Chemotherapy for hormone-refractory prostate cancer
(Review)

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ABSTRACT

Background
Prostate cancer mainly affects elderly men, and its incidence has steadily increased over the last decade. The management of this disease is replete with controversy. In men with advanced, metastatic prostate cancer, hormone therapy is almost universally accepted as the initial treatment of choice and produces good responses in most patients. However, many patients will relapse and become resistant to further hormone manipulation; the outlook for these patients is poor. Many have disease extending to the skeleton, which is associated with severe pain. Therapies for these men include chemotherapy, bisphosphonates, palliative radiotherapy, and radioisotopes. Systemic chemotherapy has been evaluated in men with hormone-refractory prostate cancer (HRPC) for many years, with disappointing results. However, more recent studies with newer agents have shown encouraging results. There is therefore a need to explore the value of chemotherapy in this disease.

Objectives
The present review aims to assess the role of chemotherapy in men with metastatic HRPC. The major outcome was overall survival. Secondary objectives include the effect of chemotherapy on pain relief, prostate-specific antigen (PSA) response, quality of life, and treatment-related toxicity.

Search strategy
Trials were identified by searching electronic databases, such as MEDLINE, and handsearching of relevant journals and conference proceedings. There was no restriction of language or location.

Selection criteria
Only published randomised trials of chemotherapy in HRPC patients were eligible for inclusion in this review. Randomised comparisons of different chemotherapeutic regimens, chemotherapy versus best standard of care or placebo, were relevant to this review. Randomised, dose-escalation studies were not included in this review.

Data collection and analysis
Data extraction tables were designed specifically for this review to aid data collection. Data from relevant studies were extracted and included information on trial design, participants, and outcomes. Trial quality was also assessed using a scoring system for randomisation, blinding, and description of patient withdrawal.

Main results
Out of 107 randomised trials of chemotherapy in advanced prostate cancer identified by the search strategy, 47 were included in this review and represented 6929 patients with HRPC. Only two trials compared the same chemotherapeutic interventions and therefore a meta-analysis was considered inappropriate. The quality of some trials was poor because of poor reporting, low-patient recruitment, or poor trial design. For clarity, trials were categorised according to the major drug used, but this was not a definitive grouping, since many trials used several agents and would be
Prostate cancer is a major clinical problem, not only because of its high incidence and mortality, but also because of the severe morbidity associated with the advanced stages of this disease. The incidence in men in Europe and the United States of America is 1 in 10,000 for those aged under the age of 40 years is 1 in 10,000 (Woolam 2000). The mean percentage of patients achieving at least a 50% reduction in PSA compared to baseline was as follows: estramustine 48%; 5-fluorouracil 20%; doxorubicin 50% (one study only); mitoxantrone 33%; and docetaxel 52%. Pain relief was reported in 35% to 76% of patients receiving either single agents or combination regimens. A three weekly regime of docetaxel significantly improved pain relief compared to mitoxantrone plus prednisone (the latter regimen approved as standard therapy for HRPC in the USA). All chemotherapeutics, either as single agents or in combination, were associated with toxicity; the major ones being myelosuppression, gastrointestinal toxicity, cardiac toxicity, neuropathy, and alopecia. Quality of life was significantly improved with docetaxel compared to mitoxantrone plus prednisone.

Authors' conclusions
Patients with HRPC have not traditionally been offered chemotherapy as a routine treatment because of treatment-related toxicity and poor responses. Recent data from randomised studies, in particular those using docetaxel, have provided encouraging improvements in overall survival, palliation of symptoms, and improvements in quality of life. Chemotherapy should be considered as a treatment option for patients with HRPC. However, patients should make an informed decision based on the risks and benefits of chemotherapy.

**PLAIN LANGUAGE SUMMARY**

Men with advanced prostate cancer and painful bone metastases are a difficult group of patients to treat. Data from recent randomised trials of chemotherapy suggest an improvement in overall survival, pain relief, and quality of life with this form of therapy. Side effects are common and can be severe. Chemotherapy offers a treatment option for men with hormone-refractory prostate cancer (HRPC), but the decision to treat should be carefully considered by the patient and clinician. More studies are needed to find new and better agents.

