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ORIGINAL ARTICLE

Intermittent tri-weekly docetaxel plus bicalutamide in patients with castration-resistant prostate cancer: a single-arm prospective study using a historical control for comparison

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Whether continuous docetaxel (DTX) chemotherapy offers an advantage over intermittent therapy for castration-resistant prostate cancer (CRPC) is unknown. In this study, we evaluated the efficacy, toxicity and quality of life (QoL) of intermittent tri-weekly DTX with bicalutamide in CRPC. Forty-two patients (group A) with CRPC were enrolled. The patients received intravenous DTX (75 mg m^{-2}) once tri-weekly with oral bicalutamide (50 mg) once daily. Patients had a DTX holiday when the prostate-specific antigen (PSA) level declined ⩾50%. DTX was restarted in patients with a PSA increase ⩾25%. Sixty patients (group B) who had matching characteristics and had continuously received DTX without bicalutamide for 10–12 cycles were also enrolled. There were no statistically significant differences in progression-free survival (8 months vs. 9 months, P=0.866) or overall survival (19 months vs. 21 months, P=0.753) between groups A and B; however, the proportions of patients in group A with all grades of neutropenia (33% vs. 58%, P=0.013) and nausea/vomiting (11% vs. 29%, P=0.024) were significantly less compared to group B. A significant improvement in the global health and fatigue scores was recorded for group A post-chemotherapy compared to pre-chemotherapy (P<0.05). The fatigue, nausea/vomiting and appetite loss scores in group B were increased post-chemotherapy compared to pre-chemotherapy (P<0.05). In conclusion, intermittent tri-weekly DTX plus bicalutamide is well tolerated and has the potential to achieve comparable disease control with an improvement in QoL for patients with CRPC.

INTRODUCTION

Castration-resistant prostate cancer (CRPC) is now the second most common cause of male cancer-related mortality.[1] Early-stage prostate cancer can be cured by radical surgery or radiation therapy. However, approximately 10%–20% of men with prostate cancer have metastatic disease, and many others develop metastases despite primary treatment.[2,3] Although most patients with advanced metastatic disease initially respond to androgen deprivation with medical or surgical castration, the response to hormonal treatment lasts for a median duration of 18–24 months. Thus, most patients eventually become androgen deprivation-resistant and develop CRPC.[4]

Recently, data from two large phase III clinical trials (TAX327 and SWOG 9916) have shown a survival benefit for treatment with docetaxel (DTX)-containing chemotherapy regimens compared to mitoxantrone-based therapy in patients with CRPC.[5,6] A maximum of 12 cycles was given in the SWOG trial, and the treatment duration in all three arms of the TAX327 trial was 10 cycles, a length of time that

was arbitrarily selected. The optimal duration of this regimen has not been established;[7,8] however, standard DTX chemotherapy is typically administered without pauses until unacceptable toxicity or disease progression. Thus, responding patients are exposed to uninterrupted chemotherapy for prolonged periods, with a consequent increased risk of toxicity. The potential benefit obtained with chemotherapy might be hampered by the threat of long-term toxicity. Long-term adverse effects associated with continuous DTX treatment include asthenia, oedema, peripheral neuropathy and cytopaenia.[9]

Intermittent chemotherapy represents an attractive therapeutic approach that might achieve comparable disease control with less toxicity and an improvement in the quality of life (QoL). Intermittent chemotherapy was first evaluated in patients with breast and colorectal cancers without adversely impacting overall survival (OS).[10–12] Interestingly, not only has the lack of benefit of prolonged chemotherapy been questioned by Cara,[13] Tannock[14] and Norton,[15] continuous chemotherapy has also been shown to result in the

development of chemotherapy resistance.[8,14,16] Patients with CRPC who previously had discontinued DTX treatment have recently been reported to be sensitive to DTX re-treatment.[17,18] Similarly, three single-arm trials have reported that the intermittent DTX approach displays comparable efficacy in patients with CRPC;[19–21] however, the three trials all used weekly DTX regimens rather than a tri-weekly regimen, which has a proven benefit with an OS increase of 2.5 months compared to controls.[5,6]

