ANTICANCER RESEARCH *40*: 4291-4297 (2020)
doi:10.21873/anticanres.14431

Comparison of Tolerability Between 2-Weekly and 3-Weekly Docetaxel Regimen in Castration-resistant Prostate Cancer

YUSUKE SHIMURA[1,2], YUKIO SUGA[2], SHINGO ITAI[1], HIROAKI IWAMOTO[3], YUTA TAKEZAWA[3], HIROSHI YAEGASHI[3], KOUJI IZUMI[3], TSUTOMU SHIMADA[1], YOSHIMICHI SAI[1], RYO MATSUSHITA[2] and ATSUSHI MIZOKAMI[3]

[1]*Department of Hospital Pharmacy, University Hospital, Kanazawa University, Kanazawa, Japan;*
[2]*Department of Clinical Pharmacy and Healthcare Science, Faculty of Pharmacy, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan;*
[3]*Department of Integrative Cancer Therapy and Urology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan*

Abstract. *Background: The tolerability of 2-weekly docetaxel at 25-35 mg/m^2 for castration-resistant prostate cancer (CRPC) has not been fully evaluated. The aim of this study was to evaluate its tolerability compared to 3-weekly docetaxel at 60-75 mg/m^2 in patients with CRPC. Patients and Methods: In this retrospective study, data were compared with respect to efficacy and safety between 2-weekly and 3-weekly docetaxel regimens in patients with CRPC. Results: Time to treatment failure and prostate-specific antigen (PSA) response rate did not differ significantly between the two regimens. Compared to 3-weekly administration, incidence of severe leukopenia and febrile neutropenia was significantly lower ($p<0.05$), and relative dose intensity was significantly higher ($p<0.05$) for the 2-weekly schedule. Docetaxel dosage and PSA response were identified as independent risk factors for severe leukopenia. Conclusion: Two-weekly treatment seems better tolerated than three-weekly treatment in Japanese patients with CRPC.*

Prostate cancer is estimated to account for 26% of new cancer cases worldwide (1), and the number of patients with prostate cancer is rapidly increasing in Japan (2). For advanced prostate cancer, hormone therapy or surgery are used as the initial treatment but most cases become resistant to treatment within 2-3 years and progress to castration-resistant prostate cancer (CRPC) (3).

Since the effectiveness of 3-weekly docetaxel at 75 mg/m^2 with prednisone at 10 mg/day was reported in the TAX327 study in 2004 (4), docetaxel has been used for metastatic CRPC (mCRPC) as an international standard treatment. In Japan, a phase II study (ARD6562 study) was conducted to confirm the effectiveness of 3-weekly docetaxel at 70 mg/m^2 with prednisolone at 10 mg/day (5). Based on these results, 3-weekly docetaxel at 75 mg/m^2 was approved in Japan for CRPC in 2008, and docetaxel has been widely used in clinical practice for the treatment of CRPC. However, as the majority of patients with CRPC are elderly individuals and docetaxel resulted in grade 3-4 neutropenia for 93% of patients in a Japanese phase II trial (5), management of side-effects associated with docetaxel is frequently difficult. Several 2-weekly regimens that reduced the individual dosages for docetaxel and shortened the interval between doses by 1 week have been devised. In an international phase III study, 2-weekly docetaxel at 50 mg/m^2 was better tolerated than 3-weekly docetaxel at 75 mg/m^2 (6). Based on these results, 2-weekly docetaxel at 50 mg/m^2 is listed in the National Comprehensive Cancer Network guidelines as an alternative for 3-weekly docetaxel at 75 mg/m^2 (7). On the other hand, in Japan changes in methods of docetaxel administration such as reduced dosage or extended dose interval have been suggested in order to reduce side-effects of docetaxel (8-11). However, the tolerability of 2-weekly docetaxel regimens has not yet been fully evaluated.

The aim of this study was therefore to evaluate the tolerability of 2-weekly docetaxel at 25-35 mg/m^2, taking into account the Japanese physical constitution and side-effects based on the above-mentioned international phase III comparative study (6), compared to that with 3-weekly docetaxel at 60-75 mg/m^2.