**BACKGROUND**

Prostate cancer is the second leading cause of cancer-related death in men in Europe and the United States of America. The incidence of prostate cancer for men under the age of 40 years is 1 in 10,000 compared with a 1 in 7 for those aged over 60 (Woolam 2000). Prostate cancer is a major clinical problem, not only because of its high incidence and mortality, but also because of the severe morbidity associated with the advanced stages of this disease. Treatment for clinically localised disease consists of early intervention with surgery, radiation therapy, androgen suppression, or observation. Long-term clinical outcomes are generally quite good for all these treatment options (Catalona 1999; Zelefsky 2003); although it is not clear if one approach provides a superior increase in survival or quality of life. However, in as many as 10% to 50% of men with prostate cancer the disease will progress (Goktas 1999) and spread to the pelvic lymph nodes and bone. The major complication associated with bone metastases is severe pain, and for these patients treatment is primarily palliative.

The growth of prostate cancer is highly dependent on circulating androgens, in particular testosterone. The standard treatment for metastatic prostate cancer is hormone ablation therapy either by surgical castration (orchidectomy) or medical castration with luteinising hormone-releasing antagonists (LHRH) with or without anti-androgens. Androgen ablation therapy induces palliation of symptoms in many patients; however, over time the majority become refractory to hormone therapy with less than 50% alive at 5 years.

Chemotherapy for HRPC has had a modest impact on the treatment of this disease. In one study, the combination of mitoxantrone with prednisone was reported to induce a palliative response in 29% of patients with symptomatic disease compared to 12% receiving prednisone alone (Tannock 1996). Quality of life was also improved with the combination arm. In another trial, mitoxantrone combined with hydrocortisone was shown to induce a delay in disease progression and an improved quality of life (Kantoff 1999); however, in both trials there was no improvement in overall survival with chemotherapy.

In two phase II trials in patients with hormone refractory cancer, combining estramustine with other microtubule inhibitors induced favourable responses. Estramustine plus vinblastine was assessed in 36 patients and a greater than 50% reduction in prostate-specific antigen (PSA) was observed in 61% of patients (Hudes 1992). Similarly, when estramustine plus etoposide was administered to 42 patients, pre-treatment PSA levels fell by at least 75% in 28% of patients (Pienta 1994). Paclitaxel has also shown synergy with estramustine when given as a 96-hour infusion with a 68% PSA response in patients with bone-only disease (Hudes 1995). Triple drug combinations have also been evaluated in patients with...
HRPC. The toxicity, efficacy and pharmacokinetics of docetaxel were evaluated in combination with oral estramustine and dex-amethasone in a phase I study in patients with metastatic disease (Petrylak 1999). In minimally pre-treated patients, 6 out of 24 experienced grade 3/4 granulocytopenia. A greater than 50% decrease in PSA was seen in 70% and 50% of minimally pre-treated and extensively pre-treated patients, respectively. The combination of oral estramustine, oral etoposide and intravenous paclitaxel was also reported to be active in patients with advanced prostate cancer (Smith 1999). This regime was tolerable and did not impact on quality of life.

During the 1980s, metastatic prostate cancer was reported to be unresponsive to chemotherapy with a response rate of less than 9% (Yagoda 1993). However, much progress has been made since then and the results from randomised clinical studies has led to the approval of mitoxantrone combined with corticosteroids for the palliative treatment of HRPC (Tannock 1996; Kantoff 1999). The encouraging results of recent clinical trials suggest a need to systematically evaluate the role of chemotherapy in this disease. The present review will assess the published evidence on chemotherapy for advanced prostate cancer to evaluate the effectiveness of this treatment and, if possible, summarise the data by meta-analysis.

OBJECTIVES

To determine the effectiveness and toxicity of chemotherapy in the management of hormone refractory prostate cancer; to undertake subgroup analysis; and where data are available, to establish the efficacy of different chemotherapeutic regimes.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All phase II and phase III randomised controlled trials or quasi-randomised trials comparing chemotherapy with placebo or one chemotherapeutic regime with another regime were eligible for assessment for this review. There were no language restrictions and studies initiated in any country will be considered providing they comply with other inclusion criteria. Only studies that report some or all of the outcome measures will be included for review.

Types of participants

Patients with advanced prostate cancer refractory to hormone therapy (HRPC). The definition of hormone refractory may vary between trials, but in general patients that have one of the following: progressive measurable disease; at least one new lesion on bone scan; or biochemical progression as measured by serum PSA during castrate levels of testosterone (Bubley 1999) will be considered hormone refractory. Symptomatic and asymptomatic patients will be included as well as trials including patients receiving prior chemotherapy. Chemotherapy for patients with newly diagnosed metastatic prostate cancer, or patients that have not received hormone therapy and therefore may be androgen dependent, will be the subject of a separate review.

