Comparable efficacy and good tolerability of 2-weekly vs 3- weekly docetaxel in castrate resistant metastatic prostate cancer

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Abstract: Background: Docetaxel administered every 3 weeks is the standard treatment protocol for patients with metastatic, castration resistant prostate cancer. In a prospective, phase 3 study, we try to investigate the efficacy and tolerability of the 2-weekly administration of docetaxelas an alternative in case of intolerance to the 3-weekly regimen. **Methods:** Eligible patients had advanced prostate cancer (metastasis, a prostate-specific-antigen test result of more than 10.0 ng/mL, and WHO performance status score of 0–2), chemotherapy-naive, had undergone surgical or chemical castration, with adequate bone marrow, hepatic, and renal function and had been referred to a treatment center in Tanta university hospital. Enrolment and treatment were done between June 2010 and November 2012. Patients were assigned 75 mg/m² docetaxel intravenously on day 1 of a 3-week cycle, or 45 mg/m² docetaxel intravenously on days 1 and 15of a 4-week cycle. 10 mg oral prednisolone was administered daily to all patients. The primary endpoint was time to treatment failure (TTTF). **Results:** Twenty one patients were randomly assigned to the 2-weekly docetaxel group and 22 to the 3-weekly group and were included in the analysis. The 2-weekly administration was associated with non significant longer TTTF than was 3-weekly administration (5.8 months, 95% CI 3.9 –7.6 *vs*4.5 months, 2.6–6.3; p=0.568). In general, toxicities were similar between both arms. Thirty three percent of patients in the 2-weekly group and 45% in the 3-weekly group had grade 3–4 neutropenia (p=0.41). Patients who received 3-weekly docetaxel had more frequent neutropenic infections and nausea than did those who received 2-weekly docetaxel. Severe adverse events were seen more frequently in the 3-weekly docetaxel group than in the 2-weekly docetaxel group but without statistically significant difference (e.g. infections with neutropenia: p=0.62). There was no grade 3/4 neuropathy. **Conclusion:** The 2-weekly docetaxel regimen seems to be well tolerated in patients with castration resistant advanced prostate cancer and is a feasible option for men who present with comorbidities and who are judged unlikely to tolerate large single doses of docetaxel.
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1.Introduction

Prostate cancer is the second most common cancer in men. The incidence of prostate cancer increases 2% annually from 1995-2001. An estimated 241,740 new cases will be diagnosed in 2012, accounting for 29% of new cancer cases in men in 2012.[1]

Approximately 15% of diagnosed patients will die because of advanced metastatic disease. Androgen deprivation therapy via medical or surgical castration represents the standard treatment of patients with advanced metastatic disease, although progression typically occurs within 1–2 years of initial response[2, 3].

Secondary hormonal therapy is an option in some patients, although responses are transient with currently available agents. Prostate cancer that has progressed despite castrate levels of androgens (<50 ng/ml) is termed castration resistant prostate cancer (CRPC), and clinical manifestations include rising prostate-specific antigen (PSA) concentration in90%, bone metastases in 90%, substantive pain in 35%, and soft-tissue/lymph node metastases in 20% of patients [4].

Several treatment options are available for patients with hormone-refractory prostate cancer, including docetaxel plus prednisone[5] docetaxel plusestramustine[6]cabazitaxelplus prednisone[7]abiraterone[8]sipuleucel-T,[9]enzalutamide(formerly MDV3100)[10,11] and ^{223}radium.[12] Besides docetaxel and cabazitaxel, a few other chemotherapy agents, such as mitoxantrone, estramustine, and vinblastine, have some activity in patients with advanced prostate cancer.[13]

Docetaxel was the first chemotherapy to improve survival in CRPC, as demonstrated in two independent phase III trials reported in 2004[5,6]. In the TAX 327 trial, 1006 patients received docetaxel every 3 weeks (Q3W), docetaxel weekly, or mitoxantrone, with all three arms receiving low-dose prednisone daily. Compared with mitoxantrone, docetaxelQ3W significantly extended overall survival (median 19.2versus 16.3 months, P = 0.004) and was