Two important mechanisms underlying the development and progression of CRPC, which can be exploited therapeutically, are the overexpression of IL-6 and hypersensitivity or mutation of the androgen receptor, both of which contribute to CRPC.[22–26] Unfortunately, the current DTX regimen does not have a role in these mechanisms. It has been demonstrated that bicalutamide (BCL) can effectively block the effect of IL-6 on a mutated androgen receptor, resulting in the apoptosis of prostate cancer cell lines (DU-145 and LNCAP) *in vitro*.[27] BCL alone has been shown to be safe and have some activity against CRPC.[28–30] When combined with tri-weekly DTX, BCL has a synergistic effect, as confirmed by a phase III trial in androgen-dependent prostate cancer.[31] In addition, a recent study reported that deferred BCL therapy could be at least partially useful after DTX failure for patients with CRPC.[32]

In the present study, we conducted an open-label, non-randomized, historically controlled study to evaluate the approach of intermittent DTX with BCL in patients with CRPC.

MATERIALS AND METHODS

Patients and inclusion criteria
From January 2007 to September 2012, we conducted a single-centre, prospective, open-label, non-randomized, historically controlled study in our institution with an experimental cohort of 42 patients (group A) and a retrospective control group comprising 60 patients (group B) whose inclusion and exclusion criteria matched those of the investigational group.

Eligible patients had an Eastern Cooperative Oncology Group performance status of 0–3, histologically proven adenocarcinoma of the prostate gland and evidence of progressive metastatic disease despite androgen deprivation therapy (ADT). Specifically, progressive metastatic disease included new lesions on a bone scan or three consecutive increases in prostate-specific antigen (PSA) levels over the PSA nadir achieved by ADT separated by 2 weeks. Patients had a serum testosterone concentration < 50 ng dl^{-1} and prior treatment with maximum androgen blockade (luteinizing hormone-releasing hormone agonist or bilateral orchiectomy plus flutamide) with evidence of treatment failure. Flutamide treatment was stopped for at least 4 weeks. Patients had adequate bone marrow, liver, heart, kidney and lung function, defined as a white blood cell count $\geqslant 4000$ per mm^3, granulocyte count $\geqslant 2000$ per mm^3, platelet count $\geqslant 100\,000$ per mm^3, bilirubin $\leqslant 1.5$ mg dl^{-1}, alanine aminotransferase and aspartate aminotransferase $\leqslant 2$ times the institutional upper limit of normal, creatinine $\leqslant 2.0$ mg dl^{-1} or a calculated creatinine clearance $\geqslant 50$ ml min^{-1}, left ventricular ejection fraction $\geqslant 50\%$ by echocardiography and forced expiratory volume in 1 s/forced vital capacity $\geqslant 70\%$. Patients had no history of myocardial infarction within 6 months of study entry and no history of deep venous thrombosis. Patients who were previously treated with BCL and who had undergone prior secondary hormonal therapy, except for withdrawal of flutamide, were excluded. Patients who required DTX dose reduction were also excluded.

The study was performed after approval by the Human Investigations Committee of the Hubei Medical University. Informed consent was obtained from each patient.

Treatment
In group A, the patients received intravenous DTX (75 mg m^{-2}) with dexamethasone on day 1, oral prednisone (5 mg twice daily) and BCL (50 mg once daily for 21 days during each 21-day cycle; intermittent regimen). The group B patients were administered the same tri-weekly DTX and prednisone doses continuously for 10–12 cycles without BCL (continuous regimen).

DTX chemotherapy in group A was suspended when patients achieved a $\geqslant 50\%$ PSA decline associated with stable radiographic scans (the first three cycles of DTX were required as induction chemotherapy before the first drug holiday). During the DTX holiday, patients continued oral prednisone and BCL. DTX was restarted when the PSA level increased $\geqslant 25\%$ or if there was any other evidence of disease progression by imaging using the Response Evaluation Criteria in Solid Tumours criteria (computed tomography scans of the thorax, abdomen and pelvis were performed every 3–6 months) and the Prostate Cancer Working Group 2 bone scan criteria (bone scans performed every 3–6 months). After chemotherapy was resumed, patients in whom the response to re-treatment met the eligibility criteria could have additional chemotherapy holidays. The number of such holidays and re-treatment cycles was not restricted.

