

Outcomes of Dose-Attenuated Docetaxel in Asian Patients with Castrate-Resistant Prostate Cancer

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Abstract

Introduction: High levels of toxicities have been observed when docetaxel is administered at the standard dose of 75 mg/m² every 3 weeks (Q3W) in the real-world treatment of Asian patients with metastatic castrate-resistant prostate cancer (CRPC). This study aimed to evaluate the efficacy and tolerability of 2 attenuated regimens more widely used in an Asian setting to minimise toxicity – 60 mg/m² Q3W and weekly docetaxel (20 mg/m² to 35 mg/m²). **Materials and Methods:** Medical records of 89 CRPC patients between December 2003 and April 2013 were reviewed. Pairwise statistical analysis was performed, comparing efficacy and safety outcomes of 75 mg/m² Q3W and weekly docetaxel with 60 mg/m² Q3W. Treatment endpoints used were prostate-specific antigen (PSA) response (decrease of ≥50% from baseline), pain improvement after cycle 2, overall survival, time to disease progression and radiological response. **Results:** Patients who received docetaxel at 75 mg/m² Q3W were younger than those who received 60 mg/m² Q3W (62 years and 66 years, respectively; *P* = 0.0489). Both groups had similar response rates. Compared with patients on 60 mg/m² Q3W, more patients on weekly regimens were symptomatic at baseline (63.2% and 87.5%, respectively; *P* = 0.0173). Longer overall survival was observed in the 60 mg/m² Q3W arm than the weekly docetaxel arm (16.9 months and 10.6 months, respectively; *P* = 0.0131), though other measures of response did not differ significantly. **Conclusion:** Our data supports the use of 60 mg/m² Q3W docetaxel which has similar efficacy and an acceptable toxicity profile compared to the standard 75 mg/m² Q3W regimen. Weekly docetaxel has significant palliative benefits among symptomatic patients despite lower overall survival.

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Introduction

The incidence of prostate cancer is rising in Asia.¹ In Singapore, prostate cancer is the third most prevalent cancer among males, with an age-standardised rate of 28.0 per 100,000 a year from 2007 to 2011.² Castration resistance develops in a subset of prostate cancer patients, during which disease progression occurs despite castrate levels of androgens. Docetaxel chemotherapy is a standard treatment for castrate-resistant prostate cancer (CRPC) patients with metastatic disease, as it has been shown to improve survival rates and pain control at a dose of 75 mg/m² every 3 weeks (Q3W),³ as well as at a dose of 60 mg/m² when combined

with estramustine.⁴ In May 2004, docetaxel was approved by the United States Food and Drug Administration (US FDA) for the treatment of metastatic CRPC with a dosing guideline of 75 mg/m² Q3W.

A lower dose of docetaxel (60 mg/m² Q3W) is widely administered in breast cancer, lung cancer and prostate cancer in Asian countries such as Japan and Singapore^{5,6} due to observations of increased toxicity⁷ with the higher dose (75 mg/m² Q3W). There have been no data regarding this attenuated regimen in terms of efficacy and safety in Asian prostate cancer patients. An alternative weekly chemotherapy regimen in prostate cancer is also commonly

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used to minimise toxicities experienced, especially for patients who are at a higher risk of developing serious myelosuppressive effects. While symptomatic benefits have been reported, there is less benefit to overall survival compared to 75 mg/m² Q3W docetaxel.^{3,8,9} A recent study with a 2-weekly regimen was studied in a prospective randomised manner, showing that it was a better tolerated option compared to the Q3W regimen amongst CRPC patients.¹⁰ However, this regimen has not been used locally at present.

In this study, we retrospectively evaluate efficacy and tolerability in a single large Asian cancer centre on the use of 60 mg/m² Q3W docetaxel in patients with CRPC, compared with patients receiving the recommended 75 mg/m² Q3W or weekly docetaxel (dosage: 20 mg/m² to 35 mg/m²; day 1, 8 Q3W) in a real-world setting.

Materials and Methods

Study Population

All CRPC patients who were treated with docetaxel-based chemotherapy between December 2003 and April 2013 were reviewed. Institutional Review Board (IRB) approval was obtained prior to study commencement.

