A randomized study of docetaxel and dexamethasone with low- or high-dose estramustine for patients with advanced hormone-refractory prostate cancer

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OBJECTIVE
To test the combination of docetaxel with two different doses of estramustine in patients with hormone-refractory prostate cancer (HRPC), to improve response rates and to lower side-effects, as docetaxel-based chemotherapy is an increasing option for men with advanced HRPC, and alone or combined with estramustine, docetaxel improves median survival.

PATIENTS AND METHODS
In all, 72 patients with metastatic HRPC were randomly assigned to receive docetaxel (70 mg/m² intravenously, on day 2 every 21 days) and estramustine (3 × 280 mg/day oral starting 1 day before docetaxel), for 5 consecutive days for arm A, or estramustine (3 × 140 mg/day oral starting 1 day before docetaxel, for 3 consecutive days) for arm B. Pre-medication with oral dexamethasone at a total daily dose of 16 mg, in divided doses twice a day was administered in arm A on day 1–5 and in arm B on day 1–3. Initially, six cycles were administered. Chemotherapy was restarted after a significant increase in prostate-specific antigen (PSA) level. Patients were monitored for any measurable PSA response and toxicity.

RESULTS
Between the arms there was no statistically significant difference in time to progression and overall survival. However, treatment B had less treatment-related toxicity than A. Independent prognostic variables were baseline factors like PSA level, haemoglobin level, Eastern Cooperative Oncology Group performance status, and bone pain at presentation.

CONCLUSIONS
In this randomized phase II study the combination of docetaxel and estramustine had substantial activity in HRPC, with a significant incidence of severe toxicity, both haematological and not. Nevertheless, treatment-related toxicity was predictable and manageable. There was no better effect with a higher dose of estramustine with docetaxel than for a lower dose. There was a slight tendency to higher toxicity for high-dose estramustine but this was not statistically significant. The present results support the assertion that estramustine is not necessary in docetaxel-based treatment regimens.

KEYWORDS
docetaxel, estramustine, hormone-refractory prostate cancer

INTRODUCTION
For men with newly diagnosed metastatic prostate cancer surgical or medical castration has been the standard treatment for >60 years. After a rapid response, with an improvement in bone pain, regression of soft-tissue metastases, and a decline in PSA levels in virtually all patients, the tumour ultimately becomes refractory to androgen blockade within a median of 18–24 months [1–3]. The median survival for patients with hormone-refractory prostate cancer (HRPC) with no further treatment is ≈12 months. Chemotherapy for HRPC had limited efficacy for improving survival [4] and palliated bone pain in ≈30% of patients. Recently, docetaxel-based chemotherapy of HRPC reportedly showed a significant improvement in survival and quality of life for the first time [5–7].

Docetaxel, a taxoid derived from the European yew tree, Taxus baccata, induces phosphorylation of Bcl-2, leading to its inactivation and subsequently cell death [8,9]. Furthermore, docetaxel promotes the assembly of microtubules, leading to cell-cycle arrest [10]. Docetaxel has been combined with estramustine due to synergistic effects in vivo [11]. Estramustine, a conjugate of oestradiol and non-nitrogen mustard that inhibits microtubule-associated proteins, assembly of the nuclear matrix and p-glycoprotein, has shown synergistic effects with docetaxel against human prostate cancer cell lines in vitro [11,12]. Recently, two multicentre randomized clinical trials showed a clear improvement in overall survival for patients with HRPC [5,6]. There was very similar survival in the docetaxel arm of the Southwest Oncology Group/Intergroup-Study 9916 (docetaxel + estramustine) and the TAX 327 study (docetaxel + prednisone) [5,6], suggesting that docetaxel alone has similar response rates as the combination of docetaxel and estramustine. However, drawing a definitive conclusion requires further randomized clinical studies. There are no studies comparing different estramustine doses combined with docetaxel. Therefore, the optimum dose of estramustine and the frequency of administration needs further refinement. Combinations with a high dose of estramustine were associated with a significant degree of nausea, diarrhoea, leucopenia and cumulative fluid retention, and a greater risk of thromboembolic events [13–15]. Therefore, in the present study we evaluated the efficacy and safety of a modified 3-weekly docetaxel and estramustine regimen in patients with HRPC.
PATIENTS AND METHODS

