported in a Japanese postmarketing surveillance article.[9] Unfortunately, this study is limited due to a nature of postmarketing surveillance which is structurally prone to underreporting of adverse events (AEs) due to the research approach in which pharmaceutical companies collect information from medical doctors. It may lead to missing data on treatment outcomes, as well as overlook and misclassify AEs. Therefore, more robust investigation on efficacy and safety profiles in elder Asians would be required. Thus, this study investigates the efficacy and safety of CBZ therapy for patients with CRPC aged 75 years or older in a multi-institutional, retrospective study.

2. Materials and methods

2.1. Patients

This study included 74 patients treated with CBZ for mCRPC, as described previously.[10,11] In brief, the patients were enrolled from 10 institutions, and the eligibility criteria included the following: (i) histopathologically diagnosed carcinoma of the prostate, (ii) confirmed failure of primary ADT, and (iii) age ≥20 years.

2.2. Exposure

CBZ was administered according to an every 3–4-week dose (20–25 mg/m^2) regimen based on the schedule reported by the TROPIC and PROSELICA trials,[5,15] with one case treated with 15 mg/m^2. Prednisolone of 5 mg was administered twice daily simultaneously with medical or surgical castration. The dose and schedule of CBZ were modified according to the severity of any AEs in each case. Treatment with CBZ was continued according to the physician's judgement, based on disease progression and AEs or patient refusal.

2.3. Endpoints

Progressive disease was defined as (i) an increase in serum PSA of >2 ng/ml and (ii) a 50% increase over the nadir and/or (iii) the appearance of a new lesion or progression of one or more known lesions classified according to the Response Evaluation Criteria in Solid Tumors, version 1.1.[12] AEs were assessed by Common Terminology Criteria for Adverse Events, version 4.0, from the National Cancer Institute (https://ctep.cancer.gov/). Clinically, significant pain was defined by the daily consumption of narcotic or nonnarcotic analgesics for pain derived from prostate cancer. Performance status was determined in accordance with the Eastern Cooperative Oncology Group criteria. Serum marker data at pretreatment including PSA, neutrophil–lymphocyte ratio, hemoglobin, alkaline phosphatase, lactate dehydrogenase, albumin, and sodium were collected. PSA flare was defined according to various definitions as follows: transient PSA increase followed by any decline below baseline.

2.4. Statistical analysis

All statistical analyses were performed using EZR, version, 1.50 software (Jichi Medical Univeristy Saitama Medical Center, Saitama, Japan).[13] Comparison between two groups was performed with Fisher and Mann-Whitney tests for categorical and continuous variables, respectively. Time to treatment failure (TTF), progression-free survival (PFS), and OS were determined by the Kaplan–Meier method, and the log-rank test was used to compare survival duration between groups. Univariate analyses were performed using the Cox proportional hazards regression model. All tests were two sided, and $P < 0.05$ was considered significant.

3. Results

3.1. Clinical characteristics

A total of 74 Japanese patients were included in this study. The clinical characteristics are listed in Table 1. Fifty patients (67.6%) aged younger than 75 years and 24 patients (32.4%) aged 75 years or older were enrolled. The median age was 69.5 years and 77.5 years, respectively. There was no significant difference in the PSA level and biopsy Gleason Score at diagnosis. Thirteen patients (17.6%) and 8 patients (10.8%) received prior local therapy in each group. The median time to CRPC was 1.21 and 1.68 years in younger (<75 years) and elder (≥75 years) patients, respectively. At pretreatment, Eastern Cooperative Oncology Group Performance Status (ECOG PS) was not worse even in elderly (≥75 years). Pain symptoms were observed more frequently in younger men than elderly (<75 years, 58.0% vs. ≥75 years, 33.3%) ($P = 0.08$, Table 1). Blood tests showed that serum albumin levels were lower in elderly (<75 years, 3.9 g/dl vs. ≥75 years, 3.6 g/dl; $P = 0.01$). Finally, metastasis to bone ($P = 0.42$), lymph node ($P = 0.45$), and viscera ($P = 1.00$) at pretreatment were comparable between younger and elder patients.

