Addition of estramustine to chemotherapy and survival of patients with castration-refractory prostate cancer: a meta-analysis of individual patient data

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See Reflection and Reaction page 959

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Summary

Background Estramustine phosphate is a mustard-oestradiol conjugate, and has hormonal and non-hormonal effects. In phase II trials of patients with cancer, response to microtubule inhibitors increases when these drugs are combined with estramustine. We aimed to assess whether combining estramustine with chemotherapy increases survival in patients with castration-refractory prostate cancer.

Methods We systematically searched for randomised clinical trials that compared chemotherapy regimens with and without estramustine in patients with histologically-proven prostate cancer and were published between 1966 and 2004. Data from these studies were verified centrally and updated individual patient data were analysed. The primary endpoint was overall survival. Secondary endpoints were prostate-specific antigen (PSA) response, time to PSA progression, and toxicity. A Cox regression model that was stratified by trial and adjusted for covariates at baseline was used.

Findings The initial search identified seven eligible trials that included 742 patients, from which data from five trials including 605 patients had been collected. Individual patient data from two trials (137 patients) were no longer available. The 605 patients had been accrued between Jan 1, 1993 and Dec 1, 2003 and randomly assigned to chemotherapy plus estramustine or to chemotherapy without estramustine. Chemotherapy (with or without estramustine) consisted of docetaxel, paclitaxel, ixabepilone, and vinblastine. Median follow-up was 2·8 years (range 0·0–3·4), and 510 deaths had occurred by the end of follow-up. Cox regression analysis stratified by trial showed that concentrations of serum haemoglobin (p<0·0001), use of chemotherapy plus estramustine (p=0·008), performance status (p=0·002), and serum PSA concentrations (p=0·04) were associated independently with overall survival. Overall survival was significantly better in patients assigned chemotherapy plus estramustine (adjusted hazard ratio [HR] 0·77 [95% CI 0·63–0·93], p=0·008). Estimated absolute increase in overall survival when estramustine was added to chemotherapy was 9·5% (SE 4·0) at 1 year after randomisation. We did not note a significant association between treatment effect on overall survival and age, concentration of serum haemoglobin, performance status, or serum PSA concentration. Patients who received chemotherapy plus estramustine had a better PSA response than those who received chemotherapy without estramustine (RR 0·53 [0·38–0·72], p<0·0001). Time to PSA progression was significantly longer in patients assigned chemotherapy plus estramustine than in those assigned chemotherapy without estramustine (HR 0·74 [0·58–0·94], p=0·01). Patients assigned chemotherapy and estramustine had more grade 3 or grade 4 thromboembolic events compared with those assigned chemotherapy without estramustine (12 of 271 *vs* 1 of 275).

Interpretation In patients with castration-refractory prostate cancer, addition of estramustine to chemotherapy increases time to PSA progression and overall survival compared with chemotherapy without estramustine. However, this benefit should be balanced with the risk of increased thromboembolic events in patients who receive estramustine and chemotherapy in combination compared with chemotherapy without estramustine.

Introduction

In 2002, prostate cancer had the highest incidence and was the second leading cause of cancer in the USA, and the third leading cause of cancer in western Europe.[1] Although advanced prostate cancer is initially sensitive to androgen deprivation, most deaths occur after the cancer has progressed to castration-refractory status, in which metastatic dissemination usually involves the bones. In patients with castration-refractory prostate cancer, chemotherapy has been shown to improve quality of life,[2] progression-free survival,[3] and overall survival.[4,5] However, the overall-survival benefit is small, with median survival lasting 18 months in large phase III randomised trials.[4,5]

Estramustine phosphate is a nornitrogen mustard-oestradiol conjugate that has been shown to have hormonal and non-hormonal effects in vivo.[6] Estramustine mainly inhibits microtubule function by binding to both tubulin[7–9] and microtubule-associated proteins.[10] In human beings, estramustine has little antitumour activity as a single drug in the treatment of patients with castration-refractory prostate cancer with responses reported in 20% of

patients.[11] However, the microtubule-inhibitory properties of estramustine led to the hypothesis that a synergistic antitumour effect could be achieved by combining estramustine with other microtubule inhibitors. This assumption was confirmed in some, but not all, in-vitro models when estramustine was added to vinca-alkaloids[12] or taxanes.[13,14]

Several phase II and III clinical randomised trials have studied the effect of adding estramustine to chemotherapy, especially to other microtubule inhibitors.[6] Although response and progression-free survival were typically higher when estramustine was added to chemotherapy compared with chemotherapy without estramustine, no trial has been powerful enough to detect an improvement in median survival of less than 50%, and the largest of these trials included only 200 patients.[15] Therefore, we undertook this meta-analysis of individual patient data from randomised trials that assessed chemotherapy with or without estramustine in patients with castration-refractory prostate cancer. The main aim was to address a controversial clinical question: is overall survival improved when estramustine is added to chemotherapy?