Eligibility criteria included histopathologically confirmed diagnosis of metastatic adenocarcinoma of the prostate. Additionally, patients must have progressed on at least one hormonal regimen, which included orchidectomy or a LHRH analogue, with documented serum testosterone at castration level (<50 ng/mL). Progression was documented as new or enlarged radiological lesions (an increase of ≥25% in the sum of the perpendicular diameters of all measurable disease, or an increase of ≥25% in the number of bone lesions) or increases of PSA level on three separate measurements at least 1 week apart. Antiandrogen withdrawal and required to continue on their LHRH agonist 1 week apart. Antiandrogen withdrawal and level on three separate measurements at least 8 weeks earlier and radionucleotide such as strontium-89 or required to continue on their LHRH agonist every 21 days, and oral estramustine 2 h after meals at a total daily dose of 420 mg, in divided doses three times a day on days 1–3. Premedication with oral dexamethasone at a total daily dose of 16 mg, in divided doses twice a day, was administered in arm A on day 1–5 and in arm B on day 1–3. The use of colony-stimulating factors and recombinant erythropoietin was not allowed in the study. Treatment continued until disease progression or there were unacceptable adverse effects. There was no limit on the number of cycles or doses for docetaxel and estramustine.

Patients were evaluated for the response radiographically or by repeated CT and radionuclide bone scan after 6, 12, 18 and 24 cycles while on the study. Weekly completed blood cell counts were required during treatment, and samples for serum PSA assay were drawn every 3 weeks (on the first day of each new cycle) during active treatment. Any worsening of a pre-existing condition after exposure to the trial medication was considered as an adverse event. The severity of the adverse events was scored according to the revised National Cancer Institute Common Toxicity Criteria, version 1. In this study, the term ‘toxicity’ referred to grade 3 and 4 adverse effects that occurred after exposure to the study drug.

The primary endpoint was the anti-tumour response, as determined by the effect of treatment on serum PSA level (decline ≥50%). In reporting the study results, PSA decreases were tabulated in accordance with the consensus guidelines in phase II trials of cytotoxic agents for the treatment of HRPC the PSA Working Group, using ≥75% or ≥50% decline in PSA, respectively [16]. The secondary endpoints were time to progression (TTP), overall survival, safety, and clinical benefit.

TTP was measured from the date of first docetaxel administration to the date of PSA progression, and was defined by a ≥25% increase in PSA level from baseline or a ≥50% increase in PSA level from the lowest value achieved, confirmed by three successive measurements at 3-week intervals. However, the date of disease progression was the date of the first increase in serum PSA level. For patients with measurable soft-tissue disease the date of progression was defined as the date of the first CT that showed either new lesions or a 25% increase in the bi-dimensional measurements of previously measured disease. For those with bone metastases, new lesions on radionuclide bone scan (but not worsening of the intensity of existing lesions) were qualified as progressive disease. A worsened PS by at least one level in the absence of objective disease progression also constituted progressive disease. Overall survival was defined as the time between the first docetaxel administration and death or date of last follow-up. In an exploratory manner, to calculate the time on primary treatment, patients receiving second-line chemotherapy were censored at the onset of the second-line treatment.

A design was used with accrual of 68 patients. With this sample size, a PSA response of 60% could be distinguished from a 40% response, with 80% power and a type I error (two-sided) of 0.05. The method for the randomization procedure was simple randomization. The intent-to-treat (ITT) population included all randomly assigned patients. Patients who received at least one cycle were assessable for response and toxicity (modified ITT). The survival curves were generated using the Kaplan–Meier [17] method, and the log-rank test [18] was used to compare treatment arms for survival duration and time to PSA progression. The relationship between any continuous covariate and survival was calculated by univariate analysis (Cox hazards regression). A multivariate Cox regression analysis for multiple proportional hazards using a backward stepwise conditional approach was used to assess which combination of variables could predict survival, after adjustment by treatment arm. First, a confirmatory analysis with a pre-specified set of variables was used, followed by an exploratory analysis to confirm the results. Fisher’s exact and Pearson’s chi-square test were used to compare demographic, clinical, and biological variables, respectively.