Types of intervention

Chemotherapy for hormone-refractory prostate cancer. The agents commonly used include estramusfrine, vinblastine, docetaxel, paclitaxel, mitoxantrone, cyclophosphamide, 5-fluorouracil, carboplatin, and prednisone, mostly in combination therapy. Trials reporting chemotherapy combined with hormone therapy will also be assessed in this review. Schedules of any drug dose, routes of administration, and drug or hormone combinations will be reviewed. Trials reporting on the combination of chemotherapy with radioisotopes in hormone refractory prostate cancer will not be addressed but will form the basis of a separate systematic review. Where possible, classes of chemotherapeutic agents will be grouped for analysis. Randomised dose escalation studies were not included for analysis.

Types of outcome measures

The main outcome measures will be overall survival, disease-specific survival, PSA response, and time to progression. The definition of PSA response is a fall of >50% from pre-treatment levels for two consecutive measurements (Bubley 1999). Secondary outcome measures include a measurement of pain response, treatment-induced toxicity, and measures of quality of life.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Prostatic Diseases and Urologic Cancers Group methods used in reviews.

Our search strategy included an electronic search of MEDLINE from 1966 to Jan 2006 to identify all relevant published randomised trials of chemotherapy in advanced prostate cancer.

The search strategy was as follows:

1 randomised controlled trial.pt.
2 controlled clinical trial.pt.
3 exp randomised controlled trials/
4 exp random allocation/
5 exp double blind method/
6 exp single-blind method/
7 or/1-6
8 animal/ not human/
9 7 not 8
10 clinical trial.pt.
11 exp clinical trials/
12 (clin$ adj25 trial$).tw.
(singl$ or doubl$ or tripl$ or trebl$) adj25 (blind$ or mask$)).tw.
exp placebos/
placebo$.tw.
random$.tw.
exp research design/
or/10-17
18 not 8
19 not 9
exp Comparative Study/
exp follow up studies/
exp prospective studies/
(control$ or prospectiv$ or volunteer$).tw.
or/21-25
26 not 8
26 not (9 or 20)
9 or 20 or 28
exp Prostatic Neoplasms/
prostatic intraepithelial neoplasia/
(prostat$ adj3 (cancer$ or carcinoma$ or malignan$ or tumor?r or neoplas$ or intraepithelial or adeno$)).tw.
or/30-32
exp drug therapy/
exp chemotherapy, adjuvant/
exp Antineoplastic Combined Chemotherapy Protocols/
exp Antineoplastic Agents/
(chemotherapy or antineoplastic or anticancer) adj3 (agent$ or protocol$ or regimen$)).tw.
exp ANTHRACYCLINES/
exp DOXORUBICIN/
exp EPIRUBICIN/
exp MITOXANTRONE/
exp PRENISONE/
exp Fluorouracil/
exp CISPLATIN/
pro-plat.tw.
exp HYDROCORTISONE/
exp SURAMIN/
exp Adrenal Cortex Hormones/
corticosteroid$.tw.
Dexamethasone/
decadron.tw.
exp VINCRIrine/
exp MITOGUAZONE/
somatuline.tw.
exp TRIMETREXATE/
vinblastin.tw.
exp CYCLOPHOSPHAMIDE/
exp MITOMYCIN/
exp ESTRAMUSTINE/
exp KETOCONAZOLE/
exp ETOPOSIDE/
exp Paclitaxel/
docetaxel.tw.
exp DACARBAZINE/
exp CARBOPLATIN/
gemcitabine.tw.
exp TOPOTECAN/
irinotecan.tw.
exp IFOFSAMIDE/
did389.tw.
exp THALIDOMIDE/
uff.tw.
oxaliplatin.mp.
exp calcitriol/
exp vinblastine/
or/34-77
29 and 33 and 78
exp calcitriol/
exp vinblastine/
Handsearching of recent Proceedings of the American Society of Clinical Oncology 1996 to 2006, Cancer, Journal of Clinical Oncology, Journal of the National Cancer Institute, Clinical Oncology, British Medical Journal, Cancer Research, Cancer Chemotherapy and Pharmacology was undertaken. In addition, the reference list in each primary reference was scrutinised for additional randomised studies.