3.2. Exposure

CBZ treatments are described in Table 2. Thirty six (72.0%) of the younger patients received ≥20 mg/m^2, and 14 (58.3%) of the elderly patients received ≥20 mg/m^2 ($P = 0.29$). Seven younger patients (14.0%) and 5 elderly (20.8%) received 10 or more courses of CBZ treatment ($P = 0.51$). The 13 (26.0%) elderly patients received 3 weeks' interval treatment and 6 (21.4%) younger patients received 3 weeks' interval treatment in each ($P = 0.86$). Twenty one (42.0%)

Table 1
Clinical characteristics between men aged <75 years and ≥75 years

Variables	<75 years (n = 50)	≥75 years (n = 24)	P-value
Age, year (median [IQR])	70 [65-72]	78 [76-80]	<0.01
PSA at diagnosis, ng/ml (median [IQR])	47.2 [14.0-325.8]	61.1 [23.1-395.3]	0.43
Biopsy Gleason Score, n (%)			
7	9 (18.0%)	3 (12.5%)	0.63
8	6 (12.0%)	6 (25.0%)	
9	25 (50.0%)	12 (50.0%)	
10	8 (16.0%)	2 (8.3%)	
NA	2 (4.0%)	1 (4.2%)	
Prior local therapy, n (%)			
Absence	37 (74.0%)	16 (66.7%)	0.81
Radical prostatectomy	5 (10.0%)	2 (8.4%)	
Radiation	6 (12%)	5 (20.8%)	
Unknown	2 (4%)	1 (4.2%)	
Time to CRPC, year (median [IQR])	1.21 [0.55-2.27]	1.68 [1.09-2.41]	0.12
NA	5	2	
Docetaxel cycle, n (median [IQR])	7.5 [6.0 - 12.0]	7.5 [5.0 - 10.0]	0.61
Prior novel AR pathway inhibitor for CRPC (%)			
Absence	8 (16.0%)	4 (16.7%)	1.00
Presence	42 (84.0%)	20 (83.3%)	
Prior radium-223 for CRPC (%)			
Absence	46 (92.0%)	24 (100%)	0.30
Presence	4 (8.0%)	0 (0.0%)	
ECOG PS at pretreatment, n (%)			
<2	38 (76.0%)	20 (83.3%)	0.83
≥2	6 (12.0%)	2 (8.3%)	
NA	6 (12.0%)	2 (8.3%)	
Pain at pretreatment, n (%)			
Absence	21 (42.0%)	16 (66.7%)	0.08
Presence	29 (58.0%)	8 (33.3%)	
PSA at pretreatment, ng/ml (median [IQR])	49.5 [15.7-197.5]	119.0 [45.4-335.0]	0.12
NLR at pretreatment (median [IQR])	4.2 [2.6-7.2]	4.3 [3.2-5.5]	0.84
NA	1	2	
Hb at pretreatment, g/dl (median [IQR])	12.2 [11.0-13.1]	11.6 [10.7-12.2]	0.29
ALP at pretreatment, U/l (median [IQR])	304 [205-479]	258 [219-471]	0.60
LDH at pretreatment, U/l (median [IQR])	245 [197-331]	276 [178-356]	0.78
Alb at pretreatment, g/dl (median [IQR])	3.9 [3.6-4.2]	3.6 [3.3-3.9]	0.01
NA	1	0	
Na at pretreatment, mmol/l (median [IQR])	139.0 [137.5-141.0]	138.9 [136.5-140.3]	0.33
Bone metastasis at pretreatment, n (%)			
Absence	4 (8.0%)	4 (16.7%)	0.42
Presence	46 (92.0%)	20 (83.3%)	
Lymph node metastasis at pretreatment, n (%)			
Absence	19 (38.0%)	12 (50.0%)	0.45
Presence	31 (62.0%)	12 (50.0%)	
Visceral metastasis at pretreatment, n (%)			
Absence	36 (72.0%)	18 (75.0%)	1.00
Presence	14 (28.0%)	6 (25.0%)	