RESULTS

Between January 2002 and July 2005, 72 patients entered the two-arm randomized study, with 38 and 34 assigned to arms A and B, respectively. There were no significant differences between the treatment arms in baseline clinical and biological characteristics. The efficacy and safety analyses included all 72 patients who comprised the modified ITT. The median age of patients was 68 years and the median (range) PSA level at study entry was 140.6 (0.7–4973) ng/mL; 77% of patients had bone metastases, 39% had two or more
organisms involved, and 45% had tumour-related bone pain (Table 1). The total number of chemotherapeutic cycles in arm A and B was 278 and 241, respectively, with a median (range) in arm A of 6 (1–25) and in arm B of 6 (1–19).

The primary objective of the study was to evaluate the response as determined by the decrease in PSA level. There was a PSA decline of ≥75% and ≥50% in 37% and 55% in arm A, and 38% and 68% in arm B, respectively. In arm A 45% of the patients had a PSA decline of ≤50%, vs 32% in arm B. The two-by-two test showed no statistically significant difference between the arms (P = 0.442). The median (SEM, 95% CI) time to PSA progression (Fig. 1) was 11 (1.5, 7–14) months in arm A and 14 (3, 0, 8–19) months in arm B (P = 0.089).

Survival was analysed at a median (95% CI) follow-up of 14.5 (11–16) months, when 33 patients (46%) had died. The estimated follow-up of 14.5 (11–16) months, when 33 patients (46%) had died. The estimated median (SEM, 95% CI) overall survival was not significantly different between the arms, at 21 (7.5, 6–35) and 22 (2.2, 18–27) months in arms A and B, respectively (P = 0.4149; Fig. 2). At 3, 6, 12, 24 and 34 months, 95%, 79%, 63%, 50% and 31% were alive in arm A, and 100%, 96%, 92%, 41% and 22% of patients were alive in arm B, respectively (log rank P = 0.415).

Table 2 shows that the baseline characteristics associated with an improvement in overall survival in univariate analysis were ECOG PS (P < 0.001), 0 vs 1 vs 2, 36 vs 17 vs 6 months, respectively; log rank, P < 0.001), baseline bone pain (P < 0.001), pain vs no pain, 33 vs 12 months; log rank P < 0.001), baseline haemoglobin level (P = 0.001, Cox regression; threshold ≥7.5 vs ≤7.5 mmol/L, 33 vs 16 months, respectively; log rank P = 0.003), baseline PSA level (P = 0.097, threshold ≥100 vs ≤100 ng/mL, 17 vs 36 months, respectively; log rank P = 0.004).

The multivariate analysis of prognostic variables (Table 2) adjusted by treatment arm showed a significant association between overall survival and ECOG PS (P < 0.001) and bone pain at presentation (P < 0.001). A poor ECOG PS and bone pain at presentation were associated with a worse prognosis.

For other prognostic factors, overall survival was correlated with a PSA decline and median haemoglobin level during treatment. The estimated median survival for patients with a ≥75% decrease in serum PSA was not reached, at a mean (SEM, 95% CI) of 31.7 (2.79, 26.3–37.2) months, and for patients with a 50–75% decrease in serum PSA level the estimated median (SEM, 95% CI) was 27 (6.9, 13.4–40.1) months. By contrast, the estimated median TTP for patients with a PSA decrease of less than half was 16 (3.8, 8.5–23.4) months (log rank P = 0.001). The median haemoglobin level was also associated with overall survival (P < 0.004, Cox regression, threshold ≥6.9 vs ≤6.9 mmol/L, 33 vs 18 months, respectively; log rank P = 0.007).

