ORIGINAL ARTICLE

Chemotherapy plus estramustine for management of castration-resistant prostate cancer: Meta-analysis of randomized controlled trials

C. Zhang, T. Jing, F. Wang, X. Gao, C. Xu, Y. Sun

Department of Urology, Shanghai Hospital, Second Military Medical University, Shanghai, China

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Abstract

Objective: Estramustine, an agent with both hormonal and non-hormonal effects in men, is supposed to be effective in treating castration-resistant prostate cancer. However, previous studies have reported conflicting results. We conducted this meta-analysis to evaluate the efficacy and toxicity of additional estramustine to chemotherapy.

Methods: Data sources including PubMed, Medline, EMBASE, and Cochrane Controlled Trials Register were searched to identify potentially relevant randomized controlled trials. Prostate specific antigen (PSA) response, overall survival, and grades 3–4 toxicity were analyzed.

Results: Seven randomized controlled trials, a total of 839 patients, were enrolled. The pooled odds ratio for PSA response was 3.02 (95% CI = 1.69–5.39, p = .0002); the pooled hazard ratio for overall survival was .95 (95% CI = .80–1.14, p = .58); the pooled odds ratio for nausea/vomiting and cardiovascular toxicity were 3.90 (95% CI = 1.05–14.45, p = .04) and 2.22 (95% CI = 1.15–4.30, p = .02). No significant difference was detected for neutropenia, anemia, thrombocytopenia, diarrhea, fatigue, or neuropathy (p > .05).

Conclusions: According to this meta-analysis, chemotherapy with additional estramustine increased the PSA response rate. However, it increased the risk of grade 3 or 4 adverse effects such as nausea/vomiting and cardiovascular events, and the overall survival was not improved for castration-resistant prostate cancer patients.

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PALABRAS CLAVE
Cáncer de próstata; Estramustina; Quimioterapia; Metaanálisis

Quimioterapia con estramustina en el manejo del cáncer de próstata resistente a la castración: metaanálisis de ensayos controlados aleatorizados

Resumen

Objetivo: La estramustina, un agente con efectos tanto hormonales como no hormonales en los hombres, se supone que es eficaz en el tratamiento de cáncer de próstata resistente...
Chemotherapy plus estramustine for management of castration-resistant prostate cancer

Background

Prostate cancer is the second most common malignant neoplasm and a significant cause of death by cancer in men. It is estimated that there were more than 240,000 new cases and 28,000 deaths due to prostate cancer in the United States in 2012. Huggins et al. demonstrated the androgenic dependence of prostate cancer more than 70 years ago, and since then androgen deprivation therapy has been increasingly applied to metastatic and recurrent prostate cancer, as well as to locally advanced disease. Although symptomatic improvement and control of the disease can be achieved in 80–90% of men, all patients with advanced prostate cancer will in time become castration-resistant 18–24 months after the primary androgenic ablation. For these patients, the prognosis is negative and the median life expectancy is 12–18 months after becoming castration-resistant. The treatment options for men with castration-resistant prostate cancer (CRPC) are very limited. Chemotherapy has been shown to improve overall survival, progression-free survival and quality of life.

Chemotherapy based on docetaxel and cabazitaxel can extend median survival from 2.5 to 3 months. Additionally, cytotoxic agents are employed to relieve symptoms and extend survival. However, the impact of these drugs is modest, which suggests the need for improved therapy for CRPC.

Estramustine is a combination of mustard, nitrogen and 17 β-estradiol, with both hormonal and nonhormonal effects in men. Clinically employed as estramustine phosphate, estramustine reduces serum testosterone levels and inhibits microtubule dynamics by binding to tubulin and microtubule-associated proteins. After its absorption in the gastrointestinal tract, estramustine is metabolized into estrone and estradiol, which are distributed preferentially in the prostate tissue. They are therefore able to selectively interrupt prostate cancer cells and cause the inhibition of mitosis at the expense of increasing the adverse effects such as anemia, nausea, vomiting, fatigue and cardiovascular toxicity. Estramustine has been employed to treat CRPC for many years with limited effect as a single agent. However, a synergistic effect can be achieved when combined with other chemotherapy agents, especially with other microtubule inhibitors, in order to increase overall survival for patients with prostate cancer. This hypothesis was supported in a number of in vitro models and clinical trials, while others showed no significant differences. Therefore, we have performed this meta-analysis to evaluate and compare the efficacy and toxicity of estramustine added to chemotherapy for the treatment of CRPC.