Two regimens were interrupted when disease progressed or unacceptable adverse events occurred. Treatment delays $\leqslant 2$ weeks in duration were permitted in cases of severe treatment-related toxicity. Patients were hospitalized if grade 3–4 neutropenia was observed, and granulocyte-colony stimulating factor was used for treatment.

Treatment assessment
The PSA level was assessed at baseline and every 4 weeks thereafter, and diagnostic imaging was performed every 12 weeks. The end points of this study were the time-to-PSA progression, toxicity and QoL. PSA progression was defined as a 25% increase from baseline while receiving chemotherapy and was confirmed by a second measurement 4 weeks later. Progression-free survival (PFS) was defined from the date of the first chemotherapy treatment to the date of PSA progression, which was determined in patients on intermittent chemotherapy from the start of chemotherapy to the date of chemotherapy resistance while receiving DTX. OS was calculated as the time from study entry until the date of death from any cause or censored at last follow-up. The Cancer Institute Common Toxicity Criteria (version 4.0) was used to evaluate patients for toxicity. The QoL parameters were assessed with a QoL questionnaire (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30) at baseline (the day before chemotherapy was started) and every 4 weeks thereafter for 12 months after starting chemotherapy.

Statistical analysis
SPSS (version 19.0) was used for statistical analysis. Descriptive statistics were used to characterize patients at study entry and during DTX holidays. Patient age, PSA level and the interval from ADT-to-CRPC were compared using the Mann–Whitney U test. Other patient demographics and toxicity rates were compared using a Chi-square test. The Kaplan–Meier method was used to characterize PFS and OS. The stratified log-rank test was used to test for differences in time-to-PSA progression and OS by treatment. A paired-samples t-test was performed to analyse the difference between pre- and post-chemotherapy scores for each QoL item. $P < 0.05$ represented statistical significance (two-sided).

RESULTS

Patient characteristics

The study included 102 patients; 42 were enrolled prospectively and 60 were selected to serve as historical controls. The patient characteristics are summarized in **Table 1**. The baseline clinicopathological characteristics were generally well balanced between the two groups, and no significant differences were noted.

Chemotherapy holiday

The median follow-up period was 20 months (range, 3–24 months). In group A, 28 of the 42 patients (66.7%) entered the first treatment holiday. Of these 28 patients, 22 had a ⩾50% PSA reduction and 6 had a PSA level <4 ng ml^{-1}, which was confirmed by a second measurement 4 weeks after the first three cycles. Fourteen patients did not enter the first holiday for the following reasons: 12 patients had disease progression; 1 patient transferred to hospice care during the third DTX infusion and 1 patient had a grade 3 allergic reaction to DTX. **Figure 1a** shows that the median length of the first DTX holiday was 5.3 months (range: 2–20 months); two patients had first holidays of 19 and 20 months. The distribution of the duration of the first DTX holiday is shown in **Figure 1b**, which indicates that a significant percentage of the patients had a DTX holiday duration ⩾6 months. After the first holiday had been taken, a median of three cycles of DTX (range: 2–5) were administered, and 11 (26.2%) patients qualified for a second holiday. **Figure 1a** shows that the median for the second holiday was 2.8 months (range: 1–7 months). Five patients (11.9%) were permitted a third holiday, with a median duration of 1.5 months (range: 1–4 months) after a median of two cycles of infusions (range: 2–4; **Figure 1a**). No patient entered a fourth DTX holiday.

Chemotherapy exposure to DTX

The median dose of DTX was 123.80 mg (range: 101.30–140.50 mg) in group A and 123.65 mg (range: 110.52–155.60 mg) in group B among the evaluated patients; no statistically significant difference was observed between the two groups (P=0.287). The median dose intensity was 225 mg m^{-2} per 6 months (range: 225–375 mg m^{-2} per 6 months) in group A and 525 mg m^{-2} per 6 months (range: 450–600 mg m^{-2} per 6 months) in group B; there was a statistically significant difference (P=0.000) between the two groups.