Correspondence to: Yukio Suga, Department of Clinical Pharmacy and Healthcare Science, Faculty of Pharmacy, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Takara-machi 13-1, Kanazawa, Ishikawa 920-8641, Japan. Tel: +81 762672831, Fax: +81 762672831, e-mail: suga@staff.kanazawa-u.ac.jp

Key Words: Leukopenia, febrile neutropenia, time to treatment failure, docetaxel, prostate cancer.

Table I. *Patients' characteristics*.

Characteristic	2-Weekly (n=26)	3-Weekly (n=26)	*p*-Value
Age, years	69 (49-81)	73 (52-85)	0.107[a]
ECOG PS, n			
0	0	0	0.385[b]
1	20	17	
2	4	8	
3	2	1	
Metastatic site, n			
Bone			
Yes	25	25	>0.99[b]
No	1	1	
Visceral			
Yes	10	7	0.375[b]
No	16	19	
Previous treatment, n			
Radiation			
Yes	15	12	0.405[b]
No	11	14	
Estramustine			
Yes	13	21	**0.020**[b]
No	13	5	
Serum PSA at initiation of docetaxel, ng/ml			
Median (range)	46.85 (0.45-1,110)	63.89 (0.04-1,980)	0.453[a]
WBC count at initiation of docetaxel, $\times 10^9$/l			
Median (range)	5.65 (2.37-12.70)	6.30 (4.31-11.77)	0.092[a]
Combination corticosteroid, n			
Prednisolone	17	22	0.109[b]
Dexamethasone	9	4	

ECOG PS: Eastern Cooperative Oncology Group performance status; PSA: prostate-specific antigen; WBC: white blood cell. [a]Mann–Whitney *U*-test; [b]chi-squared test. Statistically significant *p*-values are shown in bold.

Patients and Methods

The effectiveness and safety of 2-weekly docetaxel at 25-35 mg/m^2 and 3-weekly docetaxel at 60-75 mg/m^2 were analyzed in this retrospective cohort study of patients with CRPC who received docetaxel at the Department of Urology at Kanazawa University Hospital between September 2008 and June 2018.

Protocols of chemotherapy. Patients received 60-75 mg/m^2 docetaxel on day 1 in a 3-week cycle or 25-35 mg/m^2 on day 1 in a 2-week cycle. Patients who received other docetaxel regimens and patients in whom the docetaxel regimen was changed during treatment were excluded from analysis. The regimen of docetaxel was initially only 3-weekly but a 2-weekly regimen was applied in consideration of the Japanese physique and side-effects with 3-week administration. Regimen selection was left to the attending physician but the 2-weekly regimen tended to be used for more recent cases. In addition, prednisolone or dexamethasone was administered daily as a combination drug.

Data sources. We investigated patient characteristics (age, Eastern Cooperative Oncology Group Performance Status, site of metastasis, previous treatment history, docetaxel dosage, concomitant medications), period of docetaxel administration, presence or absence of dose reduction, and blood data [prostate-specific antigen (PSA), white blood cell (WBC) count, red blood cell count, platelet count].

Definition and outcomes. Time to treatment failure was measured as the time from initiation of docetaxel to its discontinuation in each regimen. PSA response was measured as a ≥50% reduction from baseline maintained for 3 or more weeks. The relative dose intensity (RDI) was obtained by dividing the dose intensity delivered by the planned dose intensity. Grade of toxicity was determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (12). Grade 3 or more hematotoxicity (leukopenia or anemia), febrile neutropenia (FN) and other adverse events likely to occur with docetaxel administration were assessed as side-effects.

Statistical analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences for Windows version 25 software (IBM, Armonk, NY, USA), using Fisher's exact test, the chi-squared test, the Mann–Whitney *U*-test, log-rank testing, and logistic regression analysis. Values of $p<0.05$ were considered statistically significant.

The present study was performed after receiving approval from the Medical Ethics Committee at Kanazawa University (protocol no. 2016-175).