Materials and methods

Data resources

The data resources were limited to controlled, randomized prospective trials in the last 20 years (1993–2013). Searches were performed on PubMed, EMBASE and the Cochrane Central Register of Controlled Trials using the following search terms: (1) prostatic neoplasms; (2) estramustine. Additionally, reference lists of all previous primary articles and systematic reviews were analyzed to obtain information on additional trials. The latest search was conducted on April 11, 2013.

Study selection and quality assessment

Two reviewers (CZ and TJ) independently evaluated the study titles and abstracts for possible selection. The full text of the corresponding articles was then reviewed. The trials were considered eligible if they met the following requirements: (1) The patients were diagnosed with prostate adenocarcinoma; (2) progressive diseases were observed despite androgenic ablation; (3) patients were randomly assigned to different treatment arms; (4) a chemotherapy (control) group was compared to the same regimen plus estramustine (experimental) group; and (5) at least one of the outcome measures was reported.
The quality of each included trial was assessed using the Jadad score on a scale of 0–5. The following parameters were evaluated: randomization method, masking and completion of follow-up. The trials with a score of 3 or more were considered high quality.

Data extraction

Two reviewers (CZ and TJ) independently examined the included trials and extracted the data with a custom form. The pertinent data included: (1) basic study information including the name of the journal, the publication date, the period of inclusion, the location and the authors; (2) population characteristics including the study duration, the randomization method, the number of patients, age, functional state and PSA reference point; (3) the chemotherapy regimens of the experimental and control groups; (4) the outcome variables including PSA response, overall survival and grade 3–4 adverse effects. PSA response was defined as a reduction of at least 50% in PSA levels (from the reference level), in accordance with the consensus of clinical guidelines of the PSA Workgroup. If overall survival and the hazard ratio were not directly available in the study, the method described by Parmar et al. was applied to interpret the survival curve data. We used a spreadsheet created by Tierney et al. to calculate the hazard ratio and the standard error.

Statistical analysis

All statistical analyses were performed with Review Manager version 5.0 software (The Cochrane Collaboration, Oxford, England), using 2-tailed p-values and a 95% confidence interval (95% CI). The time-to-event data were analyzed by combined hazard ratio (HR). Dichotomous results were evaluated using the combined odds ratio (OR). Heterogeneity among the trials was analyzed using the test Q with calculated I², which indicated that the percentage of variability in effect was due to the heterogeneity and not to randomization. A value of I² of 50% or more was considered significant heterogeneity. The fixed effects model was used to combine the data. In the event of significant heterogeneity, the results were presented using the random effects model. The sensitivity analysis was performed using the following subgroups to assess reliability: (1) the I² was more than 50%, the largest group of trials that passed the heterogeneity test; (2) high-quality trials; (3) studies whose publication date was after 2007; and (4) studies in which estramustine was combined with docetaxel. The results were considered statistically significant for p < .05. Publication bias was investigated through a search of asymmetry in the funnel plot.

Results

Characteristics and quality of the trials

The flow diagram for the study inclusion is shown in Fig. 1. Of the 128 potentially relevant studies listed by the medical search engines, 7 randomized prospective controlled trials were included in the meta-analysis. The chemotherapy regimen contained docetaxel (3 trials), epirubicin (1 trial), ixabepilone (1 trial), paclitaxel (1 trial) or vinblastine (1 trial). A minimum dosage of estramustine of 560 mg a day for 5 days in the trials. A total of 839 participants were included in this meta-analysis. The main characteristics of the included trials are listed in Table 1. At the start of the study, parameters such as age, serum PSA levels, Gleason score and functional state showed no statistically significant differences.

Prostate-specific antigen response

PSA response data were available for the 7 trials. The OR grouped by PSA response was 3.02 (95% CI = 1.69–5.39, p = .0002 [Fig. 2]). In comparison with the control group, the chemotherapy plus estramustine group had a significantly improved PSA response rate. Significant heterogeneity was observed (I² = 68%, p = 0.005), and the random effects model was applied.

Overall survival

The survival data were extracted from the survival curves of 5 trials that included 620 cases. The HR grouped by overall survival was not statistically significant (HR = 0.95, 95% CI = 0.80–1.14, p = 0.58) between the chemotherapy groups with or without estramustine (Fig. 3A). There was no significant heterogeneity (I² = 0%, p = 0.96), and the fixed effects model was applied. When only the trials published after 2007 were taken into consideration, there was no survival benefit (HR = 1.06, 95% CI = 0.77–1.46, p = 0.73 [Fig. 3B]).
Table 1  Characteristics and quality of the included trials.

