2-weekly versus 3-weekly docetaxel to treat castration-resistant advanced prostate cancer: a randomised, phase 3 trial

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Summary

Background Docetaxel administered every 3 weeks is a standard treatment for castration-resistant advanced prostate cancer. We hypothesised that 2-weekly administration of docetaxel would be better tolerated than 3-weekly docetaxel in patients with castration-resistant advanced prostate cancer, and did a prospective, multicentre, randomised, phase 3 study to compare efficacy and safety.

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), had received no chemotherapy (except with estramustine), had undergone surgical or chemical castration, and had been referred to a treatment centre in Finland, Ireland, or Sweden. Enrolment and treatment were done between March 1, 2004, and May 31, 2009. Randomisation was done centrally and stratified by centre and WHO performance status score of 0–1 *vs* 2. 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. 10 mg oral prednisolone was administered daily to all patients. The primary endpoint was time to treatment failure (TTTF). We assessed data in the per-protocol population. This study is registered with ClinicalTrials.gov, number NCT00255606.

Findings 177 patients were randomly assigned to the 2-weekly docetaxel group and 184 to the 3-weekly group. 170 patients in the 2-weekly group and 176 in the 3-weekly group were included in the analysis. The 2-weekly administration was associated with significantly longer TTTF than was 3-weekly administration (5·6 months, 95% CI 5·0–6·2 *vs* 4·9 months, 4·5–5·4; hazard ratio 1·3, 95% CI 1·1–1·6, p=0·014). Grade 3–4 adverse events occurred more frequently in the 3-weekly than in the 2-weekly administration group, including neutropenia (93 [53%] *vs* 61 [36%]), leucopenia (51 [29%] *vs* 22 [13%]), and febrile neutropenia (25 [14%] *vs* six [4%]). Neutropenic infections were reported more frequently in patients who received docetaxel every 3 weeks (43 [24%] *vs* 11 [6%], p=0·002).

Interpretation Administration of docetaxel every 2 weeks seems to be well tolerated in patients with castration-resistant advanced prostate cancer and could be a useful option when 3-weekly single-dose administration is unlikely to be tolerated.

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Introduction

Androgen deprivation is a standard treatment for advanced prostate cancer and leads to reductions in symptoms in 70–80% of patients.[1] Nevertheless, this treatment is not curative, and most patients develop castration-resistant disease within a median of 2 years.[1,2] Several treatment options are available for patients with hormone-refractory prostate cancer, including docetaxel plus prednisone,[3] docetaxel plus estramustine,[4] cabazitaxel plus prednisone,[5] abiraterone,[6] sipuleucel-T,[7] enzalutamide (formerly MDV3100),[8,9] and ^{223}radium.[10] Besides docetaxel and cabazitaxel, a few other chemotherapy agents, such as mitoxantrone, estramustine, and vinblastine, have some activity in patients with advanced prostate cancer.[11]

Docetaxel was approved for the treatment of metastatic, androgen-refractory prostate cancer by the US Food and Drug Administration in 2004. Approval was based mainly on two randomised trials that showed longer median survival of around 2 months in patients assigned docetaxel than in those who received mitoxantrone plus prednisone.[3,4] In the TAX 327 study,[3] 1006 patients with advanced prostate cancer received 5 mg prednisone twice daily plus 12 mg/m² mitoxantrone every 3 weeks, 75 mg/m² docetaxel every 3 weeks, or 30 mg/m² docetaxel once weekly for 5 of every 6 weeks. Median survival favoured the two docetaxel arms, being 18·9 months and 17·4 months, respectively, versus 16·5 months in the mitoxantrone group.[3] An updated analysis based on a longer follow-up time confirmed these results.[12] In the Southwest Oncology Group (SWOG) 9916 trial,[4] patients received 60 mg/m² docetaxel plus estramustine every 3 weeks or mitoxantrone plus prednisone. Median survival was significantly longer in the docetaxel group than in the mitoxantrone group (17·5 *vs* 15·6 months p=0·02).