Methods

Search strategy and selection criteria

We searched, without language restrictions, Medline and the National Cancer Institute Physician Data Queries clinical trials registry for papers published in 1966–2004. The search strategy used the following search terms: (1) "prostatic neoplasms"; (2) "estramustine"; (3) "randomised controlled trial ("phase III" and "phase II and random").

We hand-searched the reference lists of review articles for additional publications, and asked participating trialists if they were aware of studies not retrieved by the trial search. We also reviewed abstract booklets and presentations of meetings in 1994–2004 (ie, American Society of Clinical Oncology [ASCO], European CanCer Organisation [ECCO], and European Society for Medical Oncology [ESMO]).

We considered all published and unpublished randomised controlled trials that included patients with histologically proven prostate cancer who had evidence of cancer progression after androgen deprivation treatment (surgical castration or chemical androgen deprivation by use of a luteinising hormone-releasing hormone [LHRH]-agonist); and also trials that included patients who had undergone non-surgical castration and who had continued LHRH-agonist treatment while receiving chemotherapy.

Since 1993 patients on antiandrogen treatment have been required to stop antiandrogen treatment before inclusion in trials. Trials that did not restrict inclusion of patients with measurable disease were also eligible. Trials were included if patients were randomly assigned to treatment without previous knowledge of treatment assignment, if they compared chemotherapy to the same chemotherapy plus estramustine, and if they started accrual in 1977 or after and completed accrual before December, 2003.

Data extraction

Individual patient data were collected centrally by KF, ALM, SM, and JPP (Secretariat of the MECaP Trialists' Collaborative Group). From each eligible study, we recorded date of birth or age, performance status, serum concentration of prostate-specific antigen (PSA), haemoglobin concentration, allocated treatment, date of randomisation, date of last follow-up, survival status, date of first PSA failure, date of confirmation of PSA failure, PSA response,[16] any grade 3 or grade 4 thromboembolic complication or febrile neutropenia.

Data were checked for internal consistency and with the published results. Amendments were made when necessary after discussions with the investigators. The re-analysis of each trial was submitted to the investigators for validation.

Statistical analysis

The analysis was undertaken on an intention-to-treat basis: patients were analysed according to treatment allocated, irrespective of whether they received that treatment. With more than 450 recorded deaths, we considered that an absolute increase in survival from 50% to 60% at 1 year (assuming exponential survival) was possible, with a 0·05 significance level and a power of 90% (two-sided log-rank test).

The primary endpoint was overall survival. Survival duration was defined as the time from randomisation until death from any cause, or was censored on the date of the last follow-up assessment. Secondary endpoints included: PSA response (defined as a decrease in serum PSA of >50% for at least 4 weeks);[16] time to PSA progression (defined as time from the date of randomisation to date of progression, with PSA progression defined as a confirmed increase in PSA concentration of over 25% above the nadir in patients who did not have a PSA response, or as a confirmed increase in PSA concentration of over 50% above the nadir in patients who had a PSA response[16])—patients who died without documented progression were censored at their date of death, and those alive were censored at the date of last follow-up; and toxicity, restricted to grade 3 and grade 4 neutropenia and thromboembolic events.

For the primary assessment of the effect of the addition of estramustine on overall survival, we used a Cox regression model stratified by trial and adjusted for age, performance status, concentration of serum haemoglobin, and serum PSA concentration at baseline to account for possible confounding by covariates that were associated with outcome. We dichotomised PSA concentration and age at baseline by their median values across the entire dataset (PSA concentration of 130 ng/mL and age of 70 years); for the concentration of serum haemoglobin, we applied a cut-off of 120 g/L, which is a classical cut-off

	Inclusion period	Patients, n	Chemotherapy regimen	Estramustine dosage	Reference
Hoosier Fox	1993–95	192	Vinblastine 4 mg/m² intravenously every 7 days; 14 days on treatment and 14 days off treatment	600 mg/m² daily for 42 days; one cycle every 56 days	15, 20
USON	1998–99	166	Paclitaxel 100 mg/m² intravenously every 7 days on days 2, 9, 16; one cycle every 28 days	280 mg three times daily on days 1–3, 8–10, and 15–17	21
MSKCC	2001–03	96	Ixabepilone 35 mg/m² intravenously every 21 days	280 mg three times daily for 5 days	22
French group	2001–02	92	Docetaxel 70 mg/m² intravenously on day 2; one cycle every 21 days	280 mg twice daily for 5 days	23
MDACC	1993–94	59	Vinblastine 6 mg/m² intravenously every 7 days; 42 days on treatment and 14 days off treatment	280 mg twice daily for 42 days	Unpublished

MSKCC=Memorial-Sloan Kettering Cancer Center. USON=US Oncology Network. MDACC=MD Anderson Cancer Center.