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Inclusion period</th>
<th>Location</th>
<th>Jadad score</th>
<th>Patients, n</th>
<th>Chemotherapy regimen</th>
<th>Estramustine dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Machiels/2008</td>
<td>2004–2006</td>
<td>Belgium</td>
<td>3</td>
<td>149</td>
<td>35 mg/m² of docetaxel on days 2 and 9; 1 cycle every 21 days</td>
<td>280 mg 3 times a day on days 1–5 and 8–12</td>
</tr>
<tr>
<td>Caffo/2008</td>
<td>2002–2005</td>
<td>Italy</td>
<td>3</td>
<td>95</td>
<td>70 mg/m² of docetaxel every 21 days</td>
<td>280 mg 3 times a day on days 1–5 and 8–12</td>
</tr>
<tr>
<td>Ersoy/2008</td>
<td>N/A</td>
<td>Turkey</td>
<td>2</td>
<td>47</td>
<td>30 mg/m² of epirubicin weekly for 8 weeks; thereafter, once a month for 4–6 months</td>
<td>280 mg 3 times a day</td>
</tr>
<tr>
<td>Eymard/2007</td>
<td>2001–2003</td>
<td>France</td>
<td>2</td>
<td>92</td>
<td>70 mg/m² of docetaxel every 21 days</td>
<td>280 mg 2 times a day on days 1–5 and 8–12</td>
</tr>
<tr>
<td>Galsky/2005</td>
<td>2001–2003</td>
<td>United States</td>
<td>3</td>
<td>92</td>
<td>35 mg/m² of ixabepilone every 21 days</td>
<td>280 mg 3 times a day on days 1–5 and 8–12</td>
</tr>
<tr>
<td>Berry/2004</td>
<td>1998–1999</td>
<td>United States</td>
<td>2</td>
<td>163</td>
<td>100 mg/m² of paclitaxel on days 2, 9 and 16; 1 cycle every 28 days</td>
<td>280 mg 3 times a day on days 1–5 and 8–10 and 15–17</td>
</tr>
<tr>
<td>Hudes/1999</td>
<td>1993–1995</td>
<td>United States</td>
<td>3</td>
<td>201</td>
<td>4 mg/m² of vinblastine weekly for 6 weeks; 1 cycle every 8 weeks</td>
<td>600 mg a day for 6 weeks</td>
</tr>
</tbody>
</table>

Figure 2  Comparison of the PSA response rate between the experimental and control groups.

A. Overall survival

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hazard ratio log</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard ratio</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall effect</td>
<td></td>
<td></td>
<td></td>
<td>2.40 [1.24, 4.64]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2 = 18.86$, $df = 6$ (p = 0.005); $I^2 = 68%$</td>
<td></td>
</tr>
<tr>
<td>Overall effect test: $Z = 3.72$ (p = 0.002)</td>
<td>Better control</td>
<td></td>
<td></td>
<td></td>
<td>Better estramustine</td>
</tr>
</tbody>
</table>

B. Overall survival in trials published after 2007

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Hazard ratio log</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard ratio</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall effect</td>
<td></td>
<td></td>
<td></td>
<td>1.06 [0.62, 1.72]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td></td>
<td></td>
<td></td>
<td>$\chi^2 = 68%$, $df = 1$ (p = 0.91); $I^2 = 0%$</td>
<td></td>
</tr>
<tr>
<td>Overall effect test: $Z = 0.35$ (p = 0.73)</td>
<td>Better control</td>
<td></td>
<td></td>
<td></td>
<td>Better estramustine</td>
</tr>
</tbody>
</table>

Figure 3  Comparison of overall survival between the experimental and control groups. (A) Including all trials. (B) Including trials published after 2007.
Figure 4  Comparison of toxicities between the experimental and control groups. (A) Nausea/vomiting. (B) Cardiovascular episodes.

Toxicity

The grade 3–4 adverse effects included neutropenia, anemia, thrombocytopenia, diarrhea, nausea, vomiting, fatigue, neuropathy and cardiovascular toxicity and were calculated using the grouped OR. The OR grouped by nausea/vomiting in the 7 trials was 3.90 (95% CI = 1.05–14.45, p = .04 [Fig. 4A]), indicating that the patients in treatment with estramustine were more susceptible to gastrointestinal symptoms. We detected significant heterogeneity ($I^2 = 52\%$, p = .06), and the random effects model was applied. The OR grouped by cardiovascular toxicity was 2.22 (95% CI = 1.15–4.30, p = .02 [Fig. 4B]). With the exception of nausea/vomiting and cardiovascular toxicity, the incidence rates for other adverse effects were comparable between the 2 groups (Table 2).

Sensitivity analysis and publication bias

The sensitivity analyses of PSA response, overall survival and toxicity showed similar results or no changes (results not shown). A broad search strategy was selected to minimize potential publication bias. The funnel plots, adopted for all comparisons, showed no publication bias (results not shown).