associated with higher rates of PSA response (i.e. 50% reduction in PSA from baseline; 45% versus 32%, P < 0.001) and pain control (35% versus22%, P = 0.01). Patients who received docetaxel weekly experienced similar responses to docetaxel Q3W but without significantly extended overall survival (median 17.8 months) [5]. An updated analysis based on a longer follow-up time confirmed these results.[14] In the SWOG 99-16 trial, 770 men received either docetaxelQ3W plus estramustine and dexamethasone or mitoxantrone plus prednisone [6]. Similar to TAX-327, patients in the docetaxel arm had increased survival compared with the mitoxantrone arm (17.5 versus 15.6 months, P = 0.02). Following these trials, 3-weekly intravenous administration of docetaxel in combination with oral prednisone has become the standard first-line chemotherapy for castration-resistant advanced prostate cancer.[15,16] Various doses (from 20 mg/m2to 40 mg/m2) have been assessed. We hypothesized that2-weekly administration of docetaxel might be tolerated as well as or better than 3-weekly docetaxel in patients with prostate cancer, and might lead to longer times on treatment and better treatment outcomes with fewer adverse events. We did an open- prospective, phase 3 trial to test this hypothesis.

2. Methods

Patients

We screened and treated eligible patients referred to Tanta university hospital between June 2010 and November 2012. Inclusion criteria were histologically confirmed prostate cancer that had progressed during endocrine treatment; surgical castration or treatment with a luteinising-hormone releasing hormone analogue; no previous cancer chemotherapy; WHO performance status score 0–2; age older than 18 years; presence of distant metastases; and a prostate-specific-antigen (PSA)test result of more than 10.0 ng/mL followed by rising values in two or more consecutive measurements performed at least 2 weeks apart. At least four weeks had to have elapsed between the withdrawal of antiandrogens (six weeks in the case of bicalutamide) and enrollment, so as to avoid the possibility of confounding as a result of the response to anti-androgen withdrawal. Exclusion criteria were any history of cancers other than prostate cancer; any medical condition that precluded administration of chemotherapy; impaired liver function (bilirubin concentration in serum more than 1.5 times the upper limit of normal), alanine or aspartate amino transferase concentrations more than three times the upper limit of normal, alkaline phosphatase activity more than five time the upper limit of normal, except in the presence of bone disease and the absence of liver disorders; impaired renal function (serum creatinine more than 1.5 times the upper limit of normal); blood neutrophil counts lower than 1.5×10^9/L; platelet count lower than 100×10^9/L; or haemoglobin concentration lower than 110 g/L.

Procedures

Patients received 75 mg/m2docetaxel on day 1 of a 3-week cycle. Those in the 2-weeklygroup received 45 mg/m2 docetaxel on days 1 and 15 of a4-week cycle. Each dose of docetaxel was administered intravenously over 60 min. Patients in both groups also received 10 mg oral prednisolone daily. Eight mg dexamethasone two times daily were started 1 day before and stopped1 day after administration of all docetaxel infusions. The dose of docetaxel was reduced if unacceptable toxic effects were noted.

Adverse effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0[17] and were reported on the last day of each cycle. In the case of grade 4 haematological or grade 3 or higher non-haematological toxic effects, the dose of docetaxel was reduced from 75 mg/m2 to 60 mg/m2 in the 3-weekly group, and from 45 mg/m2 to 35 mg/m2 in the 2-weekly group.

Treatment failure was defined as a grade 4 hypersensitivity reaction or intolerance of the lowest dose allowed. Dosing was delayed until recovery to normal neutrophil concentration or recovery from other serious adverse events. If the docetaxel dose was delayed for more than 3 weeks, the patient was taken off trial medication. Granulocyte colony-stimulating factors were not recommended unless patients had at least one episode of febrile neutropenia or developed a severe infection. Treatment with bisphosphonates, erythropoietin, and palliative radiation therapy was allowed.

Cancer stage was confirmed by CT of the abdomen and pelvis, chest radiography or CT, an isotope bone scan, and radiography of known bone lesions within 6 weeks before study entry. Electrocardiography was done within3 weeks before study entry. Blood-cell counts, PSA concentrations in serum, and blood biochemistry were measured and physical examinations were undertaken before study entry. Blood biochemistry was assessed the day before each treatment cycle.