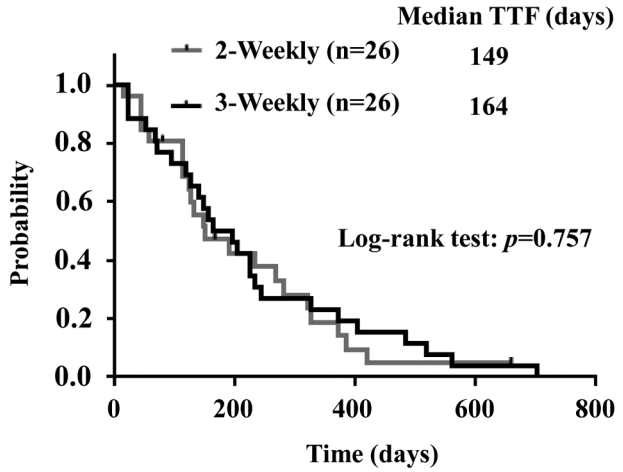

Figure 1. *Time to treatment failure (TTF). Kaplan–Meier survival curves for TTF in groups treated with 2-weekly (n=26) and 3-weekly (n=26) docetaxel therapy.*

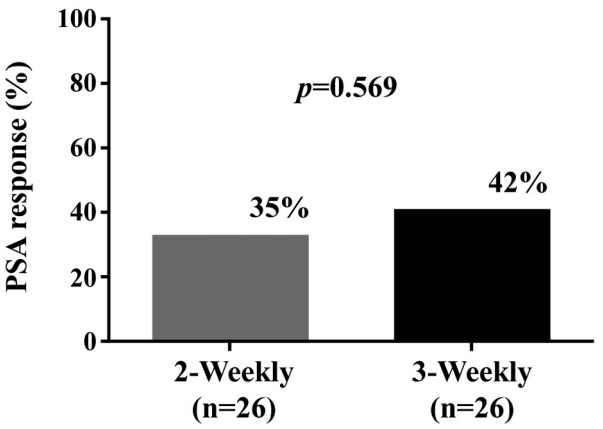

Figure 2. *Rate of PSA response in groups treated with 2-weekly (n=26) and 3-weekly (n=26) docetaxel therapy.*

Results

Patient characteristics. The two treatment groups included 26 patients each. The frequency of previous treatment with estramustine was 50% for the 2-weekly and 81% for the 3-weekly schedules, representing a significant difference (odds ratio=0.238, 95% confidence interval (CI)=0.069-0.824; p=0.020). No significant differences were observed in any other characteristics (Table I).

Time to treatment failure. The median time to treatment failure was 149 days (95% CI=61-237 days) with the 2-weekly and 164 days (95% CI=95-233 days) for the 3-weekly regimens, showing no significant difference between them (p=0.757) (Figure 1).

PSA response. The rate of PSA response was 35% for the 2-weekly and 42% for the 3-weekly regimen, showing no significant difference between methods (odds ratio=0.722, 95% CI=0.235-2.216; p=0.569) (Figure 2).

Incidence of severe leukopenia, FN, and other side-effects. The incidence of grade 3 or more leukopenia was 19% for the 2-weekly and 81% for the 3-weekly regimens (odds ratio=0.057, 95% CI=0.014-0.225; p<0.001). The incidence of FN was 4% for the 2-weekly and 27% for the 3-weekly (odds ratio=0.109, 95% CI=0.012-0.959; p=0.021). The incidences of severe leukopenia and FN were significantly lower with the 2-weekly schedule (Figure 3). No significant differences between groups were evident in the incidence of other side-effects at grade 3 or more, such as anemia, thrombocytopenia, skin disorders (including nail disorders), oral mucositis, edema, neuropathy, and diarrhea (not shown).

RDI. The median RDI was 90% (range=56-100%) for the 2-weekly regimen and 76% (range=48-100%) for the 3-weekly. The RDI was significantly higher with the 2-weekly schedule (p=0.049) (Figure 4).

Risk factors for severe leukopenia. As a result of univariate analysis, we divided the patients into two groups according to the presence or absence of grade 3 or more leukopenia. These groups displayed significant differences in age, docetaxel administration schedule, PSA response rate, and RDI. Furthermore, as a result of multiple logistic regression analyses using the presence or absence of leukopenia of grade 3 or more as an objective variable, and factors showing significant difference from univariate analyses as explanatory variables, docetaxel schedule (adjusted odds ratio=0.024, 95% CI=0.002-0.244; p=0.002) and PSA response (adjusted odds ratio=16.501, 95% CI=1.562-174.259; p=0.020) were identified as independent risk factors for severe leukopenia (Table II).