Discussion

Estramustine has been tested in several randomized controlled trials and has been described in clinical guidelines. However, lacking sufficient data, the use of estramustine is still controversial. This meta-analysis compared the efficacy and toxicity of chemotherapy with and without estramustine.

Several studies have revealed the relationship between patient outcomes and PSA response rate, which indicates that the PSA response rate can serve as an alternative endpoint. There have been reports that a better PSA response can be accompanied symptom relief, increased quality of life and longer survival. Petrylak et al. found that the median survival of patients with advanced prostate cancer, with a reduction of PSA levels greater than 30%, was

### Table 2  Meta-analysis of grades 3–4 toxicity.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Trials, n</th>
<th>Patients, n</th>
<th>Events, n</th>
<th>Heterogeneity</th>
<th>OR (95% CI)</th>
<th>p-value</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EMP</td>
<td>Ctrl</td>
<td>EMP</td>
<td>Ctrl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7</td>
<td>408</td>
<td>413</td>
<td>43</td>
<td>62</td>
<td>0%</td>
<td>0.52</td>
<td>0.98</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.63; 1.53)</td>
<td>0.94</td>
</tr>
<tr>
<td>Anemia</td>
<td>6</td>
<td>313</td>
<td>316</td>
<td>13</td>
<td>16</td>
<td>46%</td>
<td>0.12</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.39; 1.70)</td>
<td>0.58</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>313</td>
<td>316</td>
<td>2</td>
<td>4</td>
<td>0%</td>
<td>0.43</td>
<td>0.66</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.19; 2.38)</td>
<td>0.53</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>268</td>
<td>269</td>
<td>9</td>
<td>2</td>
<td>0%</td>
<td>0.69</td>
<td>3.52</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.95; 13.03)</td>
<td>0.06</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>385</td>
<td>389</td>
<td>26</td>
<td>31</td>
<td>44%</td>
<td>0.11</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.50; 1.46)</td>
<td>0.56</td>
</tr>
<tr>
<td>Neuropathies</td>
<td>5</td>
<td>341</td>
<td>344</td>
<td>23</td>
<td>26</td>
<td>0%</td>
<td>0.73</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.50; 1.62)</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Ctrl: chemotherapy-only group; EMP: chemotherapy plus estramustine group.
Chemotherapy plus estramustine for management of castration-resistant prostate cancer

significantly extended ($p < .001$). The 7 trials included in this meta-analysis described the PSA response rate. $^{19-25}$ Our analysis suggested that chemotherapy with estramustine is associated with a better PSA response rate (OR, 3.02; 95% CI 1.69–5.39; $p = .0002$), which is consistent with the individual trials.

Despite the fact that the PSA response can be important for evaluating the prognosis, overall survival is the most critical endpoint for patients with CRPC because their survival is relatively short and easy to observe. Estramustine has hormonal and nonhormonal effects. Its hormonal effects can be especially beneficial for patients with incomplete androgen deprivation. Unfortunately, we have not been able to detect a benefit to survival with estramustine in this meta-analysis. The survival data was extracted from the survival curves of 5 trials that included 620 cases in both groups. $^{19,22-25}$ The HR grouped by overall survival was 0.95 (95% CI 0.80–1.14; $p = 0.58$). Compared with the control group, the chemotherapy plus estramustine group showed no advantages. One of the reasons for this could be that the effect of estramustine, which is a second-line treatment, was limited.

Additionally, in the included trials, estramustine was used in conjunction with other agents that are able to extend overall survival. Docetaxel is a standard chemotherapy agent for the treatment of prostate cancer. It can extend the median survival and dilute the survival benefit of estramustine. Another reason could be that the majority of the studies included in this meta-analysis were phase 2 trials, which were not designed to detect the small difference in overall survival. Although large-scale, well-designed, randomized, controlled phase 3 trials can help to better address this issue, it is unlikely that estramustine will be included in future trials due to its uncertain efficacy and adverse effects and the arrival of a variety of new drugs and agents, such as abiraterone and enzalutamide. Meta-analyses are designed to resolve this type of problem. Our meta-analysis has a greater statistical power when compared with each individual trial, which makes the results more reliable.