Serum PSA was measured every 2 cycles and tumor imaging was done as indicated. Response to treatment was assessed according to the RECIST criteria [Response Evaluation Criteria In Solid Tumors] (version 1.0).[18] A PSA response was defined as a decrease from the pretreatment concentration in serum by 50% or more that was confirmed by a second measurement at least 4 weeks

later, with no clinical or radiographic evidence for disease progression during this time period. PSA progression was defined as an increase in PSA concentration in serum of 25% or more from the lowest value.[19]

Statistical analysis

The primary endpoint was time to treatment failure (TTTF). It was calculated from the date of randomization to the date of first disease progression (PSA progression or measurable metastasis), unacceptable toxic effects, death, or discontinuation of chemotherapy for any reason. The secondary endpoints were tumor response, PSA response, overall survival (calculated from the date of randomization to the date of death), time to disease progression ([TTP] calculated from the date of randomization to the date of cancer progression or death).We analyzed frequencies of events with Pearson'sχ2 test or Fisher's exact test. Survival was estimated with the Kaplan-Meier method, and survival between groups was compared with the log-rank test. All the statistical analyses were done by SPSS (version 17.0).

3. Results

Forty three patients were enrolled during the period between June 2010 and November 2012 (21 patient in the 2-weekly arm and 22 patients in the 3-weeks arm).The median age and performance status were comparable between both groups [66 years in the 2-weekly group vs 63yearsin the 3-weekly group, (p=0.53); while, PS≤1 was85.7% in the 2-weekly vs 86.3% in the 3-weekly group:(P=0.88)]. The median PSA concentration was higher but without statistically significant difference in the 2-weekly group (P=0.68).

The baseline characteristics of the patients were similar in the two treatment groups (table 1).

Table (1): Patient characteristics.

	2-weekly(n=21)	3-weekly docetaxel (n=22)
Median age (years)	66	63
range	52-74	50-75
mean	64.4	63.3
WHO performance status score(% of patients)		
0	19	13.6
1	66.7	72.7
2	14.3	13.6
Site of metastatic disease*(% of patients)		
Bone	100	96
Node	65	50
Visceral	20	27
Median serum PSA concentrations(ng/mL)	119 (41-210)	105 (44-190)
Therapy before study entry*(%)		
Prostatectomy	5	6
Prostate radiotherapy	40	35
Hormonal therapy	100	100
Radiotherapy since progression (%)	50	45
Receiving bisphosphonates (%)	30	28

We administered 151 cycles of 3-weekly docetaxel and160 cycles of 2-weekly docetaxel (320 doses). The median number of cycles per patient was six cycles in the three week group versus 7 cycles in the biweekly group (range 1–20 in the 3-weekly group and1–17in the 2-weekly groups; p=0.36).

The median duration of follow-up of patients alive after randomization was 15 months (4–19m) at the end of the study. The follow-up time of the last patient who entered to the study exceeded 4months.No patients were lost to follow-up.

At the end of the study, the treatment failure rate was 86%. The most frequent cause of treatment failure was progressive disease (11 [50%] in the 3-weekly group; 10 [47%] in the 2-weeklygroup). Other reasons were adverse events (5 [23%] and 4 [19%]), patients' refusal to continue treatment (1in the 3-weekly group [4%]), death (two in the 3-weekly group [9%] and two in the 2-weeklygroup [9%]), or other or unknown reasons (1 in the 3-weekly group [5%] and 1 in the 2-weeklygroup [5%]).

Adverse events that led to the discontinuation of treatment included fatigue, musculoskeletal changes, and infection. The causes of treatment failure did not differ between the2 treatment groups (p=0・852).

The median TTTF was longer in the2-weekly group than in the 3-weekly group (5.8

months, 95% CI 3.9 –7.6*vs*4.5 months, 2.6–6.3; p=0.568; figure 1) with no statistical significance.

The frequencies of PSA response to chemotherapy did not differ between the 2 treatment groups (table 2).

Time to disease progression (TTP) was longer in the 2-weekly group than in the 3-weekly group, as was overall survival (table 2, figure 2,3).

Only 9 (21%) of patients received second-line chemotherapy, and the frequencies were similar in the two treatment groups (5 [23%] in the 3-weekly group, and 4 [19%] in the 2-weekly group, [p=0.767]).

All eligible patients received treatment and were included in the safety analysis (table 3).

Most AEs were of grades 1 and 2. In general, toxicities were similar between both arms. Seven (33%) of the 21 patients in the 2-weekly group and 10 (45%) of 22 in the 3-weekly group had grade 3–4 neutropenia (p=0.41).No patients died from treatment associated toxic effects. The frequencies of anaemia and thrombocytopenia did not differ between treatment groups. Patients who received 3-weekly docetaxel had more frequent neutropenic infections and nausea than did those who received 2-weekly docetaxel but without statistically significant difference. Severe adverse events were seen more frequently in the 3-weekly docetaxel group than in the 2-weekly docetaxel group but without statistically significant difference (eg. infections with neutropenia: p=0.62). There was no grade 3/4 neuropathy.