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For the **study protocol** see http://www.terveysportti.fi/kotisivut/sivut.koti?p_sivusto=58 in the online version

The docetaxel regimen was associated with more adverse events than was mitoxantrone plus prednisone, including neutropenic fever, fatigue, diarrhoea, nail changes, sensory neuropathy, and alopecia.[3,4]

3-weekly intravenous administration of docetaxel in combination with oral prednisone has become the standard first-line chemotherapy for castration-resistant advanced prostate cancer.[13] Various doses (from 20 mg/m² to 40 mg/m²) have been assessed. We hypothesised that 2-weekly administration of docetaxel might be better tolerated 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. As, to our knowledge, a 2-weekly regimen has not been compared with 3-weekly docetaxel as first-line cytotoxic therapy for advanced prostate cancer in a randomised trial, we did an open-label, parallel-group, prospective, multicentre, phase 3, randomised trial to test this hypothesis.

Methods

Patients

We screened and treated all eligible patients referred to 11 study centres in Finland, Ireland, and Sweden between March 1, 2004, and May 31, 2009. Inclusion criteria were histologically or cytologically confirmed prostate cancer that had progressed during endocrine treatment; surgical castration or treatment with a luteinising-hormone-releasing hormone analogue; no previous cancer chemotherapy except with estramustine; 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. 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 aminotransferase 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 $1·5 \times 10^9$/L; platelet count lower than 100×10^9/L; or haemoglobin concentration lower than 110 g/L.

The study protocol was approved by the institutional review committees at all study centres. All study participants provided written informed consent.

Randomisation and masking

The randomisation schedule was generated centrally at Tampere University Hospital, Tampere, Finland. We used minim.exe software to assign patients to groups in a 1:1 ratio. Allocation to treatment groups was based on the minimisation method, which aims to keep imbalance between the groups to a minimum.[14] Groups were stratified by study centre and WHO performance status score (0–1 *vs* 2) at randomisation.

Procedures

Any systemic cancer therapy was discontinued at least 3 weeks before enrolment. Patients received 75 mg/m² docetaxel on day 1 of a 3-week cycle. Those in the 2-weekly group received 50 mg/m² docetaxel on days 1 and 15 of a 4-week cycle. Each dose of docetaxel was administered intravenously over 60 min. Patients in both groups also received 10 mg oral prednisolone daily. 7·5–8·0 mg dexamethasone daily was started 1 day before and stopped 1–2 days after administration of all docetaxel infusions.

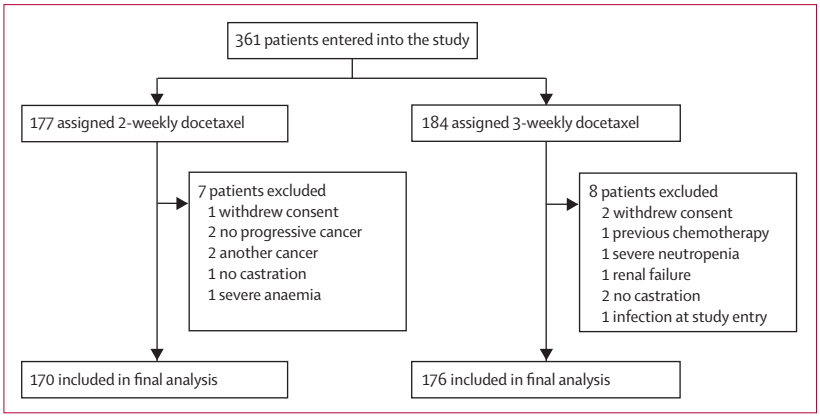

Figure 1: **Trial profile**

	2-weekly docetaxel (n=170)	3-weekly docetaxel (n=176)
Median (range) age (years)	68 (46–85)	69 (45–87)
WHO performance status score		
0	54 (32%)	60 (34%)
1	106 (62%)	105 (60%)
2	10 (6%)	11 (6%)
Site of metastatic disease*		
Bone	147 (87%)	155 (88%)
Liver	10 (6%)	14 (8%)
Lung	13 (8%)	5 (3%)
Lymph nodes or other	73 (43%)	89 (51%)
>2 metastatic sites	62 (37%)	80 (46%)
Median (IQR) serum PSA concentrations (ng/mL)	116 (45–271)	109 (52–246)
Therapy before study entry*		
Prostatectomy	20 (12%)	22 (13%)
Prostate radiotherapy	98 (58%)	93 (53%)
Hormonal therapy	155 (91%)	164 (93%)
Estramustine	12 (7%)	20 (11%)

Data are number (%) unless stated otherwise. PSA=prostate-specific antigen.
*Patients could have more than one.