Data Collection

Medical records, blood tests and radiographic assessment results, inpatient discharge summaries as well as chemotherapy prescriptions and administration records were reviewed. Information about the patients' baseline characteristics, treatment details and outcomes were collected. Eastern Cooperative Oncology Group (ECOG) performance status scores were also obtained. The following treatment endpoints were used: a decrease in prostate-specific antigen (PSA) from baseline of more than 50%, symptomatic improvement of pain experienced after the end of the second cycle, radiological response based on the Response Evaluation Criteria in Solid Tumors (RECIST), overall survival and time to disease progression. For patients who terminated treatment due to disease progression or intolerable side effects, the date of disease progression was defined as the date of the last cycle of docetaxel chemotherapy received. For patients who ended treatment while still responding satisfactorily and experienced little to no side effects, the date of progression was defined to be the date during which a different line of treatment commenced.

Information was also collected for selected adverse events experienced during chemotherapy treatment (the period from the initiation of chemotherapy to 3 weeks after the last dose was administered). These included the number

and cause of hospitalisations, febrile neutropaenia which resulted in hospitalisation and grade 3 or 4 neutropaenia defined by the Common Toxicity Criteria for Adverse Events (CTCAE) (version 4.0).

Statistical Analysis

Pairwise analysis was performed comparing the 75 mg/m² Q3W and weekly group (20 mg/m² to 35 mg/m²) against the 60 mg/m² Q3W group. All statistical analysis was performed using R version 3.0.1. Pearson's chi-square test of independence and Fisher's exact test was used to compare categorical variables such as patients' race, number of prior hormonal manipulations, PSA response and reason for stopping chemotherapy treatment. Welch's t-test was used to compare the means of patient age and number of cycles of docetaxel received. Overall survival and time to disease progression data was analysed using the Cox proportional hazards model. A *P* value of ≤ 0.05 was deemed as statistically significant.

Results

Baseline Characteristics

The baseline data of the 89 patients reviewed is shown in Table 1. A total of 38 patients started their treatment with 60 mg/m² Q3W, 11 started with 75 mg/m² Q3W and 40 started with a weekly regimen (doses range from 20 mg/m² to 35 mg/m²).

The mean age of the 75 mg/m² group (62 years) was lower than that of the 60 mg/m² group (66 years) (*P* = 0.0489). The racial composition of the 75 mg/m² group was also significantly different, with a higher proportion of Malays (27.3% vs 10.5%), Indians (18.2% vs 5.3%) and Caucasian/Euradians (18.2% vs 0.0%), and a lower proportion of Chinese (36.4% vs 84.2%) (*P* = 0.0047) than that of the 60 mg/m² group. There was a higher proportion of patients on the weekly regimen who were symptomatic before the start of treatment (87.5%) than those on the 60 mg/m² Q3W regimen (63.2%) (*P* = 0.0173).

Treatment Endpoint

The outcomes of the docetaxel treatment administered are summarised in Table 2. Kaplan-Meier curves for overall survival and treatment progression are shown in Figures 1 and 2, respectively, and waterfall plots of PSA change after the first and second cycle are shown in Figure 3. No significant difference between the groups was observed in the rate of PSA response (>50% decline in PSA from baseline), symptomatic response (reduction of pain after the second cycle) and radiological response. No difference was observed either in the time to disease progression