The numbers of patients whose docetaxel doses were reduced did not differ between the 2 treatment groups (9 in the 3-weekly docetaxel group [40%], and 7 in the 2-weekly docetaxel group [33%]; p=0.62).

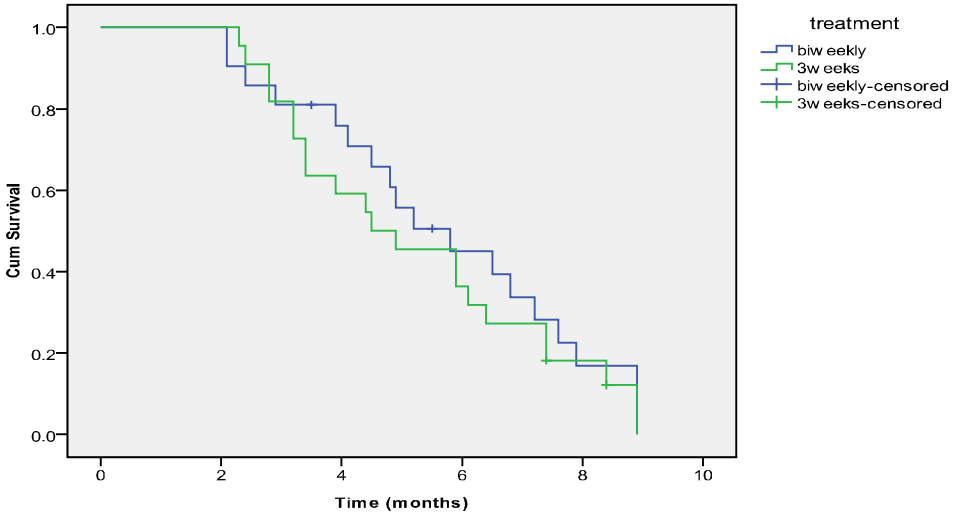
Doses were delayed in the 2-weekly group more frequently than in the 3-weekly group (40 [12%] of 320 doses *vs*10 [6%] of151 doses, p<0.00).

Table (2): Summary of outcomes

	2-weekly(n=21)	3-weekly docetaxel (n=22)	P value
Median (95% CI) TTTF (months)	5.8 (3.9 –7.6)	4.5 (2.6–6.3)	0.568
Median (95% CI) TTP or death (months)	16(14.3-17.6)	14(10.6-17.3)	0.712
Median (95% CI) overall survival (months)	18(17.2-18.7)	15(11.6-18.3)	0.487
PSA response	75	69.5	0.97
Best response to treatment (%)			
Complete or partial response	21	18	
Stable disease	52	55	0.99
Disease progression	29	27	
Medians and 95% CIs are estimated values from Kaplan-Meier analyses. TTTF=time to treatment failure. TTP=time toprogression. PSA=prostate-specific antigen.			