Table 1: **Trials assessing chemotherapy with or without estramustine in patients with prostate cancer**

	Chemotherapy without estramustine (control; n=305)	Chemotherapy plus estramustine (n=300)
Median age, years (range)	70 (45–94)	69 (43–89)
Performance status,* n (%)		
0	137 (45)	141 (47)
1	129 (42)	125 (42)
2 or 3	39 (13)	33 (11)
Median serum PSA, ng/mL (range)†	118 (0·1–5104·0)	134 (0·1–8666·0)
Haemoglobin (g/L)		
≥120	178 (58)	201 (67)
<120	88 (29)	60 (20)
NA	39 (13)	39 (13)

NA=not available because data missing. *ECOG performance status, one missing value in estramustine group. †20 patients had missing data (eight in control group, 12 in estramustine group). Data on number of bone metastases were not available from several trials.

Table 2: **Baseline characteristics of patients from randomised trials assessing chemotherapy with or without estramustine**

	Hazard ratio (95% CI)	p
Treatment		0·008
Chemotherapy without estramustine	1·00	
Chemotherapy plus estramustine	0·77 (0·63–0·93)	
Age, years		0·17
≤70	1·00	
>70	0·87 (0·71–1·06)	
Serum PSA, ng/mL		0·04
≤130	1·00	
>130	1·25 (1·02–1·54)	
Performance status		0·002
0 or 1	1·00	
2	1·66 (1·21–2·27)	
Haemoglobin (g/L)		<0·0001
<120	1·00	
≥120	0·59 (0·46–0·75)	

Table 3: **Multivariate Cox regression analysis of overall survival, stratified by trial**

used for defining anaemia. An adjusted hazard ratio (HR) for the effect of adding estramustine was calculated in this Cox model. HR can be interpreted as the risk of failing (ie, death) for patients in the chemotherapy plus estramustine arm compared with that risk for patients in the arm assigned chemotherapy without estramustine. An HR of 1 implies that there is no difference in outcome between the treatment arms.

For the unadjusted analysis of overall survival and the analysis of time to PSA progression, the stratified (by trial) log-rank test was used. HR for individual trials and for the overall comparison was computed by use of a fixed effects model.[17] χ^2-heterogeneity tests were used to test for gross statistical heterogeneity. Findings are also presented as absolute differences at relevant timepoints (1 year and 2 years) calculated from periodical HR stratified by trial.[17] Survival curves are shown as simple (non-stratified) Kaplan-Meier curves. All p values are two-sided. A comparison of the findings in the following groups of trials that were classified according to the type of chemotherapy drug was planned as an exploratory analysis: trials using a taxane or an epothilone B analogue; and trials using a vinca-alkaloid. For these analyses, an HR was calculated for each trial and a combined HR stratified by trial was calculated for each drug category. A test for interaction was used to decide whether any substantial differences existed in the treatment effect between these drug categories. To study the interaction between the treatment effect and covariates, analyses stratified by trial were done for each covariate value. The findings were then combined to provide an overall HR for the covariate and compared by a test for heterogeneity.

The secondary endpoints, PSA response and toxicity, are displayed as risk ratios (RR). RR compares the probability of the event of interest in each treatment arm, and an RR of 1·0 implies no difference between compared arms. The arm chemotherapy without estramustine arm was used as a reference category for the toxicity analysis, whereas the chemotherapy plus

estramustine arm was the reference category for the PSA-response analysis. Consequently, less than unity (1·0) indicates a benefit with the chemotherapy plus estramustine arm compared with the chemotherapy without estramustine arm, and corresponds to a higher PSA response in the chemotherapy plus estramustine arm and less toxicity in the combined group. RR for the treatment effect were calculated for individual trials. The Mantel-Haenszel test, stratified by trial, was used to compute the overall treatment effect.

The study was based on a prespecified protocol that described the inclusion criteria, the trial search, evaluation criteria, data collection, and a predefined statistical-analysis plan. The meta-analysis was done according to published recommendations.[18] The protocol is available from the authors on request. Published and unpublished studies were included in this meta-analysis based on individual data, as previously recommended.[19] Under French law, no requirement was needed to submit this meta-analysis for approval by an Internal Review Board.