Table 1. Demographics/Baseline Information of Patients

	60 mg/m ² Q3W n (%)	75 mg/m ² Q3W n (%)	<i>P</i> Value*	Weekly n (%)	<i>P</i> Value†
No. of patients	38	11		40	
Age at first treatment, mean (range)	66 (50,83)	62 (52,68)	0.0489	68 (53,88)	0.240
Race, n (%)			0.0047		0.719
Chinese	32 (84.2)	4 (36.4)		34 (85.0)	
Malay	4 (10.5)	3 (27.3)		4 (10.0)	
Indian	2 (5.3)	2 (18.2)		1 (2.5)	
Caucasian/Eurasian	0 (0.0)	2 (18.2)		1 (2.5)	
Number of cycles, median (range)	5 (1,9)	7 (2,15)	0.0924	4 (1,8)	0.138
Symptomatic					
Symptomatic	24 (63.2)	9 (91.8)	0.300	35(87.5)	0.0173
Pain	20 (52.6)	6 (54.5)	1.00	24 (60.0)	0.648
Impending/current obstructive uropathy	4 (10.5)	2 (18.2)	0.605	12 (30.0)	0.0489
Gleason score					
6 – 7	12 (31.6)	2 (18.2)	0.695	14 (35.0)	0.807
8 – 10	23 (60.5)	7 (63.6)		22 (55.0)	
Not available	3 (7.9)	2 (18.2)		4 (10.0)	
Prior treatment					
Prostatectomy	4 (10.5)	2 (18.2)	0.605	6 (15.0)	0.738
Radical radiotherapy	11 (28.9)	2 (18.2)	0.703	11 (27.5)	1.00
Palliative radiotherapy	13 (34.2)	3 (27.3)	1.00	22 (55.0)	0.0736
Hormonal manipulations					
≤2	6 (15.8)	0 (0.0)	0.327	15 (37.5)	0.102
3 – 4	23 (60.5)	9 (81.8)		21 (52.5)	
≥5	7 (18.4)	2 (18.2)		4 (10.0)	
ECOG performance score					
≤2	27 (71.1)	9 (81.8)	1.00	27 (67.5)	1.00
3 – 4	2 (5.3)	0 (0.0)		3 (7.5)	
Not evaluated	9 (23.7)	2 (18.2)		10(25.0)	
Extent of disease					
Bone metastasis	33 (86.8)	10 (90.9)	1.00	36 (90.0)	0.734
Visceral metastasis	10 (26.3)	3 (27.3)	1.00	13 (32.5)	0.624
Lymph nodes involvement	22 (57.9)	6 (54.5)	1.00	27 (67.5)	0.483

ECOG: Eastern Cooperative Oncology Group; Q3W: Every 3 weeks

*Statistical analysis performed comparing the 75 mg/m² Q3W group and the 60 mg/m² Q3W group.

†Statistical analysis performed comparing the weekly docetaxel group and the 60 mg/m² Q3W group.

between patients in the 75 mg/m² and 60 mg/m² groups as well as the weekly and 60 mg/m² group. The median overall survival of the 60 mg/m² Q3W chemotherapy arm (median: 16.9 months) was higher than that of the weekly docetaxel arm (median: 10.6 months) (hazard ratio [HR]: 1.91; *P* = 0.01), but did not differ significantly from the overall survival of the 75 mg/m² Q3W group (median: 18.0 months) (HR: 1.34, *P* = 0.5).

Adverse Events

Table 3 outlines the adverse events experienced during chemotherapy treatment. There was no significant difference in the frequency or cause of hospitalisation between the groups. The incidence of febrile neutropaenia and of treatment termination due to toxicity-related reasons between the groups also did not differ significantly. Of the 89 patients reviewed, 4 (4.5%) died within 4 weeks of last

Table 2. Docetaxel Chemotherapy Outcome

	60 mg/m ² Q3W n (%)	75 mg/m ² Q3W n (%)	<i>P</i> Value [†]	Weekly n (%)	<i>P</i> Value [†]
>50% fall in PSA from baseline			0.300		1.00
No. evaluated	36	11		39	
Response	18 (50.0)	8 (72.7)		18 (46.2)	
Reduction of pain at the end of second cycle			0.430		0.178
No. evaluated	19	6		19	
Response	18 (94.7)	5 (83.3)		14 (73.7)	
Time to treatment progression			0.72		0.191
No. evaluated	38	11		40	
Median (range), months	3.6 (0, 50.8)	7.9 (0.7, 14.6)		3.0 (0, 22.1)	
Hazard ratio		0.883		1.35	
Overall survival			0.453		0.0131
No. evaluated	38	11		40	
Median (range), months	16.9 (1.9, >58.2)	18.0 (7.4, 31.2)		10.6 (1.4, 59.4)	
Hazard ratio		1.34		1.91	
Radiological response			0.226		0.606
No. evaluated	8	6		16	
Partial response	3 (37.5)	3 (50.0)		8 (50.0)	
Stable disease	2 (25.0)	3 (50.0)		5 (31.3)	
Progressive disease	3 (37.5)	0		3 (18.8)	
Reason for stopping treatment			0.913		0.705
No. evaluated	38	11		40	
Progressive disease	9 (23.7)	2 (18.2)		14 (35.0)	
Toxicity	14 (36.8)	6 (54.5)		11 (27.5)	
PD + toxicity	5 (13.2)	1 (9.1)		3 (7.5)	
Completed treatment	6 (15.8)	2 (18.2)		5 (12.5)	
Patient preference	1 (2.6)	0 (0.0)		1 (2.5)	
Oncologist's preference	1 (2.6)	0 (0.0)		4 (10.0)	
Death	2 (5.3)	0 (0.0)		2 (5.0)	