Table 1: **Baseline characteristics of patients**

The dose of docetaxel was reduced if toxic effects deemed unacceptable were noted. Adverse effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 2·0,[15] and were reported on structured forms 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 50 mg/m² to 40 mg/m² in the 2-weekly group. If toxic effects recurred, further reductions to 45 mg/m² then 30 mg/m² or to 30 mg/m² then 20 mg/m², respectively, were allowed. 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 within 3 weeks before study entry. Blood-cell counts, PSA concentrations in serum, and blood biochemistry were measured and physical examinations were undertaken within 14 days before study entry.

Blood biochemistry was assessed immediately before each treatment cycle, and blood-cell counts were measured immediately before and on day 8 of each cycle. Serum PSA was measured every 6 weeks, 0–3 days before administration of docetaxel, and tumour imaging was done every 12 weeks with CT, radiography and isotope bone scanning. Response to treatment was assessed according to the Response Evaluation Criteria In Solid Tumors (version 1.0).[16] 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.[17] PSA concentrations were measured after alternate 3-weekly cycles. PSA measurements were done at the same time in the 2-weekly group (ie, every 6 weeks) to avoid a bias between treatment groups in the primary endpoint and to maintain blinding of those assessing outcomes. To avoid unnecessary early treatment discontinuation because of a rise in PSA concentration