PSA = prostate-specific antigen; NA = not available; CRPC = castration-resistant prostate cancer; AR = androgen receptor; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IQR = interquartile range; NLR = neutrophil–lymphocyte ratio; Hb = hemoglobin; Alb = albmin; ALP = alkaline phosphatase; LDH = lactate dehydrogenase.

of younger patients and 16 (66.7%) of the elderly patients received the CBZ treatment as the third line or less in each.

3.3. *Efficacy*

The data of PSA flare were available from 70 patients including 47 patients younger than 75 years and 23 patients aged 75 years or older. The median follow-up from starting CBZ treatment was 0.6 years. Four (8.5%) patients younger than 75 years and 2 (8.7%) patients aged 75 years or older showed PSA flare (P = 1.00). PSA response data were available from 67 patients including 43 patients younger than 75 years and 24 patients aged 75 years or older. The waterfall plot of PSA decrease after CBZ treatment is described in Fig. 1A. Among them, 24 (55.8%) younger patients and 19 elderly patients (79.2%) showed PSA decrease (Fig. 1A). The median (interquartile range) PSA decline was −8.8% (−48.4% to 17.5%) and −32.3% (−50.2% to −7.2%) from baseline for younger and elderly patients, respectively (P = 0.16). Intriguingly, 15 (62.5%) patients aged 75 years or older achieved ≥30% PSA decrease compared with 14 (32.6%) patients younger than 75 years (P = 0.02). However, ≥50% PSA decrease was comparable between younger and elder patients (<75 years, 23.3% vs. ≥75 years, 25.0%;

Table 2
The profiles of CBZ treatment between men aged <75 years and ≥75 years

Variables	<75 years	≥75 years	P-value
Median CBZ dose [IQR], mg/m2	25 [20-25]	25 [20-25]	0.33
Treatment dose			
≤20 mg/m2	14 (28.0%)	10 (35.7%)	0.29
>20 mg/m2	36 (72.0%)	14 (58.3%)	
Total treatment cycle			
<10 cycles	43 (86.0%)	19 (79.2%)	0.51
≥10 cycle	7 (14.0%)	5 (20.8%)	
Treatment interval			
3 weekly	13 (26.0%)	6 (21.4%)	0.86
4 weekly	33 (66.0%)	15 (62.5%)	
Single-course treatment	4 (8.0%)	3 (12.5%)	

IQR = interquartile range; CBZ = cabazitaxel.

P = 1.00). Eventually, TTF, PFS, and OS are described in Fig. 1B–D. The median TTF, PFS, and OS in men with <75 years vs. ≥75 years were 0.24 vs. 0.33 years (P = 0.53, Figs. 1B), 0.23 vs. 0.43 years (P = 0.32, Figs. 1C), and 0.69 vs. 1.17 years (P = 0.082, Fig. 1D), respectively. The risks of treatment failure [hazard ratio (HR), 95% confidence interval (CI): 0.89, 0.52–1.50; P = 0.66], progression (HR, 95% CI: 0.77, 0.45–1.30; P = 0.33), and any-cause death (HR, 95% CI: 0.57, 0.30–1.08; P = 0.09) for patients aged ≥75 years were comparable with those for patients aged <75 years.

Table 3
The safety profiles of cabazitaxel treatment between men aged <75 years and ≥75 years

Variables	<75 years	≥75 years	P-value
Hematological AEs			
Grade ≥3 neutropania	36 (72.0%)	18 (75.0%)	1.00
Febrile neutropenia	17 (34.0%)	6 (25.0%)	0.59
Nonhematological AEs			
Grade ≥3	12 (24.0%)	5 (20.8%)	1.00
Grade 5	5 (10.0%)	0 (0.0%)	0.17

AE = adverse event.