METHODS OF THE REVIEW

The literature search was screened by two reviewers (MS and CH), and by consensus, with relevant articles retrieved. Data were extracted from each identified paper independently by two or more reviewers and included information on trial design, participants, the type of intervention, and outcome measures. Where necessary, authors of relevant reports were contacted to clarify any queries. The quality of each trial was graded according to the concealment of allocation, adequate descriptions of patient numbers and reasons for patient withdrawal as detailed in the Cochrane Handbook. To quantitate quality, each trial was given a 3 point score based on: 1. the randomisation method; 2. blinding; and 3. description of patient withdrawals. One point was given if the trial was randomised and an additional point given if the method of randomisation was appropriate - for example, central randomisation by telephone. If the intervention allocation was blinded to the investigators, then one point was scored for this category, and one point awarded if the patients who were lost, either to withdrawals or dropouts, were described.

The data will be analysed and described using Review Manager Version 4.2.7 supplied by the Cochrane Collaboration. Data
analysis will compare chemotherapy with placebo or control (standard therapy), one chemotherapy regime with another, or chemotherapy with hormone therapy, and comparisons made for each outcome. Comparable outcome data from each trial will be combined in a meta-analysis where possible. For dichotomous data the odds ratio will be calculated with the 95% confidence interval. Trials will be assessed for consistency of effect using chi-squared statistics at a significance level of $P < 0.1$. A fixed-effect model will be used if there is no evidence of heterogeneity between studies. All analyses will be performed on an intention-to-treat basis. For continuous data, such as may be reported for pain assessment, summary analysis will be presented as a weighted-mean difference.

The definition of HRPC in each trial will be recorded and a subgroup analysis undertaken to explore the influence of this factor on patient outcome. The reasoning for this is that individuals classified as hormone refractory due to PSA progression are likely to have a much better outcome than those defined according to the number of bony lesions. The trial outcome would therefore bias results in favour of the former group.

**DESCRIPTION OF STUDIES**

Forty-seven trials published between 1977 and 2005 met the inclusion criteria for this review. Although there were no language restrictions on eligibility, all 47 trials were in English. The number of patient randomised in the studies was extremely large, totaling 6929. The chemotherapeutic agents used in these trials were extramustine (n = 21), doxorubicin (n = 14), 5-fluorouracil (n = 14), cyclophosphamide (n = 10), mitoxantrone (n = 6), methotrexate (n = 6), cisplatin (n = 4), docetaxel (n = 4), epirubicin (n = 4), CC-nitrosourea (n =4), mitomycin C (n = 3), vinblastine (n = 3), vincristine (n = 2), paclitaxel (n = 2), oxaliplatin (n = 1), melphalan (n = 1), hydroxyurea (n = 1), etoposide (n =1), peplomycin (n = 1), vinorelbine (n = 1), prednimustine (n = 1) and ixabepilone (n = 1). One trial compared chemotherapy with thalidomide (Dahut 2004).

In eight trials the comparative arm was hormone therapy (Abratt 2004; Andersstrom 1995; Berry 2002; De Kernion 1988; Johanson 1991; Kantoff 1999; Murphy 1979; Rangel 1992), and the included agents were prednisone (n = 2), medroxyprogesterone acetate (n = 2), hydrocortisone (n = 2), flutamide (n = 1) and ketoconazole (n = 1). A detailed description of the interventions used for all the trials, is presented in the 'Characteristics of included studies' table. Only five trials compared chemotherapy with either placebo or non-chemotherapy standard treatment (Iversen 1997; Murphy 1977; Scott 1976; Smalley 1981; Tveter 1990).

The definition of HRPC was reasonably similar for all trials and was generally defined as men with advanced and progressive prostate cancer that had failed to respond to standard hormone therapy. Seven trials stated that disease progression was observed despite castrate level of testosterone (Albrecht 2004; Abratt 2004; Daliani 1995; Droz 2003; Galsky 2005; Millikan 2001; Millikan 2003) ranging from $< 0.2$ ng/mL to $< 50$ ng/mL. The definition of disease progression was reported in 24 trials and included the appearance of new lesions (n = 22), an increase in size (generally 25%) of existing lesions (n = 19), an increase in pain (n = 12), a reduction in performance status (n =13) and weight (n = 7), and an increase in PSA levels (n =13). No trial used a rising PSA level as the sole indicator of disease progression.

All trials stated that the included patients had metastatic disease. However, it was not possible to define accurately the frequency of bone metastases because not all trials categorised these data. Where this could be clearly identified (21 trials), the mean number of patients with bone metastases was 85% (range 44% to 100%). The median age of patients ranged from 55 to 86 years. The baseline performance status was measured using several assessment protocols and included Karnofski 40% to70%, WHO 0% to 2%, ECOG 0% to 3%, SWOG 0% to 3%, and Zubrod < 3%. Thirteen trials reported that patients were symptomatic with an incidence of 59% to 100%.