Role of the funding source

This research was supported by the Institut Gustave-Roussy and the Ligue Nationale Contre le Cancer. The sponsor of this analysis provided a general salary for ALM (not specific to this study), and had no role in study design, data collection, data analysis, data interpretation, or in writing of the report. ALM, SM, and JPP had access to the raw data. 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

Five trials that randomly assessed patients who received a chemotherapy treatment (control group) versus the same chemotherapy plus estramustine were identified in the PSA screening era—ie, when serum PSA became commonly measured in clinics.[15,20–23] Three additional trials which randomly tested a chemotherapy regimen (namely prednimustine, cisplatin, and vincristine, respectively) with and without estramustine were done by the National Prostate Cancer Project group in the pre-PSA era.[24–26] The oldest trial[26] had to be excluded because the accrual had started before the date fixed in our inclusion criteria (1977) and because most of the patients in the chemotherapy without estramustine arm crossed over to the estramustine group when they progressed. 137 patients were included in the two eligible pre-PSA trials.[24,25] Despite our efforts, we were not able to retrieve their data and they are not included in the present meta-analysis (we repeatedly contacted the authors and individual patient data are no longer available). Table 1 shows the number of patients and regimens used in the five trials from the PSA era. 605 of 742 of all eligible patients were assigned to chemotherapy plus estramustine versus chemotherapy without estramustine. Of these five trials, one was a phase III trial[15,20] and four were phase II trials.[21–23] Four trials had already been published as articles,[15,21–23] and one trial (Logothesis C J, MD Anderson Cancer Center, Houston, TX, USA, personal communication) has not been published. Chemotherapy (with or without estramustine) consisted of docetaxel (one trial),[23] paclitaxel (one trial),[21] ixabepilone (one trial),[22] and vinblastine (two trials).[15,20] Estramustine was given at various doses and schedules in these trials (table 1).

Baseline characteristics from 605 patients were collected (table 2). Median concentration of serum PSA at baseline was 134 ng/mL in the chemotherapy plus estramustine arm, and 118 ng/mL in the chemotherapy without estramustine arm.

No follow-up data for overall survival were available for two of the 605 patients; therefore, data from 603 patients were available for the analysis of overall survival. Median

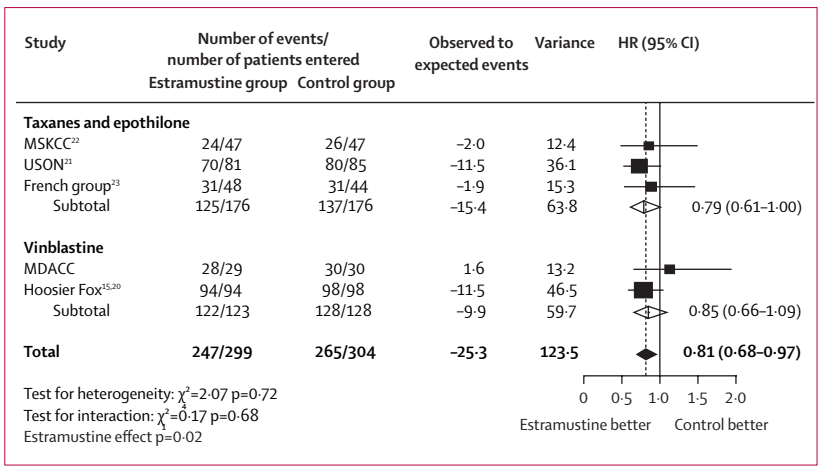

Figure 1: Overall survival

MSKCC=Memorial-Sloan Kettering Cancer Center. USON=US Oncology Network. MDACC=MD Anderson Cancer Center. Centre of each square is the HR for individual trials and the corresponding horizontal line its 95% CI. The area of squares is proportional to the amount of information obtained from the trial. The broken line and the centre of the black diamond represent the overall pooled HR and the extremities of the diamond represent its 95% CI. Trials are ranked chronologically by the date when the trial was started (oldest appearing first). The white diamonds represent the HR of the two different chemotherapy categories.