3.4. Toxicity

In terms of hematological AEs, grade 3 or more neutropenia occurred in 36 patients (72.0%) aged <75 years and in 18 patients aged (75.0%) ≥75 years (P = 1.00, Table 3). Grade 3 or more febrile neutropenia occurred in 17 patients (34.0%) aged <75 years and in 6 patients (20.8%) aged ≥75 years (P = 0.59, Table 3). Grade 3 or more nonhematological AEs occurred in 12 patients (24.0%) aged <75 years and in 5 patients (24.0%) aged ≥75 years (P = 1.00, Table 3). Notably, grade 5 AEs were observed in 5 men aged <75 years while there were no grade 5 nonhematological AEs in men aged ≥75 years (P = 0.13, Table 3).

4. Discussion

In total, 74 patients including 24 (32.4%) patients aged 75 years or older were enrolled in our study. Clinical background enrolled in this study was quite similar between both groups, although the lower serum albumin levels in patients aged 75 years or older may reflect worse nutritional condition. In terms of efficacy, there were no significant differences in TTF, PFS, and OS between younger patients and elder patients. Consistent with this, Kosaka et al. [14] and Yamamoto et al. [15] reported the comparable efficacy between younger patients and elder patients in 47 and 55 patients with CRPC including 8 (17.0%) and 31 (56.4%) patients aged 75 years or older, respectively. Moreover, Matsubara et al. [9] also reported comparable efficacy in 49 (7.4%) patients aged 80 years or older among 659 Japanese with CRPC in a postmarketing surveillance study.

In this study, there was no significant difference in concentration, treatment cycles, and interval weeks for CBZ treatment between both age groups. Patients aged ≥75 years were treated with similar dose intensity with CBZ compared with those aged <75 years. Importantly, safety profiles were comparable or favorable in elderly compared with younger patients; furthermore, lethal toxicities were decreased in elderly patients. Consistent with this, Matsubara et al. [9] reported the safety for 659 Japanese patients with CRPC in a postmarketing surveillance study. The patients aged