Toxicity

Table 2 shows the haematological and non-haematological toxicities stratified by grade and treatment group. In group A, transient grade 3–4 neutropenia occurred in 10 patients, grade 3 febrile neutropenia occurred in 1 patient, grade 3 liver dysfunction occurred in 1 patient and a grade 4 allergic reaction was noted in 1 patient. The grade 3–4 treatment-related toxicities in group B were neutropenia (17 patients), anaemia (3 patients), fatigue (2 patients), oedema (2 patients), neurological issues (2 patients) and nausea/vomiting (3 patients). The patients in group A experienced a significant decrease in all grades of neutropenia (33% vs. 58%, P=0.013) and nausea/vomiting (11% vs. 29%, P=0.024). No other significant differences were noted for any grade adverse event.

QoL assessment

A significant improvement in the global health and fatigue scores was recorded for group A post-chemotherapy compared to pre-chemotherapy (P<0.05). However, the symptom report scores (fatigue, nausea/vomiting, appetite loss) in group B were significantly increased post-chemotherapy compared to pre-chemotherapy (P<0.05; **Table 3**).

Table 1 Baseline characteristics of the patients

Index	Group A (n=42)	Group B (n=60)	P
Age (year), median (range)	68 (54–86)	70.5 (57–81)	0.780
ECOG performance score, n (%)			
0	17 (40)	22 (37)	0.697
1	16 (38)	29 (48)	0.305
2	5 (12)	6 (10)	1.000[a]
3	4 (10)	3 (5)	0.623[a]
Prior treatment, n (%)			
Prostatectomy+hormonal therapy	9 (21)	16 (27)	0.545
Radiotherapy+hormonal therapy	27 (64)	37 (62)	0.788
Hormonal therapy	6 (14)	7 (12)	0.696
AAWD response, n (%)	10 (24)	16 (27)	0.924[a]
AAWD response time (month), median (range)	3.15 (1.50–5.57)	3.46 (1.00–6.47)	0.493
Site of metastasis, n (%)			
Bone	40 (95)	57 (90)	0.956
Lymph node	12 (29)	18 (30)	0.876
Liver	5 (12)	4 (7)	0.573[a]
Lung	7 (17)	10 (17)	1.000
Missing data	0	2 (3)	
PSA (ng ml^{-1}), median (range)	63.67 (12.14–1234.53)	77.00 (15.20–1111.48)	0.854
Biopsy Gleason score, n (%)			
⩽6	17 (40)	31 (52)	0.265
7	12 (29)	10 (17)	0.150
7–10	13 (31)	15 (25)	0.507
Missing data	0	4 (7)	
Time from start of ADT to CRPC (month), median (range)	19.50 (5.7–76.80)	16.00 (7.40–49.15)	0.088