PD: Progressive disease; Q3W: Every 3 weeks

*Statistical analysis performed comparing the 75 mg/m² Q3W group and the 60 mg/m² Q3W group.

†Statistical analysis performed comparing the weekly docetaxel group and the 60 mg/m² Q3W group.

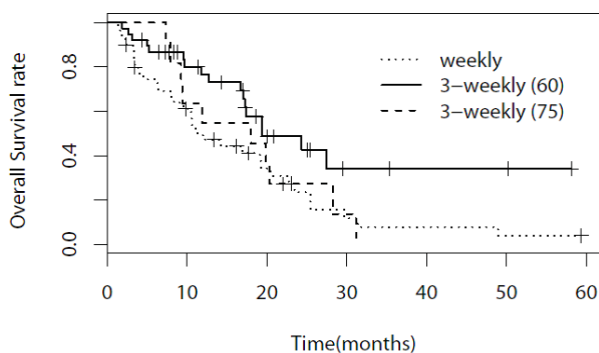


Fig. 1. Kaplan-Meier estimates for the probability of overall survival.

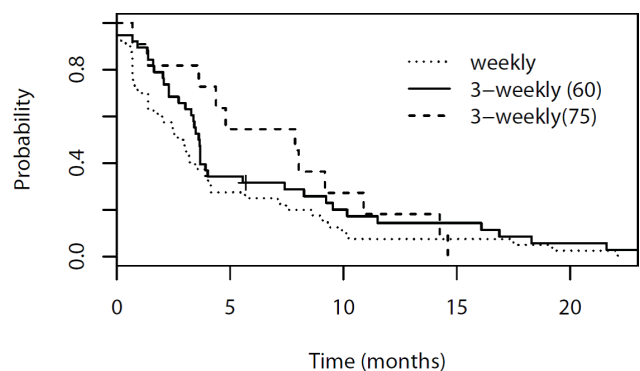


Fig. 2. Kaplan-Meier estimates for the probability of treatment progression.

Table 3. Toxicity Experienced

	60 mg/m ² Q3W n (%)	75 mg/m ² Q3W n (%)	P Value*	Weekly n (%)	P Value†
Hospitalisation					
Hospitalised	12 (29.7)	5 (45.5)	0.468	14 (36.6)	0.632
Toxicity [‡]	8 (18.9)	4 (36.4)		8 (22.0)	
PD [‡]	2 (5.4)	0 (0.0)	0.592	4 (9.8)	1.00
Others [‡]	2 (5.4) [§]	1 (9.1) [§]		2 (4.9) [§]	
Febrile neutropaenia	4 (10.8)	1 (9.1)	1.00	3 (7.3)	0.702
Stopping treatment due to toxicity					
Toxicity/PD + toxicity/ treatment-related death	21 (55.3)	7 (63.6)	0.737	16 (40.0)	0.257
Grade 3 or 4 neutropaenia					
Neutropaenia	7 (18.4)	4 (36.4)	0.237	3 (7.5)	0.187
Death during chemotherapy					
Death	2 (5.3)	0 (0.0)	1.00	2 (5.0)	1.00

PD: Progressive disease; Q3W: Every 3 weeks

*Statistical analysis performed comparing the 75 mg/m² Q3W group and the 60 mg/m² Q3W group.