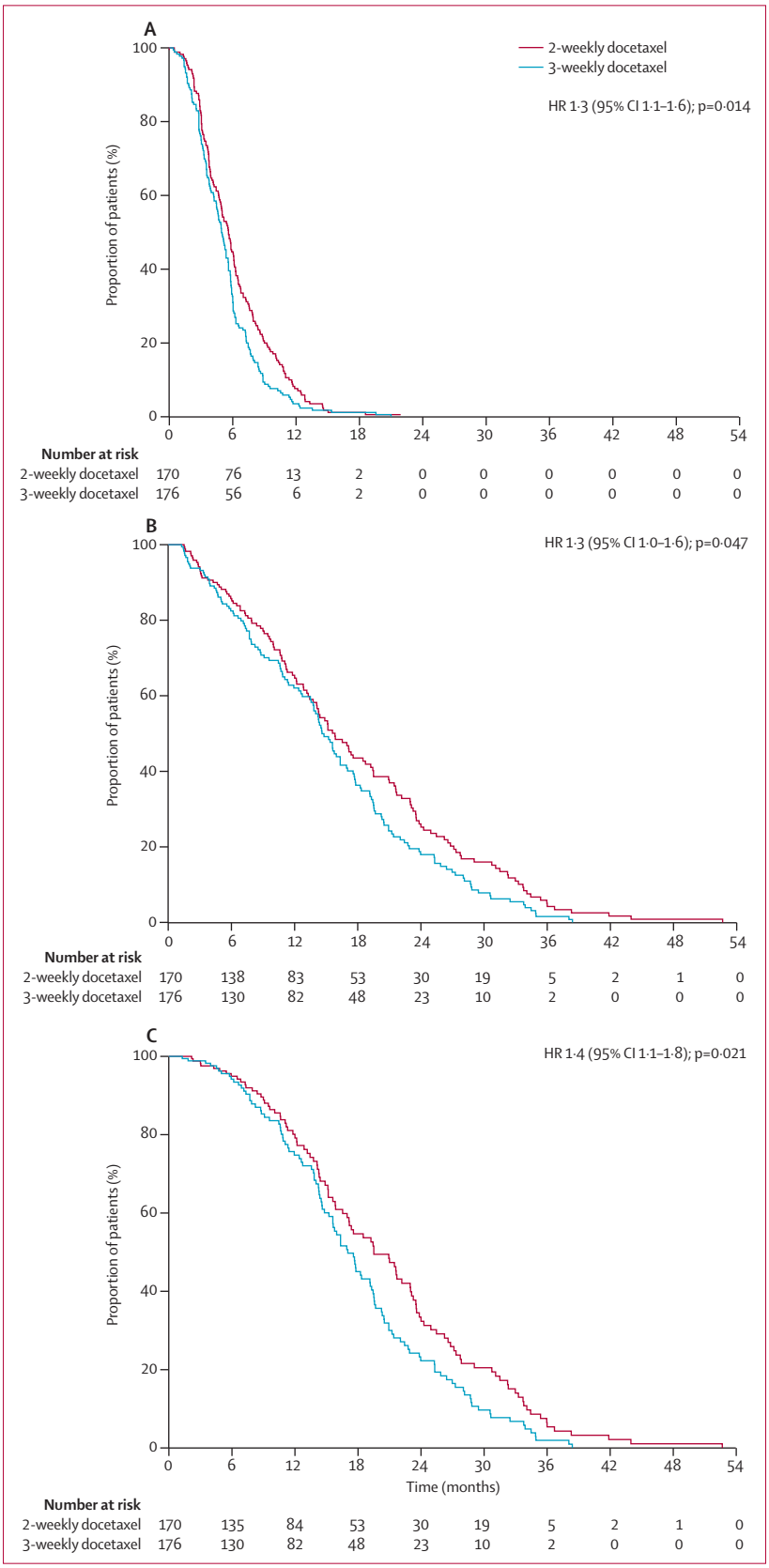

***Figure 2*: Kaplan-Meier survival analysis**
(A) Time to treatment failure. (B) Time to progression. (C) Overall survival. HR=hazard ratio.

caused by tumour flare during the first weeks of docetaxel treatment, the first PSA assessment was done 6 weeks after the start of treatment.

Quality of life was assessed with the functional assessment of cancer therapy—prostate (FACT-P) questionnaire.[18] We asked patients to complete questionnaires at baseline, every 6 weeks during treatment, at the end of the study, and until progression during follow-up. As the questionnaire is available in multiple languages, it was administered in the local language of each study centre. FACT-P is composed of 22 general questions about physical, social, emotional, and functional wellbeing and 17 items related specifically to prostate cancer. Each question or item is answered on a scale from zero to four (0=not at all, 1=a little, 2=somewhat, 3=quite a lot, and 4=very much).

After discontinuation of the protocol treatments, the participants were followed up roughly every 3 months until death or for at least 2 years.

Statistical analysis

The primary endpoint, time to treatment failure (TTTF), was calculated from the date of randomisation 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 tumour response, PSA response, overall survival (calculated from the date of randomisation to the date of death), time to disease progression ([TTP] calculated from the date of randomisation to the date of cancer progression or death), treatment safety, and quality of life.

In the calculation of sample size we assumed that TTTF would be 5 months in the 3-weekly group and 7 months in the 2-weekly group. We calculated that to achieve power of 0·80 and a two-sided significance level of 0·05, we would need to enrol 174 patients per treatment group. We expected loss to follow-up to be negligible, based on hospital records and registry of deaths in Finland, and, therefore, this factor was not taken into account in the power calculations.

We analysed frequencies of events with Pearson's χ^2 test or Fisher's exact test. Continuous variables were compared with the Mann-Whitney *U* test. Survival was estimated with the Kaplan-Meier method, and survival between groups was compared with the log-rank test. We calculated hazard ratios (HRs) and 95% CIs with the unstratified Cox's proportional hazards model. Cox's regression proportionality hazards assumptions were tested and no violations of the proportionality were found.

Adverse events are reported by the most severe grade recorded over all cycles. The grades were analysed in the categories none (grade 0), mild to moderate (grades 1 and 2), and severe (grades 3 and 4) by Pearson's χ^2 test or Fisher's exact test. The mean response was modelled as a linear combination of the population characteristics shared by all individuals (fixed effects), and patient-specific effects constituted the random effects. Patients and centres constituted potential sources of variation and were included as random effects in the models.[19] Adverse events were also modelled between treatment groups, with chemotherapy cycles and chemotherapy time taken into account, groups and their interactions as fixed variables, and the patient, centre, and WHO performance status score at baseline as random effects. The analysis was done with a generalised linear mixed-effects model with an lmer function to show results by comparisons between treatment groups, interactions of time with the groups, and by outcomes in the 3-weekly group compared with those in the 2-weekly group. A binary response (a severe adverse event *vs* none or a less severe event) at each cycle was used as a dependent variable, and the number of cycles over time as a fixed continuous variable.

Quality-of-life factors between treatment groups were analysed with Pearson's χ^2 test or Fisher's exact test.

The generalised linear mixed-effects model was applied with the R statistical software package (version 2.13.0, lme4), and all other the statistical analyses were done SPSS (version 18.0). All p values are two-tailed.

This study is registered with ClinicalTrials.gov, number NCT00255606.