Abbreviations: AAWD, anti-androgen withdrawal; ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; ECOG: Eastern Cooperative Oncology Group; PSA, prostate-specific antigen.
[a] P value from a continuity-adjusted Chi-squared test.
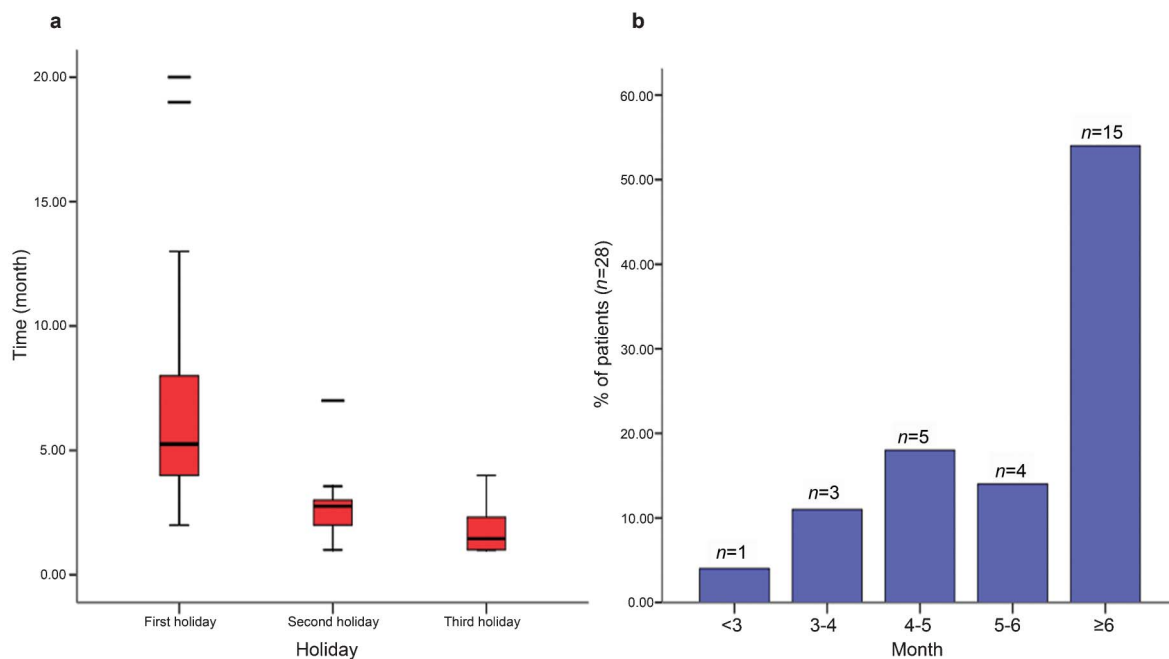
Figure 1 (**a**) Box plots of the docetaxel holiday for 28 patients by intermittent tri-weekly docetaxel plus bicalutamide treatment. The median of the first holiday was 5.3 months. Two patients were outliers (19 and 20 months) in the first holiday. The median of the second holiday was 2.8 months. One patient was an outlier (7 months) in the second holiday. The median of the third holiday was 1.5 months. (**b**) Bar chart of distribution of the first holiday for 28 patients. The first holiday lasted $\geqslant 6$ months for 50% of patients.

PFS

Figure 2a shows the PFS by treatment. The median PFS was 8 months (range: 3–23 months; 95% CI: 6.64–9.36) in group A and 9 months (range: 2–22 months; 95% CI: 7.93–10.07) in group B among the evaluated patients, with 16%±6% and 21%±6% PFS rates at 1 year in the two groups, respectively. No statistically significant difference was observed in PFS between groups A and B (*P*=0.866).

OS

Figure 2b shows OS by treatment. The median OS was 19 months (range: 7–23 months; 95% CI: 17.32–20.68 months) for group A and 21 months (range: 3–24 months; 95% CI: 19.94–20.06 months) for group B. The OS rates for groups A and B were 79%±8% and 72%±6% at 1 year and 29%±9% and 22%±6% at 2 years, respectively.

There was no statistically significant difference in OS between groups A and B (*P*=0.753). Based on the present analysis, 60.7% (17/28) and 65% of patients (39/60) died of prostate cancer in groups A and B, respectively. In group A, one patient died of cerebrovascular disease. In group B, two patients died of acute myocardial infarctions, and one patient died of primary gastric cancer.

DISCUSSION

An intermittent strategy may be desirable for two reasons. First, comparable disease control and improved QoL can be achieved with less toxicity due to less cumulative chemotherapy exposure relative to continuous chemotherapy. Second, less toxic agents can be added during the chemotherapy holiday, which may increase the time of chemotherapy rest and prolong time to chemotherapy resistance.