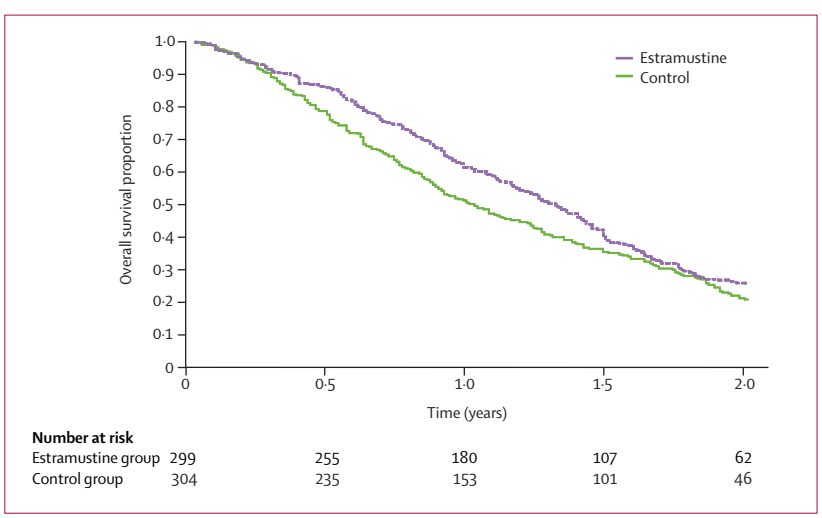

Figure 2: Overall survival curves

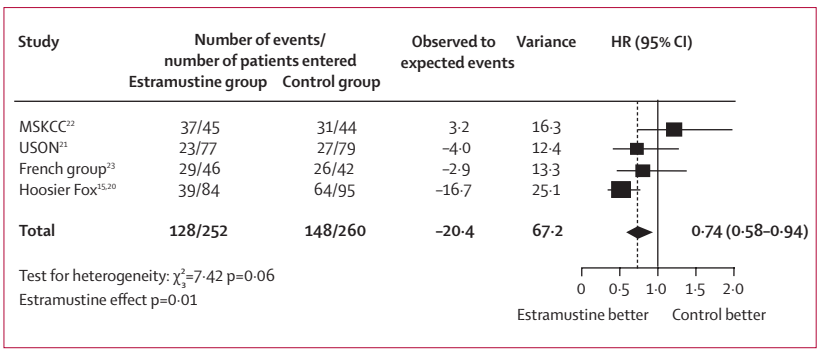

Figure 3: **Time to PSA progression**
Time to PSA progression data were available for 512 patients from four trials.

follow-up was 2·8 years (calculated by use of the reverse Kaplan-Meier method, range 0·0–3·4), and 510 deaths had occurred. In the Cox regression analysis stratified by trial, concentration of serum haemoglobin (p<0·0001), chemotherapy plus estramustine (p=0·008), performance status (p=0·002), and serum PSA concentration (p=0·04), but not age, were independently associated with overall survival (table 3). Adjusted HR for death in patients assigned chemotherapy plus estramustine compared with those assigned chemotherapy without estramustine was 0·77 (95% CI 0·63–0·93), p=0·008.

In the unadjusted analysis, overall survival was also significantly better for patients in the chemotherapy plus estramustine arm, when compared with the control arm (HR 0·81 [0·68–0·97], p=0·02). We noted no significant heterogeneity of treatment effects across trials (p=0·72). The corresponding forest plot of overall survival and the survival curves are shown in figures 1 and 2. The estimated absolute increase in 1-year overall survival was 9·5% (SE 4·0), ie, from 51·6% in the chemotherapy without estramustine arm to 61·1% in the chemotherapy plus estramustine arm; and we noted a 3·5% (SE 3·6) increase in 2-year survival from 22·2% in the chemotherapy without estramustine arm to 25·7% in the chemotherapy plus estramustine arm.

A protocol-planned exploratory analysis included the analysis of survival in patients who had received a taxane (or an epothilone B analogue) and in those who had received a non-taxane-containing regimen. We did not note a significant interaction between the favourable effect of estramustine on overall survival and the type of chemotherapy drug used (interaction test=0·68). Additionally, we did not note a significant interaction between the treatment effect on overall survival and age, concentration of serum haemoglobin, performance status, or serum PSA concentration.

PSA response was recalculated centrally on the basis of consensus criteria[16] for patients from each trial. The cumulative data showed that 141 of 271 (52%) patients with available data in the chemotherapy plus estramustine arm had a PSA response and 73 of 275 (27%) patients with available data in the chemotherapy without estramustine arm had a PSA response. Overall RR for PSA response was 0·53 (0·38–0·72), p<0·0001) for the control arm versus the estramustine arm (reference group). We did not note any significant heterogeneity in the treatment effects on PSA response (p=0·26).

Data for time to PSA progression from the smallest trial (MD Anderson Cancer Center trial) were not available, and therefore, the analysis was done on data from the four other trials (512 patients; figure 3). Combining chemotherapy with estramustine improved time to PSA progression compared with the same chemotherapy without estramustine, and unadjusted HR was 0·74 (0·58–0·94), p=0·01. The p value for heterogeneity between treatment effects across trials was p=0·06. The adjusted analysis yielded an HR of 0·62 (0·47–0·81), p=0·0005.