A strong argument against adding estramustine to chemotherapy is the additional toxicity that estramustine can cause. In this meta-analysis, we evaluated the possible adverse effects, including neutropenia, anemia, thrombocytopenia, diarrhea, nausea, vomiting, fatigue, neuropathy and cardiovascular toxicity. In the experimental group, more patients experienced nausea and/or vomiting (OR, 3.90; 95% CI 1.05–14.45; $p = .04$). A trend toward more diarrhea (OR, 3.52; 95% CI 0.95–13.03; $p = .06$) was observed, which indicated that estramustine is related to gastrointestinal episodes. Estramustine can also cause more cardiovascular episodes (OR, 2.22; 95% CI 1.15–4.30; $p = .02$). Major adverse effects have been observed when estramustine was combined with docetaxel, including gastrointestinal symptoms and cardiovascular events. $^{26,27}$ There have been reports that estramustine is associated with an increase in cardiovascular episodes. In the SWOG 99–16 study, $^{31}$ 14.2% of patients treated with estramustine combined with docetaxel experienced grade 3–4 adverse cardiovascular effects. This rate was much higher than in the other group taking mitoxantrone and prednisone ($p = .001$). In our meta-analysis, 6 studies provided relevant information. $^{19-23,25}$ Although prophylactic antiocoagulation was administered in a number of trials to neutralize the adverse effects of estramustine, the incidence rate for cardiovascular events for the experimental group was still 7.8% (28/361). This rate was higher than in the control group ($p = .02$) and required systematic prevention. $^{26}$ With the exception of nausea/vomiting and cardiovascular toxicity, estramustine appeared to be tolerated in both arms.

In 2007, Fizazi et al. $^{32}$ published a meta-analysis to determine whether estramustine was useful for the treatment of CRPC. Their meta-analysis examined data from individual patients and suggested that estramustine could improve the PSA response rate, as well as the overall survival of patients with CRPC. Three new trials were published since then. We extracted survival data from 2 of these trials. In the trial with 149 patients, $^{33}$ we observed similar survival among the groups, while in the other trial with 47 patients, $^{34}$ we detected greater survival in the experimental group. When we considered only those trials published after 2007, there was no survival benefit (Fig. 3B), which indicated that the difference in survival detected by Fizazi et al. could be nullified by the new studies. With regard to the adverse effects, only neutropenia and thrombocytopenic episodes were taken into account in the Fizazi analysis. $^{32}$ We also paid more attention to other significant adverse effects and observed an increased risk of nausea/vomiting and cardiovascular episodes. Another meta-analysis focused on the effects of estramustine added to docetaxel-based chemotherapy. $^{33}$ However, one of the trials performed by Hahn et al. $^{34}$ was not supposed to be included. The experimental group of the Hahn study was administered docetaxel and estramustine. Instead of administering docetaxel alone, vinorelbine was administered to the control group. Therefore, the conclusions of the analysis might not be precise and should be interpreted with caution. To date, only 3 controlled randomized trials, which included 336 patients treated with docetaxel-based chemotherapy, have been published. More trials and cases are needed to provide greater power. Therefore, our analysis consisted of a variety of chemotherapy regimens to include more patents.

There are several potential limitations that should be considered when interpreting these results. First, a total of 7 trials with 839 patients were included. The patient population might not be sufficiently large, and additional trials and patients are needed for a definitive conclusion. However, due to the uncertain efficacy and adverse effects of estramustine and the emergence of a variety of newer agents, the number of future trials could be limited. This meta-analysis provides more powerful evidence than any single trial. Moreover, a relatively small number of patients could provide considerable clinical importance, given that CRPC is the final stage of prostate cancer. Second, this meta-analysis was restricted to published studies. Although the funnel plots showed no notable bias, there might be ongoing and unpublished studies at the time of the drafting of this manuscript. Third, different chemotherapy regimens and estramustine dosages were applied in the various studies. Therefore, we conducted a sensitivity analysis of the studies in which estramustine was combined with docetaxel, the standard chemotherapy. The results showed that estramustine did not improve the overall survival of patients with CRPC when combined with effective cytotoxic drugs. Fourthly, more effective treatment options for CRPC are available or will be available in the near future, and
estramustine could be replaced. In a recently published article, abiraterone showed a trend toward improving overall survival in patients with metastatic CRPC. However, in a number of countries such as China, access to these new drugs can be difficult and too expensive. In the latest edition of the Chinese clinical guidelines on prostate cancer, estramustine remains a second-line treatment against CRPC. Our meta-analysis could be beneficial for urologists in China and other developing countries.

In conclusion, although chemotherapy plus estramustine can increase the PSA response rate, this treatment increases the risk of grade 3–4 adverse effects, such as nau-
sea/vomiting and cardiovascular episodes. Additionally, no significant benefit was detected in overall survival. Based on the current evidence, estramustine plays no role when combined with effective cytotoxic drugs such as docetaxel.

**Conflicts of interest**

The authors indicate that they have not received any financial support and that they have no financial conflicts of interest.

**References**

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