Table 2 Adverse events of all grades, or of grade 3–4, which occurred during treatment

Toxicity	Group A (n=42)		Group B (n=60)		All grades
	All grades	Grade 3–4	All grades	Grade 3–4	P
Neutropaenia, *n* (%)	14 (33)	4 (10)	35 (58)	10 (17)	0.013
Febrile neutropaenia	1 (2)	1 (2)	3 (5)	0	0.879[a]
Anaemia	4 (10)	0	14 (35)	2 (3)	0.072
Allergic reaction	1 (2)	1 (2)	2 (3)	0	1.000[a]
Fatigue	4 (10)	0	17 (28)	1 (2)	0.021
Oedema	6 (14)	0	15 (25)	1 (2)	0.188
Nausea/vomiting	11 (26)	0	29 (48)	2 (3)	0.024
Diarrhoea	2 (5)	0	7 (12)	0	0.392[a]
Neurological	6 (14)	2 (5)	15 (25)	2 (3)	0.118
Liver dysfunction	5 (12)	1 (2)	4 (7)	0	0.573[a]
Alopecia	16 (38)	0	21 (35)	0	0.749
Nail change	3 (5)	0	10 (20)	0	0.156
Hot flashes	5 (12)	0	6 (10)	0	1.000[a]

[a] *P*-value from a continuity-adjusted Chi-squared test.

Table 3 Cancer quality of life (QoL) questionnaire for individual domains of the QoL with pre- and post-DTX treatment

Index	Group A (n=28[a])			Group B (n=52[b])		
	Pre-DTX	Post-DTX	P	Pre-DTX	Post-DTX	P
Global health status (2–14)[c]	5.69±3.28	6.75±3.17	0.002	7.40±2.48	7.810±2.45	0.186
Functional scales[d]						
Physical functioning (5–20)	9.63±2.94	9.13±2.66	0.088	10.20±3.05	9.35±2.62	0.053
Role functioning (2–8)	4.69±1.66	4.31±1.30	0.083	4.15±1.76	3.75±1.48	0.119
Emotional functioning (4–16)	10.00±3.22	10.75±2.70	0.247	8.70±3.23	9.80±2.93	0.053
Social functioning (2–8)	4.50±1.93	4.69±1.74	0.662	4.70±1.98	4.50±1.47	0.649
Cognitive functioning (2–8)	4.50±1.03	5.06±1.85	0.108	3.90±1.89	4.50±1.70	0.062
Symptom scales[e]						
Fatigue (3–12)	6.57±1.97	5.56±1.26	0.034	5.90±1.71	7.00±1.66	0.007
Nausea and vomiting (2–8)	2.06±0.25	2.69±1.25	0.076	2.25±0.72	3.20±1.12	0.004
Pain (2–8)	3.87±1.78	3.56±1.41	0.552	4.20±1.61	3.80±1.40	0.433
Diarrhoea (1–4)	1.12±0.34	1.25±0.58	0.497	1.20±0.41	1.55±0.76	0.110
Dyspnoea (1–4)	1.13±0.34	1.31±0.60	0.188	1.15±0.49	1.25±0.44	0.428
Insomnia (1–4)	2.75±0.68	2.69±0.79	0.806	2.75±0.79	2.65±0.75	0.716
Appetite loss (1–4)	2.13±0.81	2.31±0.79	0.333	1.85±0.75	2.45±0.60	0.007
Financial difficulties (1–4)	3.44±0.73	3.06±0.92	0.083	3.10±0.64	3.25±0.44	0.379

Abbreviation: DTX: docetaxel.

[a] 28=42−14 (14 patients did not complete the intermittent regimen).

[b] 52=60−8 (8 patients had missing data).

[c] For global health status, 2 corresponded to the worst general condition and 14 corresponded to the best general condition, as perceived by the patient.

[d] For function scales, 5 (physical functioning), 2 (role, social, cognitive) and 4 (emotional) referred to no impairment in corresponding functioning, and 20, 8 and 16 corresponded to severe impairment of functioning, respectively.

[e] For symptom scales, 3 (fatigue), 2 (nausea/vomiting, pain) and 1 (diarrhoea, dyspnoea, insomnia, appetite loss, financial difficulties) corresponded to an absence of symptoms, and 12, 8 and 4 corresponded to the most intense form of symptoms, respectively.