Data on toxicity were obtained from four[15,20–23] of the five trials. Because of variation in the grading of toxicity between trials, the analysis of toxicity was restricted to neutropenia and thromboembolic events. The analysis was based on an intention-to-treat approach because no homogeneous per-protocol analysis could be applied. Grade 3 or 4 neutropenia was noted in 41 of 275 (15%) patients in the chemotherapy without estramustine arm and 16 of 271 (6%) patients in the chemotherapy plus estramustine arm (overall RR 0·41 [0·23–0·71], p=0·002).

Grade 3 or 4 thromboembolic events were documented in 1 of 275 (0·4%) patients assigned chemotherapy without estramustine, and in 12 of 271 (4%) patients assigned chemotherapy plus estramustine (overall RR 4·51 [1·29–15·70], p=0·02). We did not note significant heterogeneity in the RR between the trials for neutropenia (p=0·61) or thromboembolic events (p=0·95).

Discussion

To our knowledge, this meta-analysis of individual patient data shows for the first time that overall survival in patients with castration-refractory prostate cancer is significantly improved when estramustine is added to chemotherapy compared with the same chemotherapy without estramustine (adjusted HR 0·77 [0·63–0·93]).

Furthermore, patients who had received chemotherapy plus estramustine had a better PSA response (RR 0·53 [0·38–0·72]) and a better time to PSA progression (HR 0·74 [0·58–0·94]). We did not record any significant heterogeneity between the treatment effects on overall survival between trials or for treatment effects on time to PSA progression between trials.

The main finding of this meta-analysis is a survival benefit for patients when estramustine is added to chemotherapy. Several randomised trials have reported previously better efficacy with chemotherapy plus estramustine compared with the same regimen without estramustine, at least in terms of response and time to PSA progression.[14,18,19] However, none of the trials showed a statistically significant improvement in overall survival: the US Oncology Network trial[21] did not record a

significant benefit of adding estramustine to chemotherapy (p=0·049 by univariate and p=0·08 by multivariate analysis), and neither did the Hoosier Oncology Group and Fox Chase trial[20] (p=0·05 by univariate and p=NS by multivariate analysis). In the meta-analysis presented here, median survival for the entire population was about 16 months (range 0–90), which is similar to that reported in other large trials done in patients with castration-refractory prostate cancer during the same period,[2,3] and relatively high, considering that a significant proportion of patients from this meta-analysis did not receive a taxane and had symptomatic castration-refractory prostate cancer when they were accrued onto clinical trials. As mentioned above, three trials in the pre-PSA era[24–26] were not included in this meta-analysis. One trial was not eligible because accrual started before 1977 and because a cross-over to estramustine was done in the chemotherapy without estramustine arm. Patients from the two other trials were also treated in the late 1970s and had more advanced, symptomatic castration-refractory prostate cancer compared with those recruited in trials done during the PSA era, and had median survival of only about 6 months. These trials included 137 patients overall and were not powered sufficiently to detect a survival difference. Moreover, chemotherapy drugs used in these trials (namely prednimustine, cisplatin, and vincristine) have not been shown to be active in the treatment of prostate cancer and are no longer used in this setting.

Two other trials tested docetaxel with or without estramustine in a randomised setting after the end of the accrual period used for inclusion in the current meta-analysis. The first trial was a randomised phase II study in 95 accrued patients in Italy. Preliminary findings of this trial have been reported in abstract form: in patients receiving docetaxel with estramustine, PSA response was 75% and median progression-free survival was 30 months; and in those receiving docetaxel without estramustine, PSA response was 40% and progression-free survival was 20 months.[27] Survival data are not yet available. The other randomised trial was undertaken in Belgium and has accrued 150 patients; preliminary findings of this trial have also been reported in an abstract.[28] The researchers noted no obvious survival difference in patients randomly assigned docetaxel with or without estramustine. However, this finding might be explained, at least in part, by the fact that a proportion of patients included in this trial (25%) had previously received estramustine and had progressed while on this drug.

The five randomised trials in this meta-analysis were not powered adequately to detect a small, but clinically meaningful benefit of estramustine in overall survival (table 1): for example, the power of the largest study to detect a 25% improvement in overall survival was only 51%.[15] However, an adequately powered phase III trial will probably not be done in the near future, because of competitive ongoing and planned trials that test new drugs.