Discussion

In this study, the frequencies of docetaxel-induced severe leukopenia and FN were significantly lower and RDI was significantly higher with the 2-weekly schedule compared to the 3-weekly one. On the other hand, time to treatment failure and rate of PSA response did not differ significantly between regimens. This suggested that 2-weekly schedule was more tolerable and safer than 3-weekly.

Neutropenia is known to be a dose-limiting toxicity for docetaxel. In this study, although the 3-weekly regimen led to the same rate of severe leukopenia as previously reported (5), the 2-weekly one led a lower incidence than the 3-weekly. In the TAX327 study, a European-based, multicenter,

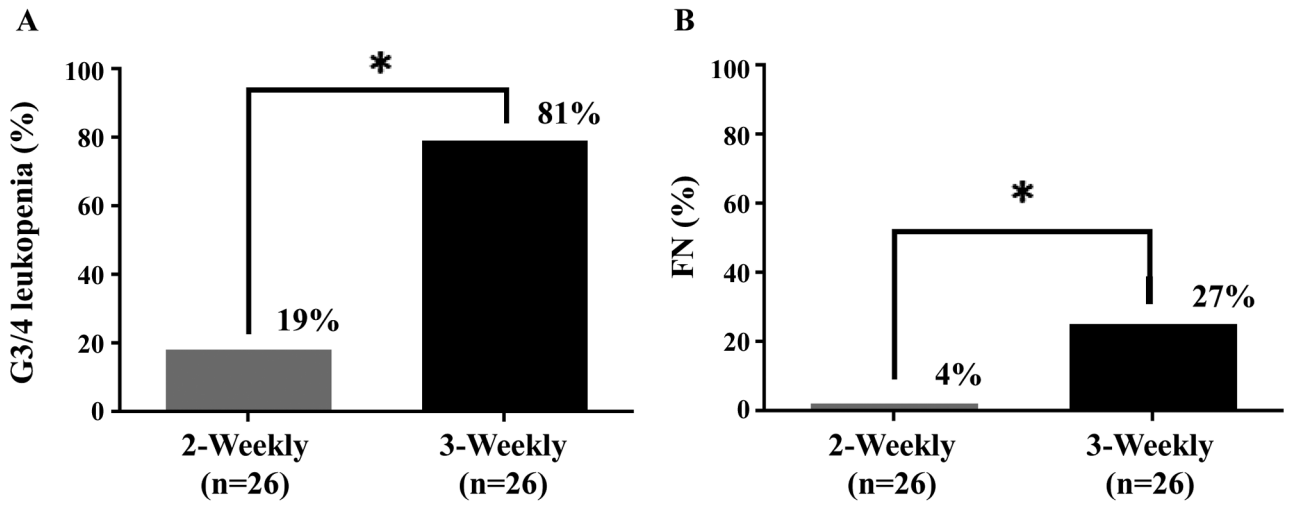

Figure 3. *Rate of severe leukopenia (grade 3 or 4) (A) and febrile neutropenia (FN) (B) in groups treated with 2-weekly (n=26) and 3-weekly (n=26) docetaxel therapy. *Significantly different at p<0.05 by chi-squared test.*

international phase III study, the frequency of grade 3 or more neutropenia was 2% with the weekly group (30 mg/m^2 for 5 weeks followed by 1 week off) and 32% with the 3-weekly group (3-weekly docetaxel at 75 mg/m^2) (4). In addition, the incidence of severe neutropenia from docetaxel was reportedly higher among Asians than among non-Asians (13), and in Japan, the incidences of severe neutropenia and FN were significantly lower with a weekly regimen (20-30 mg/m^2 on days 2 and 9 with estramustine) compared to 3-weekly docetaxel at 60-75 mg/m^2 (10). In advanced breast cancer with 3-weekly docetaxel, the frequency of side-effects increased in a dose-dependent manner (14). From these reports and our results, the frequency of leukopenia or neutropenia induced by docetaxel may have been related to the dosage of docetaxel. Furthermore, methods with reduction of the docetaxel dosage or use of divided doses were suggested to contribute to reducing the frequency of hematotoxicity, and the balance between effectiveness and side-effects such as hematotoxicity should be considered.