In the present study, the median duration of the first DTX holiday in our patients was 5.3 months, which was higher than that for patients in three single-arm phase II trials. The first two trials reported median times of 4 and 4.5 months.[9,20] The third study reported a median time of 2.8 months.[21] We believe that the first DTX holiday in the three trials and the present study differed for the following reasons. First, the DTX regimens differed. Beer[9,20] and Miller[21] used 35 mg m^{-2} and

36 mg m^{-2} of DTX weekly combined with calcitriol and estramustine, respectively. We administered DTX tri-weekly at a dose of 75 mg m^{-2} combined with prednisone. There are two advantages for the tri-weekly DTX regimen. In contrast, the two large phase III clinical trials previously described showed that tri-weekly DTX regimens demonstrated a survival benefit over mitoxantrone/prednisone (18.9 months *vs.* 16.4 months[5,6]); however, the weekly DTX regimen failed to
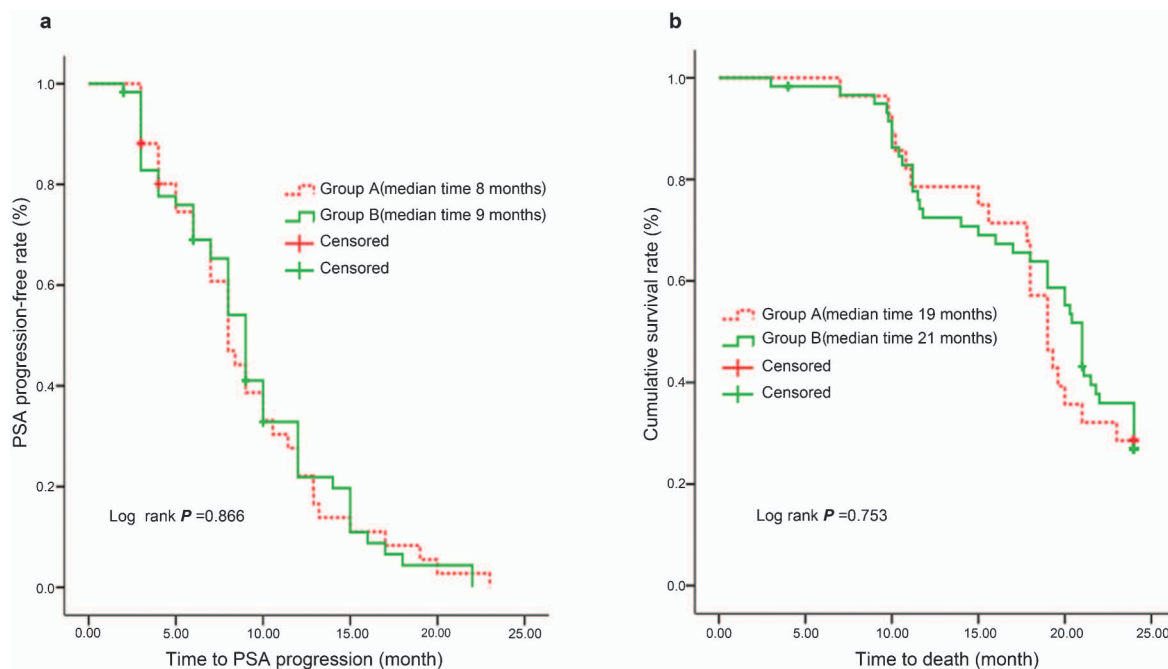
Figure 2 Kaplan–Meier estimates for time-to-PSA progression (**a**) and overall survival (**b**). PSA, prostate-specific antigen.