In this randomized phase II study the combination of docetaxel and estramustine was associated with a substantial incidence of severe toxicity, both haematological and not. Nevertheless, treatment-related toxicities

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**Table 1** The patients’ characteristics at baseline according to random assignment (74 men)

<table>
<thead>
<tr>
<th>Baseline demographic and cancer status of evaluable patients</th>
<th>Arm A</th>
<th>Arm B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>38</td>
<td>34</td>
</tr>
<tr>
<td>Median age, years</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Age distribution, years, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>2 (5)</td>
<td>0</td>
</tr>
<tr>
<td>50–65</td>
<td>9 (24)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>27 (71)</td>
<td>25 (74)</td>
</tr>
<tr>
<td>Median (range) PSA, ng/mL</td>
<td>114.6 (0.7–4973)</td>
<td>163.2 (8.9–3899)</td>
</tr>
<tr>
<td>N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site of metastases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>29 (76)</td>
<td>28 (82)</td>
</tr>
<tr>
<td>Bone + nodes</td>
<td>14 (37)</td>
<td>12 (35)</td>
</tr>
<tr>
<td>Bone + visceral</td>
<td>3 (8)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Bone + nodes + visceral</td>
<td>3 (8)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Nodes</td>
<td>17 (45)</td>
<td>14 (41)</td>
</tr>
<tr>
<td>Visceral</td>
<td>3 (8)*</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Visceral + visceral</td>
<td>3 (8)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (full activity)</td>
<td>12 (32)</td>
<td>10 (29)</td>
</tr>
<tr>
<td>1 (ambulatory)</td>
<td>20 (53)</td>
<td>17 (50)</td>
</tr>
<tr>
<td>2 (in bed ≥50% of time)</td>
<td>6 (16)</td>
<td>7 (21)</td>
</tr>
<tr>
<td>Tumour-related bone pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>18 (47)</td>
<td>15 (44)</td>
</tr>
<tr>
<td>Not present</td>
<td>20 (53)</td>
<td>19 (56)</td>
</tr>
<tr>
<td>Previous treatment to primary site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery alone</td>
<td>7 (18)</td>
<td>8 (24)</td>
</tr>
<tr>
<td>External beam radiation alone</td>
<td>5 (13)</td>
<td>4 (12)</td>
</tr>
<tr>
<td>None</td>
<td>26 (68)</td>
<td>22 (65)</td>
</tr>
</tbody>
</table>

*one patient with lung and liver metastases.

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**Table 2** The results of univariate and multivariate analyses for overall survival; the association of baseline factors with overall survival univariate and multivariate analysis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariate Hazard ratio (95% CI)</th>
<th>P</th>
<th>Multivariate Hazard ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG PS</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>6.4 (2.9–13.9)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin level</td>
<td>0.001</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Bone pain at presentation</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>8.0 (3.2–20.1)</td>
<td></td>
</tr>
<tr>
<td>PSA level at presentation</td>
<td>0.097</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>
were predictable and manageable. The toxicity was considered similar to that in other studies of 3-weekly docetaxel and estramustine [6,19]. There were no treatment-related deaths. Five patients were taken off therapy for non-haematological toxicities (venous thrombosis and asthenia). The toxicity of the study regimen in arm B was slightly lower than in arm A. The primary treatment-related side-effect in patients was granulocytopenia, with no significant difference between arm A and B (34% vs 29%, respectively; \( P = 0.663 \)).

No patient developed febrile neutropenia. The most common grade 1–2 or higher non-haematological toxicity was alopecia, which occurred in 47 patients (65%). There was nail and skin toxicity in 12% of patients in each arm. There were thrombotic complications caused by estramustine in arm A in four patients (11%) and in arm B in one (3%) (\( P = 0.206 \)). The most common grade 3–4 toxicity was for fatigue/malaise/asthenia, which was present in 10 patients (26%) in arm A and in five (15%) in arm B (\( P = 0.226 \)). Details of grade 3 and 4 toxicities occurring at any time during treatment are summarized in Table 3.