With respect to effectiveness, the TAX327 study found that the survival rate was significantly higher in the group treated with 3-weekly docetaxel but not in the weekly docetaxel group compared to the mitoxantrone group (4). On the other hand, an international phase III comparison study of 2-weekly docetaxel at 50 mg/m^2 and 3-weekly docetaxel at 75 mg/m^2 showed comparable efficacy in both groups (6). In addition, comparing 2-weekly docetaxel at 40 mg/m^2 and 3-weekly docetaxel at 75 mg/m^2 in Korean patients with mCRPC, no difference between groups was found in the duration of treatment or PSA response rate (15). Furthermore, in a Japanese report comparing a weekly

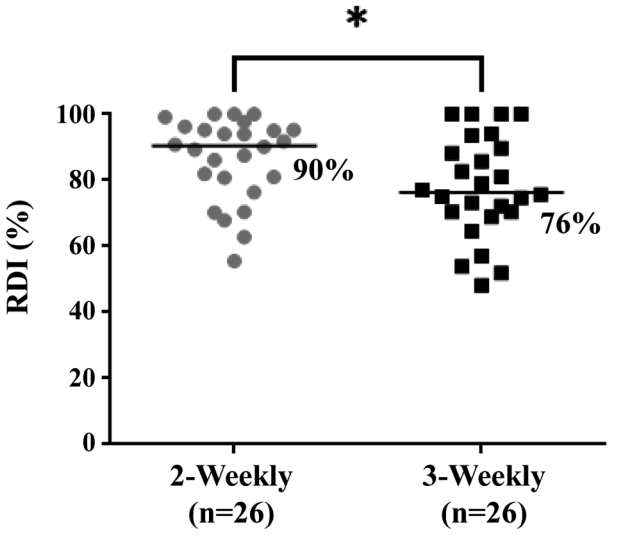

Figure 4. *Comparison of relative dose intensity (RDI) for groups treated with 2-weekly (n=26) and 3-weekly (n=26) docetaxel therapy. The bars represent the median RDI. *Significantly different at p<0.05 by Mann–Whitney U-test.*

docetaxel regimen with a 3-weekly regimen, no difference in efficacy was identified between groups (10), and similar results were shown in the present study. The reasons why efficacy was maintained with the 2-weekly regimen might be as follows: severe leukopenia is less likely to occur compared to the 3-weekly schedule, allowing relatively more frequent maintenance of a high RDI. Since reductions in RDI attenuate the therapeutic effects of multiple chemotherapy

Table II. *Risk factors for severe leukopenia*.

	Severe leukopenia			Multivariate analysis	
	Yes (n=26)	No (n=26)	*p*-Value	AOR (95% CI)	*p*-Value
Age, years					
Median (range)	73 (60-85)	69 (49-81)	**0.045**[a]	1.035 (0.933-1.148)	0.519
ECOG PS, n					
0	0	0	0.634[b]		
1	17	20			
2	7	5			
3	2	1			
Metastatic site, n					
Bone					
Yes	25	25	>0.99[b]		
No	1	1			
Visceral					
Yes	7	10	0.375[b]		
No	19	16			
Previous treatment, n					
Radiation					
Yes	14	13	0.781[b]		
No	12	13			
Estramustine					
Yes	20	14	0.080[b]		
No	6	12			
Schedule, n					
2-Weekly	5	21	**<0.001**[b]	0.024 (0.002-0.244)	**0.002**
3-Weekly	21	5			
Serum PSA at initiation of docetaxel, ng/ml					
Median (range)	52.70 (7.06-1,980)	65.80 (0.04-1,110)	0.660[a]		
PSA response, n					
Yes	15	5	**0.004**[b]	16.501 (1.562-174.259)	**0.020**
No	11	21			
RDI, %					
Median (range)	74 (48-100)	94 (56-100)	**<0.001**[a]	0.939 (0.878-1.005)	0.070
Combination corticosteroid, n					
Prednisolone	21	18	0.337[b]		
Dexamethasone	5	8			
Time to treatment failure, days					
Median (range)	159 (21-701)	147 (14-659)	0.341[a]		
WBC count at initiation of docetaxel, $\times 10^9$/l					
Median (range)	5.94 (2.37-11.77)	5.92 (3.23-12.70)	0.913[a]		

AOR: Adjusted odds ratio; CI: confidence interval; ECOG PS: Eastern Cooperative Oncology Group performance status; PSA: prostate-specific antigen; RDI: relative dose intensity; WBC: white blood cell. [a]Mann–Whitney *U*-test; [b]chi-squared test. Statistically significant *p*-values are shown in bold.