The overall benefit of adding estramustine to chemotherapy should be weighed against the morbidity associated with this drug—ie, mostly nausea or vomiting and thromboembolic complications.[29] In one study,[30] thromboembolic complications occurred in 69 of 896 patients with castration-refractory prostate cancer who were assigned estramustine. In the present meta-analysis, grade 3 or grade 4 thromboembolic events occurred in 4% of patients who were assigned estramustine plus chemotherapy versus 0·4% in those who were not assigned estramustine, which confirmed an increased risk. In a trial[31] randomly assessing low-dose or high-dose estramustine combined with docetaxel in 72 patients with castration-refractory prostate cancer, apparently similar anticancer activity was reported in the two groups, whereas the incidence of thromboembolic events was 3% in those assigned low-dose estramustine combined with docetaxel and 11% in patients assigned high-dose estramustine combined with docetaxel. The optimum estramustine dose and schedule that should be used when combined with docetaxel is still unknown. Furthermore, whether systematic thromboprophylaxis should be used, and if so which thromboprophylactic drug and doses, is also unknown; however, coumadin, aspirin, and other compounds have been proposed.[4,27]

This meta-analysis also confirmed that adding estramustine to chemotherapy decreases the risk of chemotherapy-related grade 3 or 4 neutropenia (6% *vs* 15%; RR 0·41 [0·23–0·71]), a phenomenon that has been reported previously, although its mechanism is unclear.[15]

No sufficient data were available on the actual chemotherapy dose received by patients treated with chemotherapy plus estramustine in the trials selected in this meta-analysis, thus, precluding an analysis of chemotherapy dose in relation to the incidence of neutropenia. Although the dose and schedule of estramustine used in the trials included in this meta-analysis were variable, all used a minimum dose of 560 mg/day for 3 days.

Since treatment with chemotherapy plus estramustine showed increased antitumour activity (ie, PSA response, time to PSA progression, and overall survival), this combination as first-line treatment of patients with castration-refractory prostate cancer would seem logical and reasonable, at least in those patients with no major thromboembolic risks and with or without thromboprophylaxis. Patients with poor gastrointestinal tolerance (another side-effect of treatment with estramustine) or who have a thromboembolic event should not be treated with estramustine.

Contributors

KF, ALM, SM, and JPP (Secretariat of the Meta-analysis of Estramustine in Prostate Cancer [MECaP] Trialists' Collaborative Group) wrote the protocol, checked quality of trial data, did the statistical analysis, and wrote the report. The MECaP Trialists' Collaborative Group trialists collected trial data, submitted data to the Secretariat, answered queries from the Secretariat about trial data, and validated the report.

Conflicts of interest

WRB is a member of the Sanofi-Aventis speakers bureau. The other authors declared no conflicts of interest.

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References

1 Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: Cancer incidence, mortality and prevalence worldwide, IARC CancerBase, number 5, version 2.0. Lyon: IARC Press, 2004.

2 Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol* 1996; **14:** 1756–64.

3 Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone–refractory prostate cancer: results of the cancer and leukemia group B 9182 study. *J Clin Oncol* 1999; **17:** 2506–13.

4 Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; **351:** 1502–12.

5 Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med* 2004; **351:** 1513–20.

6 Hudes G. Estramustine-based chemotherapy. *Semin Urol Oncol* 1997; **15:** 13–19.

7 Dahllof B, Billstrom A, Cabral F, Hartley-Asp B. Estramustine depolymerizes microtubules by binding to tubulin. *Cancer Res* 1993; **53:** 4573–81.

8 Laing N, Dahllof B, Hartley-Asp B, Ranganathan S, Tew KD. Interaction of estramustine with tubulin isotypes. *Biochemistry* 1997; **36:** 871–78.

9 Speicher LA, Laing N, Barone LR, Robbins JD, Seamon KB, Tew KD. Interaction of an estramustine photoaffinity analogue with cytoskeletal proteins in prostate carcinoma cells. *Mol Pharmacol* 1994; **46:** 866–72.

10 Tew KD, Glusker JP, Hartley-Asp B, Hudes G, Speicher LA. Preclinical and clinical perspectives on the use of estramustine as an antimitotic drug. *Pharmacol Ther* 1992; **56:** 323–39.

11 Joly F, Tannock IF. Chemotherapy for patients with hormone-refractory prostate cancer. *Ann Oncol* 2004; **15:** 1582–84.

12 Mareel MM, Storme GA, Dragonetti CH, et al. Antiinvasive activity of estramustine on malignant MO4 mouse cells and on DU-145 human prostate carcinoma cells in vitro. *Cancer Res* 1988; **48:** 1842–49.

13 Williams JF, Muenchen HJ, Kamradt JM, Korenchuk S, Pienta KJ. Treatment of androgen–independent prostate cancer using antimicrotubule agents docetaxel and estramustine in combination: an experimental study. *Prostate* 2000; **44:** 275–78.