	2-weekly docetaxel (n=170)	3-weekly docetaxel (n=176)	Hazard ratio (95% CI)	p value
Median (95% CI) TTTF (months)	5·6 (5·0–6·2)	4·9 (4·5–5·4)	1·3 (1·1–1·6)	0·014
Median (95% CI) TTP or death (months)	15·8 (13·6–18·1)	14·6 (13·2–16·0)	1·3 (1·0–1·6)	0·047
Median (95% CI) overall survival (months)	19·5 (15·9–23·1)	17·0 (15·0–19·1)	1·4 (1·1–1·8)	0·021
PSA response	84 (49%)	74 (42%)	..	0·486
Best response to treatment				0·952
Complete or partial response	39 (23%)	38 (22%)	..	..
Stable disease	78 (46%)	80 (46%)	..	..
Disease progression	14 (8%)	19 (11%)	..	..
Not available	39 (23%)	39 (22%)	..	..

Medians and 95% CIs are estimated values from Kaplan-Meier analyses. TTTF=time to treatment failure. TTP=time to progression. PSA=prostate-specific antigen.

Table 2: **Summary of primary and secondary outcomes**

Role of the funding source

The study sponsor had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

361 patients were screened. Two patients in the 3-weekly group and one in the 2-weekly group withdrew consent, and six patients in each group had major protocol violations or a medical disorder that precluded docetaxel

administration (figure 1). The remaining 346 patients (176 assigned 3-weekly docetaxel, 170 assigned 2-weekly docetaxel) comprise the per-protocol population. The baseline characteristics of the patients were similar in the two treatment groups (table 1).

We administered 1249 cycles of 3-weekly docetaxel and 1051 cycles of 2-weekly docetaxel (2102 doses). Overall, docetaxel treatment duration was 3747 weeks in the 3-weekly group and 4204 weeks in the 2-weekly group. The median number of cycles per patient was six in each treatment group (range 1–29 in the 3-weekly group and 1–18 in the 2-weekly groups).

The median duration of follow-up of patients alive after randomisation was 18 months (IQR 6–20) on the date of database lock (May 31, 2009); the follow-up time of the last patient who entered to the study exceeded 6 months. No patients were lost to follow-up. At the end of the study, the treatment failure rate was 100%. The most frequent cause of treatment failure was progressive cancer (91 [52%] in the 3-weekly group; 75 [44%] in the 2-weekly group). Other reasons were adverse events (52 [30%] and 65 [38%]), patients' refusal to continue treatment (nine [5%] and eight [5%]), death (two [1%] and two [1%]), or other or unknown reasons (22 [13%] and 20 [12%]). The causes of treatment failure did not differ between the groups (p=0·560). The median TTTF was longer in the 2-weekly group than in the 3-weekly group (5·6 months, 95% CI 5·0–6·2 *vs* 4·9 months, 4·5–5·4; HR 1·3, 95% CI 1·1–1·6, p=0·014; figure 2).

The frequencies of PSA response and best responses to chemotherapy did not differ between treatment groups (table 2). TTP was longer in the 2-weekly group than in the 3-weekly group, as was overall survival (table 2, figure 2). Only 74 (22%) of patients received second-line chemotherapy, and the frequencies were similar in the two treatment groups (35 [21%] in the 3-weekly group, 39 [22%] in the 2-weekly group, p=0·446).

In subgroup analyses the TTTF was longer in the 2-weekly group than in the 3-weekly groups for patients who were younger than 65 years (HR 1·7, 95% CI 1·1–2·5; p=0·009), those with a WHO performance status score of 0 (1·5, 1·0–2·2; p=0·032), for those who lived outside Finland (0·9, 0·7–1·1; p=0·029), and for patients with PSA concentrations in serum lower than the median of 114 ng/mL (1·4, 1·0–1·8; p=0·050).

All eligible patients received treatment and were included in the safety analysis. 93 (53%) of the 176 patients in the 3-weekly group and 61 (36%) of 170 in the 2-weekly group had grade 3–4 neutropenia (p<0·0001), and 25 (14%) and six (4%), respectively, had febrile neutropenia (p=0·001, table 3). 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. Severe adverse events were seen more frequently in the 3-weekly docetaxel group than in the 2-weekly docetaxel group (neutropenia: HR 2·3, 95% CI 1·2–4·2, p=0·007; leucopenia: 2·8, 1·0–7·6, p=0·046; and infections with neutropenia: 4·1, 1·1–15·4, p=0·034). When the occurrence of serious adverse events was modelled, no significant interactions were found between group and time (data not shown). The numbers of patients whose docetaxel doses were reduced did not differ between groups (3-weekly docetaxel group 72 [41%], 2-weekly docetaxel group 69 [41%]; p=0·187). Doses were delayed in the 2-weekly group more frequently than in the 3-weekly group (199 [10%] of 2102 doses *vs* 68 [5%] of 1249 doses, p<0·0001), but both doses per cycle in the 2-weekly group were delayed only 25 times.