(16, 17), the RDI would be important to maintain the effects of docetaxel. On the other hand, Kamiya *et al*. reported that a relatively low-dose docetaxel regimen showed no significant effect on survival compared to a relatively high dose (18). Furthermore, Kita *et al*. reported that reducing the docetaxel dose did not affect overall survival in Japanese patients with CRPC (19). Further study is clearly necessary to clarify optimal docetaxel dosages and dose intervals.

As mentioned earlier, the tolerability of 2-weekly docetaxel at 40 mg/m^2 administration has been reported for Korean patients with mCRPC (15). The utility of shortening the dosing interval of docetaxel under a lower-dose administration method has also been reported in Japan (8-11). Since no studies used identical dosages and dose intervals, direct comparison of regimens is difficult. In previous reports from Japan, many studies administered estramustine to all patients (8, 10, 11), while another provided this agent to about half of the cases (9). Since a meta-analysis showed that estramustine did not improve overall survival or the frequency of serious side-effects, even when adding estramustine to chemotherapy containing docetaxel and another antineoplastic agent (20), the

significance of adding estramustine is unclear. The present study examining the tolerability of 2-weekly docetaxel without estramustine in Japan would thus be meaningful.

From the results of logistic regression analysis in this study, the frequency of docetaxel-induced severe leukopenia correlated with not only the administered dosage of docetaxel but also with PSA response, independently. As the 3-weekly schedule was more likely to cause severe leukopenia, 2-weekly was more tolerable than 3-weekly. In addition, patients with severe leukopenia showed good PSA response. A correlation between PSA response and improvement of overall survival has been reported in patients with mCRPC (21). On the other hand, severe neutropenia caused by docetaxel has been identified as a factor prolonging overall survival in patients with mCRPC (22). Good response of PSA thus reflects the positive effects of docetaxel; as a result, severe leukopenia was considered to arise in patients with good PSA response. From these results, management of side-effects, particularly taking appropriate measures against hematotoxicities such as leukopenia and neutropenia, would be important in maximizing the effectiveness of docetaxel. Moreover, the present study found no association between severe leukopenia and age or previous history of radiotherapy. However, age over 75 years and previous history of radiotherapy have previously been reported as factors correlated with severe neutropenia in Japanese patients with CRPC (23). The difference between the previous report and this study may be due to administration methods such as dosage and the administration interval for docetaxel.

Limitations of this study included the small number of cases and the retrospective, single-center design. The choice of regimen was left at the discretion of the treating physician, and the 2-weekly schedule tended to be used for more recent cases. A significant difference in the history of estramustine use was seen between groups. In addition, the influence of granulocyte colony-stimulating factor was not studied. More detailed research to clarify these issues is warranted.

Conclusion

This study suggested that 2-weekly treatment was better tolerated than 3-weekly treatment in Japanese patients with CRPC because of the significantly lower frequency of severe leukopenia.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

Y. Shimura, Y. Suga, and K. Izumi participated in research design. Y. Shimura, Y. Suga and T. Shimada performed date analysis. H. Iwamoto, Y. Takezawa, H. Yaegashi, K. Izumi and A. Mizokami were involved in data collection. S. Itai, K. Izumi, T. Shimada, Y. Sai, R. Matsushita, and A. Mizokami critically reviewed the article. Y. Shimura, Y. Suga, S. Itai, K. Izumi, T. Shimada wrote or contributed to the writing of the article. All Authors read and approved the final article.

References

1 Siegel RL, Miller KD and Jemal A: Cancer statistics, 2015. CA Cancer J Clin *65(1)*: 5-29, 2015. PMID: 25559415. DOI: 10.3322/caac.21254

2 Ito K: Prostate cancer in Asian men. Nat Rev Urol *11(4)*: 197-212, 2014. PMID: 24595118. DOI: 10.1038/nrurol.2014.42

3 Harris WP, Mostaghel EA, Nelson PS and Montgomery B: Androgen deprivation therapy: Progress in understanding mechanisms of resistance and optimizing androgen depletion. Nat Clin Pract Urol *6(2)*: 76-85, 2009. PMID: 19198621. DOI: 10.1038/ncpuro1296