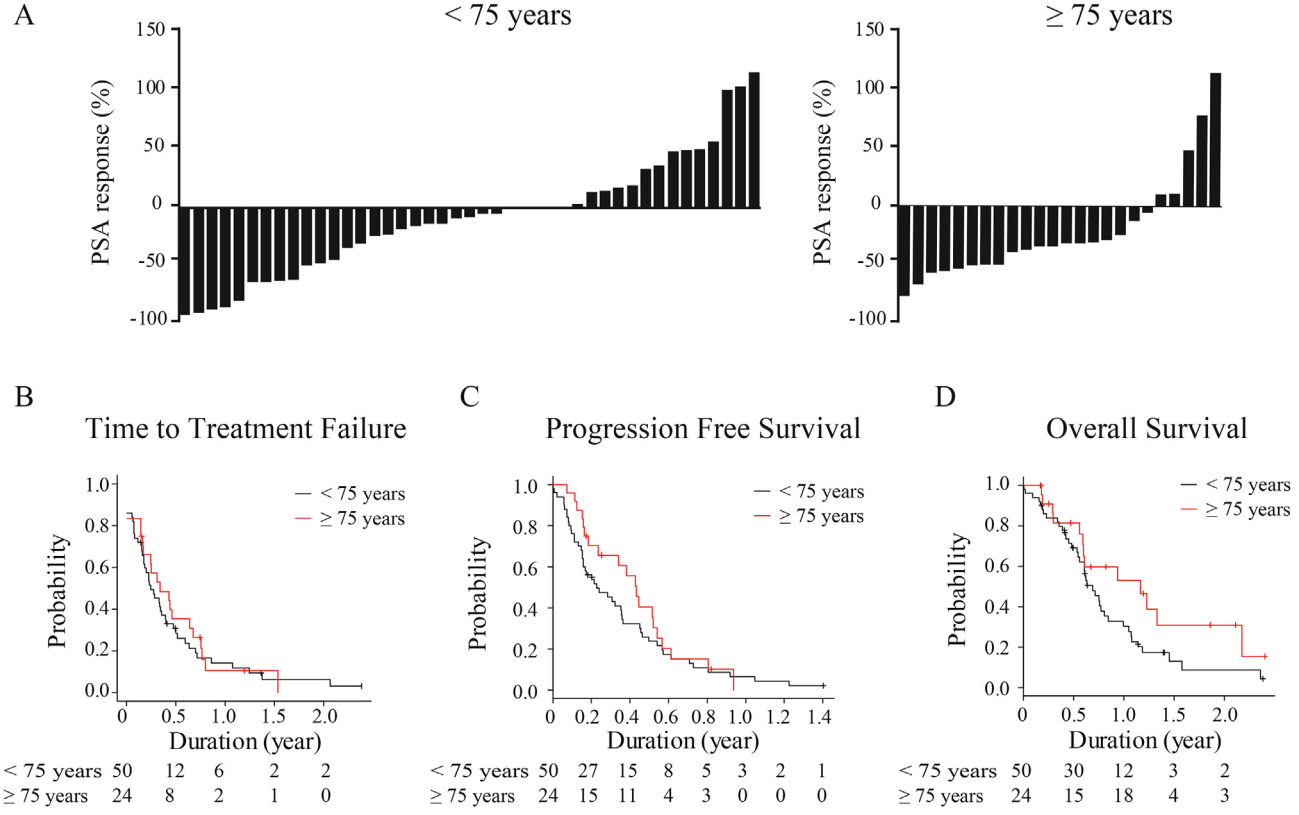

Figure 1. Anticancer efficacy of cabazitaxel treatment according to age (<75 years vs. ≥75 years) (A) Waterfall plot of the maximum decline in PSA from the baseline for patients with castration-resistant prostate cancer in patients aged <75 years (left) vs. ≥75 years (right) (B–D) Kaplan–Meier survival curves of treatment failure-free survival (B), progression-free survival (C), and overall survival (D) in patients with castration-resistant prostate cancer stratified by age. PSA = prostate-specific antigen.

80 years or older had quite similar CBZ dose and treatment cycle compared with those younger than 80 years. Among them, patients aged 80 years or older had similar AEs compared with those younger than 80 years. Meanwhile, European compassionate use programs showed increased risk of severe/febrile neutropenia in patients aged ≥75 years compared with patients aged <70 years. However, the severe febrile neutropenia was decreased by prophylactic use of granulocyte colony-stimulating factor.[16] Similarly, Yamamoto et al. [15] reported that ~80% patients aged ≥75 years required dose reduction at the initial administration while CBZ treatment was terminated due to severe AEs including febrile neutropenia in ~40% patients. Elderly patients are usually vulnerable to anticancer therapy, including chemotherapy. Therefore, this noninferior safety profile for CBZ treatment may be due to the selection of patients who could be safely treated with DTX as prior treatment.

We additionally analyzed the data by separating these patients into three groups (aged <70 years, 70–75 years, ≥75 years) owing to the limited case number, which showed consistent results with 2 subgroup analysis (data not shown). Overall, our study provides strong evidence that patients with CRPC aged 75 years or older are able to tolerate and significantly benefit from CBZ treatment. However, this study has severe limitations. First of all, clinical data were collected retrospectively, and some data were missing. Secondary, the population was quite small. Finally, the multiinstitutional nature of this study means that the treatment strategy at each institution was likely different. These could all affect the present outcome and introduce interpretation biases.

5. Conclusion

This study showed comparable efficacy and safety of CBZ treatment in elderly (≥75 years old) patients with CRPC compared with younger patients. It was suggested that patients with CRPC aged 75 years or older could benefit from CBZ treatment safely compared with those younger than 75 years. However, elderly patients are at higher risk for AEs. Therefore, appropriate patient selection and prophylactic AE treatments are important to obtain the benefit of CBZ treatment.

Conflicts of interest

There are no conflicts of interest.

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