	2-weekly docetaxel (n=170)		3-weekly docetaxel (n=176)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Haematological				
Neutropenia	40 (24%)	61 (36%)	6 (3%)	93 (53%)
Leucopenia	49 (29%)	22 (13%)	36 (20%)	51 (29%)
Anaemia	144 (85%)	1 (1%)	142 (81%)	1 (1%)
Thrombocytopenia	20 (12%)	1 (1%)	20 (11%)	0
Febrile neutropenia	0	6 (4%)	0	25 (14%)
Non-haematological				
Fatigue	125 (74%)	25 (15%)	137 (78%)	26 (15%)
Myalgia	59 (35%)	4 (2%)	62 (35%)	2 (1%)
Infection without neutropenia	50 (29%)	18 (11%)	53 (30%)	21 (12%)
Infection with neutropenia	0	11 (6%)	0	43 (24%)
Diarrhoea	61 (36%)	2 (1%)	77 (44%)	4 (2%)
Nausea	58 (34%)	2 (1%)	84 (48%)	2 (1%)
Vomiting	21 (12%)	1 (1%)	20 (11%)	0
Raised alkaline phosphatase concentration	70 (41%)	16 (9%)	82 (47%)	11 (6%)
Raised AST concentration	28 (16%)	1 (1%)	33 (19%)	1 (1%)
Arthralgia	50 (29%)	1 (1%)	67 (38%)	2 (1%)
Pain	109 (64%)	11 (6%)	113 (64%)	12 (7%)
Watery eyes	86 (51%)	3 (2%)	93 (53%)	3 (2%)

We also assessed fever in the absence of neutropenia, serum bilirubin, alanine aminotransferase, or creatinine, alopecia, anorexia, allergic reactions, nail changes, dermatological adverse events, stomatitis, sensory neuropathy, motor neuropathy, bone pain, or weight loss, but no significant differences were seen between groups. AST=aspartate aminotransferase.

Table 3: **Adverse events**

	2-weekly docetaxel (n=152)		3-weekly docetaxel (n=161)	
	Score 1–2	Score 3–4	Score 1–2	Score 3–4
Lack of energy	90 (59%)	23 (15%)	97 (60%)	19 (12%)
Content with quality of life right now	47 (31%)	84 (55%)	50 (31%)	79 (49%)
Pain	89 (59%)	21 (14%)	74 (46%)	31 (19%)
Substantial pain in a specific area	76 (50%)	30 (20%)	61 (38%)	40 (25%)
Pain inhibiting things I want to do	57 (37%)	37 (24%)	48 (30%)	32 (20%)

*Assessed with the functional assessment of cancer therapy—prostate questionnaire.[18] Every question or item is scored on a scale of zero to four: 0=not at all, 1=a little, 2=somewhat, 3=quite a lot, and 4=very much.

Table 4: **Quality-of-life results at baseline***

	2-weekly docetaxel (n=100)		3-weekly docetaxel (n=115)	
	Score 1–2	Score 3–4	Score 1–2	Score 3–4
Lack of energy	48 (59%)	30 (30%)	53 (55%)	33 (29%)
Content with quality of life right now	38 (38%)	50 (50%)	55 (58%)	49 (45%)
Pain	50 (50%)	8 (8%)	63 (55%)	14 (12%)
Substantial pain in a specific area	44 (44%)	13 (13%)	50 (44%)	18 (16%)
Pain inhibiting things I want to do	36 (36%)	12 (12%)	48 (43%)	16 (14%)

*Assessed with the functional assessment of cancer therapy—prostate questionnaire.[18] Every question or item is scored on a scale of zero to four: 0=not at all, 1=a little, 2=somewhat, 3=quite a lot, and 4=very much.

Table 5: **Quality-of-life results at the end of docetaxel treatment***

Quality-of-life features were similar in the two treatment groups at baseline (table 4), after six cycles (data not shown), and at the end of treatment (table 5). The quality-of-life results will be reported in full separately.