4 Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Theodore C, James ND, Turesson I, Rosenthal MA and Eisenberger MA: Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med *351(15)*: 1502-1512, 2004. PMID: 15470213. DOI: 10.1056/NEJMoa040720

5 Naito S, Tsukamoto T, Koga H, Harabayashi T, Sumiyoshi Y, Hoshi S and Akaza H: Docetaxel plus prednisolone for the treatment of metastatic hormone-refractory prostate cancer: A multicenter phase II trial in Japan. Jpn J Clin Oncol *38(5)*: 365-372, 2008. PMID: 18417502. DOI: 10.1093/jjco/hyn029

6 Kellokumpu-Lehtinen PL, Harmenberg U, Joensuu T, McDermott R, Hervonen P, Ginman C, Luukkaa M, Nyandoto P, Hemminki A, Nilsson S, McCaffrey J, Asola R, Turpeenniemi-Hujanen T, Laestadius F, Tasmuth T, Sandberg K, Keane M, Lehtinen I, Luukkaala T and Joensuu H: 2-Weekly *versus* 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: A randomised, phase 3 trial. Lancet Oncol *14(2)*: 117-124, 2013. PMID: 23294853. DOI: 10.1016/S1470-2045(12)70537-5

7 Mohler JL, Antonarakis ES, Armstrong AJ, D'Amico AV, Davis BJ, Dorff T, Eastham JA, Enke CA, Farrington TA, Higano CS, Horwitz EM, Hurwitz M, Ippolito JE, Kane CJ, Kuettel MR, Lang JM, McKenney J, Netto G, Penson DF, Plimack ER, Pow-Sang JM, Pugh TJ, Richey S, Roach M, Rosenfeld S, Schaeffer E, Shabsigh A, Small EJ, Spratt DE, Srinivas S, Tward J, Shead DA and Freedman-Cass DA: Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw *17(5)*: 479-505, 2019. PMID: 31085757. DOI: 10.6004/jnccn.2019.0023

8 Hatano K, Nishimura K, Nakai Y, Yoshida T, Sato M, Kawashima A, Mukai M, Nagahara A, Uemura M, Oka D, Nakayama M, Takayama H, Shimizu K, Meguro N, Tanigawa T, Yamaguchi S, Tsujimura A and Nonomura N: Weekly low-dose docetaxel combined with estramustine and dexamethasone for Japanese patients with metastatic castration-resistant prostate cancer. Int J Clin Oncol *18(4)*: 704-710, 2013. PMID: 22688162. DOI: 10.1007/s10147-012-0429-11

9 Miyake H, Sakai I, Terakawa T, Harada K and Fujisawa M: Oncological outcome of docetaxel-based chemotherapy for Japanese men with metastatic castration-resistant prostate cancer. Urol Oncol *31(6)*: 733-738, 2013. PMID: 21782481. DOI: 10.1016/j.urolonc.2011.06.006

10 Nakai Y, Nishimura K, Nakayama M, Uemura M, Takayama H, Nonomura N and Tsujimura A: Weekly, low-dose docetaxel

combined with estramustine for Japanese castration-resistant prostate cancer: Its efficacy and safety profile compared with tri-weekly standard-dose treatment. Int J Clin Oncol *19(1)*: 165-172, 2014. PMID: 23456140. DOI: 10.1007/s10147-013-0536-7

11 Nakano M, Shoji S, Higure T, Kawakami M, Tomonaga T, Terachi T and Uchida T: Low-dose docetaxel, estramustine and prednisolone combination chemotherapy for castration-resistant prostate cancer. Mol Clin Oncol *4(6)*: 942-946, 2016. PMID: 27284427. DOI: 10.3892/mco.2016.830

12 Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Available at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40 [Last accessed on 23rd June 2020]

13 Yano R, Konno A, Watanabe K, Tsukamoto H, Kayano Y, Ohnaka H, Goto N, Nakamura T and Masada M: Pharmacoethnicity of docetaxel-induced severe neutropenia: Integrated analysis of published phase II and III trials. Int J Clin Oncol *18(1)*: 96-104, 2013. PMID: 22095245. DOI: 10.1007/s10147-011-0349-5