†Statistical analysis performed comparing the weekly docetaxel group and the 60 mg/m² Q3W group.

‡Hospitalisation reason – administration of chemotherapy.

§Hospitalisation reason – bilateral percutaneous nephrostomy (PCN) change.

¶First hospitalisation cause.

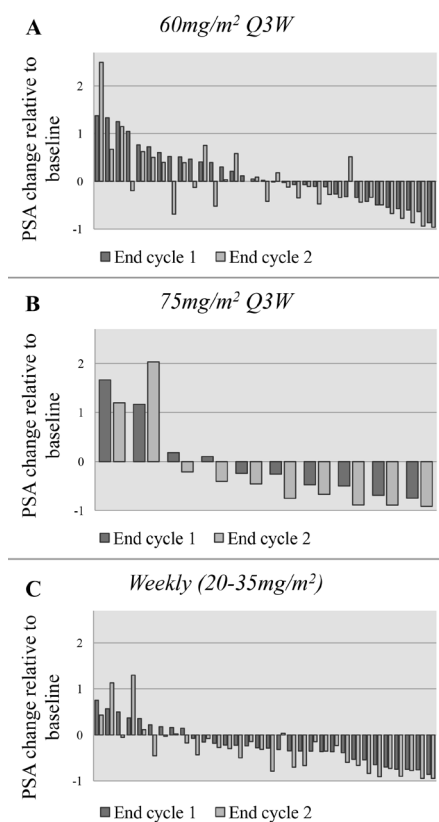


Fig. 3. Waterfall plot of PSA change at the end of cycles 1 and 2 relative to baseline for patients who received A) 60 mg/m² of docetaxel Q3W, B) 75 mg/m² of docetaxel Q3W, C) weekly docetaxel.

dose of chemotherapy. Causes of death were docetaxel-induced pneumonitis (60 mg/m² Q3W) (n = 1), ischaemic heart disease (weekly) (n = 1), progressive disease (weekly) (n = 1). Data was not available as to the cause of death for the last patient.

Regimen Change or Dose Reductions

Of the 38 patients who were treated with 60 mg/m² Q3W, 3 (7.9%) had their docetaxel dose increased to 75 mg/m² from cycle 2 (2 eventually had their doses decreased again) and 1 patient (2.6%) had his regimen changed to a weekly docetaxel regimen from cycle 4. Of the 11 who started out with 75 mg/m², 3 (27.3%) had their dose permanently decreased from cycle 2, and 1 patient (9.1%) switched to a weekly regimen from cycle 2. In addition, one of the 40 (2.5%) who started with a weekly regimen had his regimen changed to a Q3W (60 mg/m²) one from cycle 3.

Discussion

We have shown that docetaxel has significant palliative benefits in terms of symptomatic relief and PSA response regardless of regimen administered. Patients who received 60 mg/m² Q3W and patients who received 75 mg/m² Q3W had similar responses in terms of PSA decrease, pain relief, objective tumour response, time to progression and overall survival. The PSA response rates we observed (50.0% for

60 mg/m² and 72.7% for 75 mg/m²) are comparable to those reported by Tannock et al (45%) and Petrylak et al (50%).^{3,4} Median overall survival (16.8 months for 60 mg/m² and 18.0 months for 75 mg/m²) were also similar to those observed in the above studies (18.9 months in Tannock et al and 17.5 months in Petrylak et al). Hence, it is likely that treatment efficacy had not been compromised with a lower dose of docetaxel Q3W. We would like to highlight that during the study period, newer agents like abiraterone acetate, enzalutamide and cabazitaxel were not available and hence, not used by patients on this study. Usage of these newer therapies could have confounded the findings but that was not the case here.