Discussion

Docetaxel administered every 2 weeks was associated with longer TTTF and fewer occurrences of neutropenia and neutropenic infections than was 3-weekly administration in patients with castration-resistant advanced prostate cancer. Although the difference in TTTF was significant, the absolute difference between median TTTFs in the two groups was small (0·7 months). Somewhat unexpectedly, median overall survival was longer by 2·5 months in the 2-weekly docetaxel group than in the 3-weekly group. The reasons for this difference are unclear, but more frequent docetaxel dosing might improve treatment tolerability, efficacy, or both. Results for pain-related factors in the quality-of-life questionnaire were similar in the two groups. The median overall survival achieved in the 2-weekly docetaxel group (19·5 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),[12] and the docetaxel arm of the SWOG 9916 trial (17·5 months).[4] These two trials and our study involved similar populations of patients—men with advanced hormone-refractory prostate cancer and median age 68–70 years.[3,4]

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 61 (36%) of the patients in the 2-week docetaxel group and in 93 (53%) 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.[3] In a 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-weekly regimen of 50 mg/m² docetaxel might be a large enough dose to be efficacious (because of a shorter time for the cancer cells to recover) 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 randomised. In one study, 16 patients with metastatic hormone-resistant prostate cancer were treated with 30 mg/m² docetaxel administered 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 tumour 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]

Several randomised trials have investigated regimens aimed at improving the efficacy of docetaxel plus prednisone, but with little success. Bevacizumab,[25] calcitriol,[26] and GVAX[27] yielded no improvements.[2] 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,[5] 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 are warranted.

As in the TAX 327 trial,[3] we did not allow the use of granulocyte colony-stimulating factors unless patients developed febrile neutropenia or a severe infection. In Nordic countries, colony stimulating-growth factors are not widely used with chemotherapy for advanced metastatic cancer. We did not, therefore, collect data on the use of these drugs, which could be viewed as a limitation of this study. 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 a fifth of patients received second-line treatment. Most patients were treated in public hospitals and had similar access to second-line therapy. These treatments were unlikely to

Panel: Research in context

Systematic review

We searched Medline/PubMed with the terms "castration-resistant APC", "docetaxel", and "combination drug therapy" for papers published in English. We found no reports of phase 3 trials of docetaxel[28] in castration-resistant advanced prostate cancer, and only one randomised phase 2 trial showed the effectiveness of 3-weekly docetaxel combined with estramustine.[29] To avoid thromboembolic complications, however, we chose not to use combination therapy.[29,30] Additionally, 2-weekly regimens had been studied in other solid tumours and seemed to be well tolerated.[31,32]

Interpretation

50 mg/m² docetaxel administered every 2 weeks was well tolerated and improved time to treatment failure and median overall survival. This regimen seems, therefore, to offer an option for men who present with comorbidities and who are judged unlikely to tolerate large single doses of docetaxel. Further phase 3 trials with 2-weekly docetaxel to treat castration-resistant advanced prostate cancer are warranted.

have greatly affected survival because none of the treatment options that has now been shown to improve survival after docetaxel therapy (eg, cabazitaxel,[4] abiraterone,[6] and enzalutamide[9]) was available when the study was done.

We conclude that 50 mg/m² docetaxel administered every 2 weeks can improve TTTF and overall survival compared with 3-weekly docetaxel 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 (panel).

Contributors

P-LK-L, TJ, PH, ML, TT-H, and HJ contributed to the study design. P-LK-L, TL, and HJ developed the report with contributions by all authors. P-LK-L, TJ, RM, PH, CG, ML, PN, AH, JM, RA, TT-H, FL, TT, KS, and MK recruited patients. P-LK-L, TJ, PH, TT-H, IL, TL, and HJ contributed to the data collection and analysis, and P-LK-L led the analysis interpretation. P-LK-L, AH, TL, and HJ contributed to the writing of the paper. All authors contributed to review of the paper and approved the final version.

Conflicts of interest

P-LK-L and UH receive honoraria from Sanofi and Roche. RM receives honoraria from Pfizer and GlaxoSmithKline. PH is a paid consultant and adviser to Janssen and receives honoraria from Janssen and Bayer. ML is a paid consultant and adviser to Janssen and Sanofi. HJ receives honoraria from Sanofi. The other authors declare that they have no conflicts of interest.

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