**DISCUSSION**

This is the first prospective randomized trial to compare two different estramustine dosages combined with docetaxel in patients with HRPC. The overall 50% PSA response rate (55% and 68% for arm A and B, respectively) was similar to that reported by other published studies (45–74%) [19,20]. The present data indicate no difference between the treatment arms in TTP and overall survival. The median survival time of 20 months reported by Savarese et al. [19] is similar to the overall survival in the two arms of the present study, at 20.4 and 19.2 months in arm A and B, respectively. Consistent with previously published studies [7,21–23] the present univariate and multivariate analyses showed that baseline PSA level, ECOG PS, haemoglobin level and bone pain at presentation were the main predictive factors for survival. Importantly, the PSA level at study entry predicted the effect on TTP and survival; there was a trend to longer TTP and survival in patients with lower PSA levels at presentation. We identified the threshold for the baseline PSA level at 100 ng/mL, as reported earlier [23]. The design of the studies did not allow us to postulate that an early start to chemotherapy in patients with HRPC is beneficial, or if to assess the concept of lead-time bias; this requires further refinement. Importantly, low median haemoglobin levels during treatment were associated with a shorter survival. Anaemia was an independent prognostic variable, as
shown in other studies [24,25]. These findings implicate haemoglobin level as a valuable target for combination therapies with recombinant human erythropoietin. This might enhance the effectiveness of docetaxel-based chemotherapy in HRPC and improve quality of life. Overall survival was also correlated with the PSA decline after therapy (≥75% and ≥50%) in the study. Other studies reported similar results [7,23,26–28], whereas others found no strong correlation [29]. Whether the PSA response is a clinically meaningful endpoint in patients with HRPC remains controversial.

The toxicity in the two arms was similar to that in other clinical trials with docetaxel and estramustine, and was mainly haematological. Granulocytopenia was reported in 34% of patients in arm A and 29% in arm B; there was no febrile neutropenia. In accordance with the haematological toxicity, treatment in arm A was associated with a higher incidence of grade 3 and 4 fatigue/malaise/asthenia than was arm B (26% and 15%, respectively). Similar to rates in published studies [7,13,14,19,23], the rate of estramustine-induced vascular events was 11% in arm A and 3% in arm B. As reported earlier by our group, the treatment schedules used in the present study were safe, with moderate toxicity. There was a slight tendency to greater toxicity in the high-dose estramustine regimen, but this was not statistically significant. It is still not clear if estramustine is essential to the efficacy of docetaxel-based regimens. The rationale for combining estramustine and docetaxel in patients with HRPC was based on their additive or synergistic activity in vitro [30]. Estramustine interacts at the level of the nuclear matrix and microtubules, but its main activity might be a hormonal effect. Estramustine has virtually no effect as a single agent for HRPC [31]. The almost identical survival in the two arms of the present study suggest that low-dose estramustine is sufficient, or that estramustine has no additional effect, as suggested by others. In future clinical trials a direct comparison of docetaxel vs docetaxel/estramustine is urgently needed.

In conclusion, docetaxel-based chemotherapy seems to have a significant effect on the management of HRPC. The treatment is effective and reasonably well tolerated. The response rates, median TTP and median overall survival were higher than those reported for any other combined regimen [14,32,33]. Our response data are consistent with results from other single-institution studies and from multicentre, randomized studies [5,6,19,34]. We also showed that a docetaxel/low-dose estramustine combination retains the clinical efficacy of high-dose estramustine combinations, but with a lower side-effect profile. These results suggest a greater role for systemic chemotherapy in the management of HRPC. Although docetaxel might not be suitable for every patient with metastatic HRPC, it is a promising new treatment. Other docetaxel-based regimens under investigation include combinations with angiogenesis inhibitors (bevacizumab, thalidomide), antisense oligonucleotides (GTL-2040, G3139), oncolytic virus (CG7870), endothelin-A-receptor antagonists (atrasentan) and calcitriol.

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CONFLICT OF INTEREST

None declared.

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Abbreviations: HRPC, hormone-refractory prostate cancer; TTP, time to progression; ITT, intent-to-treat; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ULN, upper limit of normal.