provide a survival advantage over the control arm. The tri-weekly DTX/prednisone regimen had less toxicity compared with the estramustine-containing arm in the SWOG 9916 trial and potentially greater durability of QoL improvement compared to the weekly DTX arm in the TAX 327 study. Second, there were differences in patient characteristics. The amount of hormonal therapy is adversely related to the PSA response to DTX.[33] Only patients with prior flutamide treatment were enrolled in our study, whereas the patients in Beer's study[9,20] had received flutamide and BCL therapy. Finally, BCL might exert some activity against CRPC. The relative contribution of BCL to the intermittent therapy is analysed as follows. The use of BCL between chemotherapy periods may prevent rapid tumour re-growth and may also play a role in anti-tumour 'maintenance' agents in patients who have undergone initial cytoreduction with chemotherapy. Pre-clinical and clinical data have demonstrated that BCL exerts some anti-tumour activity in patients with CRPC, particularly for those previously treated long-term or who failed flutamide.[27–29] Our study included patients who had previously failed flutamide. Suzuki et al.[34] reported that 35.8% (83 of 232) of patients had a >50% decline in PSA, which was observed after administering an alternative drug (flutamide was replaced by BCL) to patients with CRPC, and the decline lasted >6 months. In addition, tri-weekly DTX and BCL could have a synergistic effect when combined. A phase III trial reported that BCL combined with tri-weekly DTX significantly improved the PSA response and significantly reduced PSA progression at 6 months in patients with hormone-naive metastatic prostate cancer.[31]

In the present study, there were no significant differences between the two groups with respect to the median PFS or OS. The median OS (20 months) in group A was similar to the TAX 327 study (19.2 months[6]). This finding suggests that disease control was comparable between the intermittent tri-weekly DTX with BCL schedule and the continuous regimen. However, the median OS was significantly shorter than that reported by Beer[20] (20 months vs. 41 months), who used intermittent weekly DTX plus high-dose calcitriol. This difference may have been due to different patient characteristics and different regimens; however, the median survival in our study was similar to a report by Soga,[35] who used tri-weekly DTX plus estramustine (20 months vs. 21 months). Similar to the results of our study, Miller[21] also reported a median overall survival of 19 months.

We intermittently administered DTX once tri-weekly plus BCL to patients with CRPC. This regimen was more convenient for patient visits than weekly visits and resulted in fewer cases of neutropenia and fatigue (all grades) compared with the continuous DTX schedule. Although it has been confirmed that long-term BCL treatment is safe even at large doses,[36,37] the incidence of liver toxicity was more common in group A than group B. Thus, regular monthly determinations of liver function and timely withdrawal are required.

The QoL was significantly improved based on global health and fatigue in group A. By contrast, the continuous DTX regimen resulted in a clinically meaningful decline in QoL (fatigue, nausea/vomiting and appetite loss). An improvement in fatigue was similarly reported by Mountzios,[38] who used an intermittent bi-weekly DTX schedule; however, their study lacked a control arm and did not compare the interval lengths between patients who received no chemotherapy and those treated with a secondary chemotherapy regimen. The two QoL items improved in group A for two reasons that may not be mutually exclusive because disease control in group A was comparable to group B. Additionally, this schedule had a lower DTX dose intensity due to the holiday, which reduced chemotherapy-related toxicity.

DTX-induced side effects undoubtedly diminished the patients' health status and increased their financial burden.[39] In the present study, 50% of patients had a ≥6-month DTX holiday.

Finally, we must note that the present study had several limitations, including the small number of patients and the historical controls that were associated with selection bias. In addition, intermittent DTX for CRPC is not the standard of care. In consideration of patient safety and efficacy, a group treated with intermittent DTX alone was not included; therefore, whether intermittent DTX without BCL is as effective is unknown.

CONCLUSION

Intermittent tri-weekly DTX plus BCL is well tolerated and has the potential to achieve comparable disease control with an improvement in QoL (global health and fatigue) for patients with CRPC. This strategy may be an optimal choice for patients who cannot tolerate continuous DTX chemotherapy and have a history of flutamide failure. Further prospective evaluation of a larger number of patients is warranted.

AUTHOR CONTRIBUTIONS

YFL and SFZ participated in the design of the trial, conducted the data acquisition, interpreted and statistically analyzed the data, and drafted and revised the manuscript. DLH designed the study and conducted data interpretation and revised the manuscript. WG conducted the data acquisition and designed the study. TTZ statisically analysed the data. LL designed of the trial, and HTJ, SX and HHJ interpreted the data and drafted the manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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