14 Harvey V, Mouridsen H, Semiglazov V, Jakobsen E, Voznyi E, Robinson BA, Groult V, Murawsky M and Cold S: Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. J Clin Oncol *24(31)*: 4963-4970, 2006. PMID: 17033039. DOI: 10.1200/JCO.2005.05.0294

15 Kim HS, Lee JY, Lee SJ, Lim HY, Sung HH, Jeon HG, Jeong BC, Seo SI, Jeon SS, Lee HM, Choi HY and Park SH: A retrospective feasibility study of biweekly, reduced-dose docetaxel in Asian patients with castrate-resistant, metastatic prostate cancer. BMC Urol *17(1)*: 63, 2017. PMID: 28830482. DOI: 10.1186/s12894-017-0253-z

16 Epelbaum R, Faraggi D, Ben-Arie Y, Ben-Shahar M, Haim N, Ron Y, Robinson E and Cohen Y: Survival of diffuse large cell lymphoma. A multivariate analysis including dose intensity variables. Cancer *66(6)*: 1124-1129, 1990. PMID: 2205353. DOI: 10.1002/1097-0142(19900915)66:6<1124::aid-cncr2820660608>3.0.co;2-t

17 Bonadonna G, Valagussa P, Moliterni A, Zambetti M and Brambilla C: Adjuvant cyclophosphamide, methotrexate, and fluorouracil in node-positive breast cancer: The results of 20 years of follow-up. N Engl J Med *332(14)*: 901-906, 1995. PMID: 7877646. DOI: 10.1056/NEJM199504063321401

18 Kamiya N, Suzuki H, Ueda T, Sato N, Nakatsu H, Mikami K, Sato N, Nomura K, Akakura K, Okano T, Ooki T, Naya Y, Ota S, Masai M and Ichikawa T: Clinical outcomes by relative docetaxel dose and dose intensity as chemotherapy for Japanese patients with castration-resistant prostate cancer: A retrospective multi-institutional collaborative study. Int J Clin Oncol *19(1)*: 157-164, 2014. PMID: 23299278. DOI: 10.1007/s10147-012-0510-9

19 Kita Y, Shimizu Y, Inoue T, Kamba T, Yoshimura K and Ogawa O: Reduced-dose docetaxel for castration-resistant prostate cancer has no inferior impact on overall survival in Japanese patients. Int J Clin Oncol *18(4)*: 718-723, 2013. PMID: 22791141. DOI: 10.1007/s10147-012-0443-3

20 Qin Z, Li X, Zhang J, Tang J, Han P, Xu Z, Yu Y, Yang C, Wang C, Xu T, Xu Z and Zou Q: Chemotherapy with or without estramustine for treatment of castration-resistant prostate cancer: A systematic review and meta-analysis. Medicine *95(39)*: e4801, 2016. PMID: 27684806. DOI: 10.1097/MD.0000000000004801

21 Francini E, Petrioli R, Rossi G, Laera L and Roviello G: PSA response rate as a surrogate marker for median overall survival in docetaxel-based first-line treatments for patients with metastatic castration-resistant prostate cancer: An analysis of 22 trials. Tumour Biol *35(11)*: 10601-10607, 2014. PMID: 25195134. DOI: 10.1007/s13277-014-2559-8

22 Buttigliero C, Tucci M, Vignani F, Di Stefano RF, Leone G, Zichi C, Pignataro D, Lacidogna G, Guglielmini P, Numico G, Scagliotti GV and Di Maio M: Chemotherapy-induced neutropenia and outcome in patients with metastatic castration-resistant prostate cancer treated with first-line docetaxel. Clin Genitourin Cancer *16(4)*: 318-324, 2018. PMID: 29866495. DOI: 10.1016/j.clgc.2018.05.006

23 Shigeta K, Kosaka T, Yazawa S, Yasumizu Y, Mizuno R, Nagata H, Shinoda K, Morita S, Miyajima A, Kikuchi E, Nakagawa K, Hasegawa S and Oya M: Predictive factors for severe and febrile neutropenia during docetaxel chemotherapy for castration-resistant prostate cancer. Int J Clin Oncol *20(3)*: 605-612, 2015. PMID: 25196861. DOI: 10.1007/s10147-014-0746-7

Received June 2, 2020
Revised June 20, 2020
Accepted June 24, 2020