In terms of tolerability, although toxicities were not statistically different in patients receiving 60 mg/m² Q3W compared to those who received 75 mg/m² Q3W, both hospitalisations and incidences of grade 3 or 4 neutropaenia were proportionally higher in the 75 mg/m² arm. We also observed that 36.4% of patients who initially received 75 mg/m² had their regimen changed after the first cycle of treatment due to side effects experienced. Dose reductions were likely done in order to mitigate the side effect profile and as such, support the notion that the 75 mg/m² Q3W patients had higher toxicities. Among patients who received 60 mg/m² Q3W, chemotherapy treatment was relatively well tolerated. Toxicities in terms of the incidence of grade 3 or 4 neutropaenia was similar to the randomised trials by Tannock et al and Petrylak et al (32% and 16.1%, respectively).^{3,4}

When compared to patients receiving 60 mg/m² Q3W, patients who received weekly chemotherapy had a significantly lower overall survival (median of 16.9 months and 10.6 months, respectively). However, we did not observe significant differences for other measures of response. The weekly regimen findings in our study was similar to the study by Berry et al – the median overall survival of 60 metastatic CRPC patients who received weekly docetaxel (36 mg/m² on days 1, 8, 15, 22, 29 and 36 every 8 weeks) was 9.4 months and the proportion of patients who had a PSA response, defined as $\geq 50\%$ decrease of PSA with stabilisation or improvement in performance status lasting 2 months or longer, was 41%.⁸ In a phase II trial by Beer et al, the median overall survival for a group of significantly symptomatic patients on weekly docetaxel (36 mg/m² administered weekly for 6 consecutive weeks followed by 2 weeks without treatment) with compromised performance status was 9.8 months and PSA response rate was 46%.⁹ These trials also observed low rates of treatment-related toxicity.

At our institution, patients who had received weekly docetaxel at our centre were largely more symptomatic (87.5%) than those who received 60 mg/m² Q3W (63.2%).

This was not surprising as the patients treated with a weekly regimen were likely to be less fit with higher disease burden accounting for the symptoms. Hence, a lower overall survival in the weekly group could be explained by both the lower total doses of treatment received by the group and the likelihood of higher diseases burden with shorter projected survival to start with.

There have been numerous studies comparing docetaxel pharmacokinetics (PK) in Asian countries compared to their Western counterparts. These studies seem to show that although interethnic differences were not seen in terms of docetaxel PK values, there seems to be higher toxicities seen in Asians compared to their Western counterparts.¹¹ These studies lend support to the use of the lower dose of docetaxel in our local population of advanced prostate cancer patients as well.

Limitations

This study was limited by the fact that it was a small non-randomised retrospective study of patients treated at a single institution. Treatment regimens were largely allocated by a number of different physicians. This resulted in slightly differing profiles of patients across the 3 groups. It is therefore possible that some of the comparisons here may be affected by such bias. However, since toxicities were apparently higher in the 75 mg/m² Q3W group, which would have otherwise been expected to be fitter than patients receiving 60 mg/m² Q3W, our results are likely to be representative. We are also aware that the weekly docetaxel group with a dose varying between 20 mg/m² to 35 mg/m² on day 1 and day 8 Q3W is not commonly used in many parts of the world and is peculiar to the Singapore setting and presents another limitation to the extrapolation of these results elsewhere. Another limitation was that data on other prognostic factors like haemoglobin, lactate dehydrogenase and alkaline phosphatase were not collected and hence, not controlled for in the analysis. This study also does not have data on the number of patients who needed granulocyte colony-stimulating factor (G-CSF) support as secondary prophylaxis for febrile neutropaenia. None of the physicians in this study had used G-CSF as primary prophylaxis even with the higher dose of docetaxel. This could account for the higher rates of grade 3/4 neutropaenia in this group.

Apart from the above limitations, this study reflects the treatment outcomes of a sample representative of the metastatic CRPC patients treated in Singapore in a real-world setting and provides support for the continued use of docetaxel 60 mg/m² Q3W in Asian patients with CRPC.

Conclusion

As far as we know, this is the first real-world treatment

data to show that docetaxel can be safely administered to metastatic CRPC Asian patients with a dosing guideline of 60 mg/m² Q3W instead of the standard 75 mg/m², with similar efficacy and an acceptable toxicity profile. A weekly docetaxel regimen at dosing guidelines of 20 mg/m² to 35 mg/m² has significant palliative benefits among symptomatic patients despite lower overall survival compared to the Q3W regimens.

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