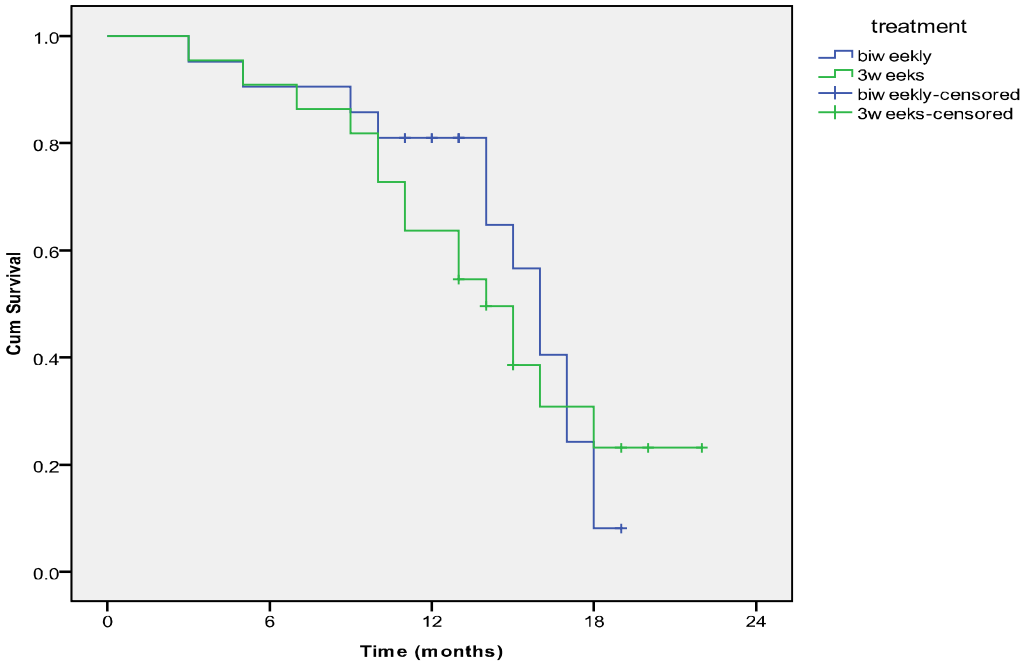
Table (3): Grade 3/4 adverse events

	2-weekly docetaxel (n=21)	3-weekly docetaxel (n=22)
Neutropenia(%)	33	45
Leucopenia(%)	16	18
Anaemia(%)	4	5
Fatique(%)	35	30
Febrile neutropenia(%)	6	9
Infection with neutropenia(%)	38	45
Infection without neutropenia(%)	14	15
Diarrhoea(%)	0	1
Arthralgia(%)	1	1
Neurotoxicity(%)	0	0
Nausea(%)	6	9



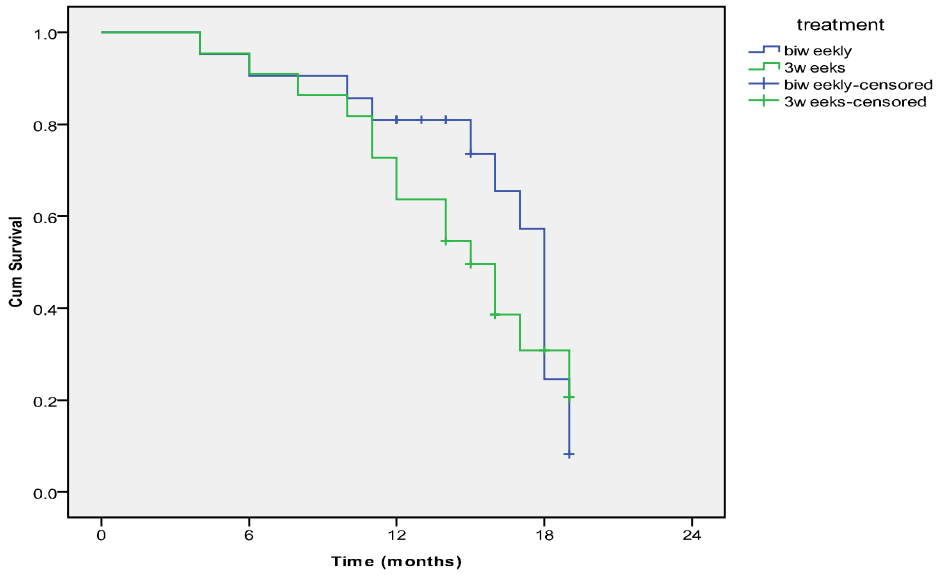
Time to treatment failure

Figure 1: Time to treatment failure.



Time to progression

Figure 2:Time to progression.



Overall survival

Figure 3: Overall survival

4. Discussion

In our study, docetaxel administered every 2 weeks was associated with longer but non significant TTTF and fewer occurrences of neutropenia and neutropenic infections than was 3-weekly administration in patients with castration-resistant advanced prostate cancer.

In Pirkko-Liisa et al recent randomized Scandinavian study, (the Patients were assigned 75 mg/m² docetaxel intravenously on day 1 of a 3-week cycle, or 50 mg/m² docetaxel intravenously on days 1 and 15 of a 4-week cycle)**,** Pirkko-Liisa et al. reported a comparable TTTF in the two weekly vs the three weekly group but with a statistically significant difference [5·6 (5·0–6·2) in the biweekly arm vs 4·9 (4·5–5·4) in the three weekly arm p= 0·014] . This is in consistent with our results, but in our study this difference was not statistically significant which may be due to the smaller number of patient in our study in comparison with that reported by Pirkko-Liisa et al(346 patients [170 patient in the biweekly arm and 176 in the 3 weekly arm]).[13]

Median overall survival was longer in the 2-weekly docetaxel group than in the 3-weekly group. Again, the difference was non significant. The reasons for this difference are unclear, but more frequent docetaxel dosing might improve treatment tolerability and efficacy. The median overall survival achieved in the 2-weekly docetaxel group (18 months) compares well with those reported for patients receiving 3-weekly or weekly docetaxel in the TAX 327 trial (19.2 and 17.8 months, respectively)[5], the docetaxel arm of the SWOG 9916 trial (17.5 months) [6] and that of **Pirkko-Liisa** et al (19.5m) [13].