**METHODOLOGICAL QUALITY**

The quality of the included studies varied, with some studies of high quality, whereas some reported trial findings poorly with important information not available. Of the 6929 patients randomised, 96% were eligible and 91% were evaluable. Nine trials recruited 50 patients or less, 11 recruited 51 to 100 patients and 27 recruited more than 100 patients (101 to 1006).

The scores summarising trial quality are presented in the table describing the characteristics of the included studies (Methods). All trials included in this review were randomised but only 15 described the method of randomisation. Blinding of intervention allocation was reported in three studies (Abratt 2004; Iversen 1997; Tveter 1990). Blinding was not possible in many cases due to the obvious difference in the schedules of comparative arms. All but three studies detailed the number of patient withdrawals and dropouts (Elomaa 1991; Herr 1982; Tveter 1990).

To account for a potential androgen withdrawal response in the evaluation of chemotherapy for HRPC, 15 trials reported a washout period from androgen deprivation therapy of between 2 to 8 weeks. In addition, no prior chemotherapy was allowed in all but two trials (Berry 2002; Droz 2003).

**RESULTS**

One hundred and seven randomised trials of chemotherapy in advanced prostate cancer were identified by the search strategy. Of
these, sixty trials were excluded, mainly because the recruited patients were not hormone refractory, but the complete list of reasons for exclusion are described in the table of excluded studies. The remaining 47 trials were, therefore, included in this review. One of the analytical aims of this review was to pool the trial data and perform a meta-analysis where possible. However, only two trials compared the same interventions (Berry 2002; Tannock 1996).

Since chemotherapeutic agents used to treat prostate cancer have different efficacies and toxicities, it was considered that, as no standard comparative arm was apparent, a meta-analysis with pooling of data was not feasible. Therefore, this review was limited to a quantitative description of the included randomised trials. For clarity, the studies have been categorised according to the drug used, however it must be emphasised, that this is not a definitive grouping, since many trials used several agents and therefore would be eligible for inclusion under a number of drug sections. Each drug category is accompanied by a table summarising data on survival, PSA response and time to disease progression. The details of each trial's aim, methods, participants, interventions and outcomes are tabulated in the 'Characteristics of included studies' table.

**Estramustine**

Estramustine phosphate is a derivative of estradiol-17-beta and has been used to treat advanced prostate cancer for approximately three decades. It was originally developed by combining oestradiol-17-beta with the alkylating agent, non-nitrogen mustard. However, its mechanism of action does not appear to be by DNA alkylation, and experimental data suggest that estramustine disrupts cytoplasmic microtubules by binding to the associated proteins and inhibiting the assembly of nuclear matrix.

In this section, 19 randomised trials that have used estramustine in the treatment of patients with HRPC are included. The methodology and patients details are shown in the table 'Characteristics of included studies' (this table contains information on all the included trials for this review). The trials vary considerably in terms of the interventions used, and therefore, are subsectioned to improve clarity.

1. **Estramustine versus Best Supportive Care or Hormones.**

In a double-blind, multicentre, randomised placebo-controlled trial, Iversen and colleagues compared the addition of estramustine phosphate plus standard palliative therapy with standard therapy plus placebo (Iversen 1997). This study enrolled 129 patients with metastatic prostate cancer and progressive disease following orchidectomy. Palliative therapy included analgesics, glucocorticoids and palliative radiotherapy. The data for median overall survival, PSA response (proportion with > 50% decline from baseline) and median time to disease progression for this study, and for all the other studies in the three estramustine sections, are shown in Table 01. There was no significant difference in overall survival between the two arms, nor for the percentage of patients achieving a PSA response. In addition, the median time to progression was similar for both groups. Adverse events were more common in patients receiving estramustine and included nausea, vomiting, diarrhoea, and gynaecomastia. Perforated duodenal ulcer was noted in three patients in this group. The data from this trial suggest that estramustine was not superior to placebo in this setting.