14 Fizazi K, Sikes CR, Kim J, et al. High efficacy of docetaxel with and without androgen deprivation and estramustine in preclinical models of advanced prostate cancer. *Anticancer Res* 2004; **24:** 2897–903.

15 Hudes G, Einhorn L, Ross E, et al. Vinblastine versus vinblastine plus oral estramustine phosphate for patients with hormone-refractory prostate cancer: a Hoosier Oncology Group and Fox Chase Network phase III trial. *J Clin Oncol* 1999; **17:** 3160–66.

16 Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 1999; **17:** 3461–67.

17 Early Breast Cancer Trialists' Collaborative Group. Treatment of early breast cancer. Vol 1. Worldwide evidence 1985–1990: a systematic review of all available randomized trials of adjuvant endocrine and cytotoxic therapy. Oxford: Oxford University Press, 1990.

18 Sacks HS, Berrier J, Reitman D, Ancona-Berk VA, Chalmers TC. Meta-analyses of randomized controlled trials. *N Engl J Med* 1987; **316:** 450–55.

19 Pignon JP, Hill C. Meta-analysis of randomised clinical trials in oncology. *Lancet Oncol* 2001; **2:** 475–82.

20 Hudes G, Ross E, Roth B, et al. Improved survival for patients with hormone-refractory prostate cancer receiving estramustine-based antimicrotubule therapy: final report of a Hoosier Oncology Group and Fox Chase Network phase III trial comparing vinblastine and vinblastine plus oral estramustine phosphate. *Proc Am Soc Clin Oncol* 2002, **21** (abstr 704)**:** 177a.

21 Berry WR, Hathorn JW, Dakhil SR, et al. Phase II randomized trial of weekly paclitaxel with or without estramustine phosphate in progressive, metastatic, hormone-refractory prostate cancer. *Clin Prostate Cancer* 2004; **3:** 104–11.

22 Galsky MD, Small EJ, Oh WK, et al. Multi-institutional randomized phase II trial of the epothilone B analog ixabepilone (BMS-247550) with or without estramustine phosphate in patients with progressive castrate metastatic prostate cancer. *J Clin Oncol* 2005; **23:** 1439–46.

23 Eymard JC, Priou F, Zannetti A, et al. Randomized phase II study of docetaxel plus estramustine and single-agent docetaxel in patients with metastatic hormone-refractory prostate cancer. *Ann Oncol* 2007; **18:** 1064–70.

24 Soloway MS, Beckley S, Brady MF, et al. A comparison of estramustine phosphate versus cis-platinum alone versus estramustine phosphate plus cis-platinum in patients with advanced hormone refractory prostate cancer who had had extensive irradiation to the pelvis or lumbosacral area. *J Urol* 1983; **129:** 56–61.

25 Soloway MS, deKernion JB, Gibbons RP, et al. Comparison of estramustine phosphate and vincristine alone or in combination for patients with advanced, hormone refractory, previously irradiated carcinoma of the prostate. *J Urol* 1981; **125:** 664–67.

26 Murphy GP, Gibbons RP, Johnson DE, et al. The use of estramustine and prednimustine versus prednimustine alone in advanced metastatic prostatic cancer patients who have received prior irradiation. *J Urol* 1979; **121:** 763–65.

27 Caffo O, Sava T, Comploj E, et al. A multicentric phase II randomised trial of docetaxel plus estramustine versus docetaxel as first line chemotherapy for patients with hormone-refractory advanced prostate cancer. *Proc Am Soc Clin Oncol* 2006; **24** (abstr 4625)**:** 247s.

28 Machiels JH, Mazzeo F, Clausse M, et al. Phase III trial of docetaxel, estramustine, and prednisone in patients with metastatic hormone-refractory prostate cancer (HRPC). *Proc Am Soc Clin Oncol* 2007; **25** (abstr 5067)**:** 251s.

29 Hahn NM, Marsh S, Fisher W, et al. Hoosier Oncology Group randomized phase II study of docetaxel, vinorelbine, and estramustine in combination in hormone-refractory prostate cancer with pharmacogenetic survival analysis. *Clin Cancer Res* 2006; **12:** 6094–99.

30 Lubiniecki GM, Berlin JA, Weinstein RB, Vaughn DJ. Thromboembolic events with estramustine phosphate-based chemotherapy in patients with hormone-refractory prostate carcinoma: results of a meta-analysis. *Cancer* 2004; **101:** 2755–59.

31 Nelius T, Klatte T, Reiher F, et al. Randomized study of docetaxel and dexamethasone with low- or high-dose estramustine for patients with advanced hormone-refractory prostate cancer. *Proc Am Soc Clin Oncol* 2006; **24** (abstr 4653)**:** 254s.