Treatment safety is a particularly important consideration for patients with advanced prostate cancer because two-thirds of prostate-cancer-related deaths occur in men aged 75 years or older, and many patients have comorbid disorders.[20] In our study, grade 3–4 neutropenia occurred in 7 (33%) of the patients in the 2-week docetaxel group vs10 (45%) in the 3-weekly group. In the TAX 327 trial, where patients received 75 mg/m2 docetaxel every 3 weeks, grade 3–4 neutropenia was seen in 106 (32%) of 332 patients, whereas only seven (2%) of 330 patients who received 30 mg/m2 docetaxel weekly had grade 3–4 neutropenia.[5] In another Scandinavian trial of adjuvant docetaxel administered at 75 mg/m2 every 3 weeks, the incidence of grade 3–4 neutropenia was even higher at 72%.[21] The frequency of severe neutropenia and febrile infections seems, therefore, to be lower when docetaxel is administered in weekly or 2-weekly regimens than in a 3-weekly regimen at similar dose intensities.

Although in the TAX 327 trial weekly docetaxel resulted in slightly shorter overall survival than did 3-weekly docetaxel, the 2-weeklyregimen of 45 mg/m2 docetaxel might be a large enough dose to be efficacious but small enough to achieve tolerability and warrants further analysis.

Few studies have investigated 2-weekly docetaxel regimens to treat castration-resistant advanced prostate cancer, and none has been

randomized except the recent Scandinavian study. In one study, 16 patients with metastatic hormone-resistant prostate cancer were treated with 30 mg/m2 docetaxeladministered every 2 weeks. PSA concentrations in serum decreased by more than 50% in six (38%) patients for a median duration of 4.5 months.[22] In another analysis, patients with androgen-independent prostate cancer were treated with 45 mg/m2 docetaxel every 2 weeks plus estramustine. PSA response was observed in 45 (53%) of 84 patients and objective tumor response in 16 (40%) of 40 patients with measurable disease, and median survival was 16.2 months.[23] Similar results were reported from a series of patients treated with 45 mg/m2 docetaxel every 2 weeks plus estramustine and zoledronic acid, in whom PSA response was seen in 22 (45%) of 49 patients and median survival was 13.3 months.[24] **Pirkko-Liisa** et al reported that the frequencies of PSA response and best responses to chemotherapy did not differ between treatment groups. The PSA response was 49% (84/170) and 42% (74/176) in the biweekly and three weekly regiment respectively (p=0.486).[13]

Several randomized trials have investigated regimens aimed at improving the efficacy of docetaxel plus prednisone, but with little success. Bevacizumab,[25] calcitriol,[26] and GVAX27 yielded no improvements.[27] Cabazitaxel plus prednisone was associated with longer survival than mitoxantrone and prednisone in patients with metastatic castration-resistant advanced prostate cancer after treatment with a docetaxel-containing regimen,[7] and 3-weekly cabazitaxel plus prednisone is being compared with docetaxel plus prednisone in a similar population (NCT01308567). Our findings suggest that studies of the safety and efficacy of 2-weekly cabazitaxel may be warranted.

As in the TAX 327 trial,[5] we did not allow the use of granulocyte colony-stimulating factors unless patients developed febrile neutropenia or a severe infection. In our center, colony stimulating-growth factors are widely used with chemotherapy for advanced metastatic cancer. More liberal administration of leucocyte growth factors might have improved tolerability of the 3-weekly 75 mg/m2 docetaxel dose and could have affected efficacy. The treatments administered after discontinuation of docetaxel varied, but only 21% of patients received second-line treatment which consists mainly of either paclitaxel or mitoxantrone in cases of intolerance or progression. These treatments were unlikely to have greatly affected survival because none of the treatment options that has now been shown to improve survival after docetaxel therapy (eg, cabazitaxel,[6] abiraterone,[8] and enzalutamide[11] was available when the study was done and until now.

We conclude that 45 mg/m2 docetaxel administered every 2 weeks is comparable to 3-weekly docetaxel regarding TTTF and overall survival in patients with castration-resistant advanced prostate cancer. The 2-weekly docetaxel regimen seems a feasible option for men who present with comorbidities and who are judged unlikely to tolerate large single doses of docetaxel.

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