To assess the efficacy of single-agent estramustine and the non-steroidal anti-androgen flutamide, the National Prostate Cancer Project (protocol 2400) conducted a prospective randomised trial comparing both agents in patients with hormone-refractory prostate cancer (De Kernion 1988). There were no complete regressions seen with either agents based on NPCP criteria, and only one patient receiving flutamide achieved a partial regression. The majority of patients were classified as having stable disease or progression (31% and 62% estramustine, 26% and 69% flutamide). Gastrointestinal toxicities, in particular nausea and vomiting, diarrhoea and anorexia were severe in 3% to 22% of patients receiving estramustine, and 6% to 23% for the flutamide group. Severe cardiovascular toxicity and oedema were more common with estramustine. There was no significant difference between treatment arms in terms of progression-free survival and overall survival. These data suggest no significant difference in the clinical benefit achieved for patients receiving these agents.

In a Swedish study, Johansson et al (Johansson 1991) randomised 105 patients with metastatic hormone-resistant prostate cancer to either estramustine or medroxyprogesterone acetate (MPA). After three months of treatment, more than 50% of patients had progressed, with no significant difference between estramustine or MPA (P = 0.28). During the first year of treatment 70% of the patients had died, again with no statistical difference for survival rates between groups (P = 0.23). Therapy was discontinued in eight patients receiving estramustine because of side effects (nausea, vomiting and diarrhoea) and in three patients receiving MPA (oedema, cardiovascular toxicity, and increased pain). Remissions were noted in 13 patients on MPA (12 to 56 weeks) and four on estramustine (22 to 28 weeks) which was reported to be significantly different (P = 0.05). Based on this latter finding, it was concluded that MPA was preferable to estramustine in this category of patients.

A randomised trial from the National Prostate Cancer Project (NPCP protocol 200), evaluated estramustine and streptozotocin as single agents and compared them to standard therapy in patients who had received at least 2000R pelvic irradiation (Murphy 1977). All had progressive disease following hormonal therapy. Nausea and vomiting were the most frequent toxicities encountered; the collective incidence of which was 59% on the estramustine arm, 50% on the streptozotocin arm, and 33% on the standard therapy. Objective responses, which included patients classified with stable disease and partial regression, were seen in 30%, 32% and 19% of patients receiving estramustine, streptozotocin and standard therapy, respectively. The duration of response was significantly longer...
for patients on estramustine than for those on streptozotocin or standard therapy (Table 01). Survival data were categorised according to response and no overall survival data could be extracted from this paper, although mean survival times were greater for patients benefiting from chemotherapies (17.5 to 20 months for estramustine and streptozotocin versus 10 months for standard therapy). Estramustine was reported to have an advantage over streptozotocin in terms of weight gain, performance status, pain relief and correction from anaemia, but again individual data for each arm were not reported. The authors advocate estramustine.

2. Single Agent Estramustine versus Single Agent Cytotoxics

Estramustine was compared to low dose epirubicin in a very small randomised study in prostate cancer patients that had relapsed after hormone therapy (Elomaa 1991). Palliation, in terms of pain control and quality of life (National Prostate Cancer Project criteria), was improved in 63% to 68% for both arms. Time to disease progression was similar for both treatment groups and overall survival was the same. There was no grade 3 or 4 neutropenia and thrombocytopenia for either group and gastrointestinal toxicity was restricted to grade 1 or 2 in 43% for estramustine and 36% for epirubicin. Based on practical clinical considerations and cost, the authors recommended estramustine as the first-line treatment for patients with hormone-resistant, painful prostate cancer and epirubicin as second-line treatment.

Single-dose estramustine was compared to single dose mitomycin C for the treatment of HRPC in an EORTC, phase II, randomised trial (Newling 1993). In the schedules used, both agents appeared to be equally ineffective as regards time to disease progression and overall survival (Table 01). Toxicity was clinically significant for both agents, and treatment was stopped because of toxicity in 40% of patients receiving estramustine (mainly gastrointestinal) and 32% for mitomycin C (mainly marrow suppression). Multivariate analysis suggested that WHO performance status and pain at entry were important prognostic factors in determining the duration of survival.

A randomised study by Loening et al (Loening 1983) evaluated estramustine, methotrexate and cisplatin as single agents in HRPC patients. The main outcomes were objective and subjective responses based on the National Prostate Cancer project criteria. There was only one complete objective response to methotrexate, whereas those classified as progressing at 12 weeks, included 66% on estramustine, 59% on methotrexate and 64% for cisplatin. Performance status was similar for the three arms, although more patients on methotrexate (19%) and cisplatin (22%) had an improvement of pain compared to estramustine (6%). Median survival times were not significantly different for each group (Table 01). Nausea, vomiting and anorexia were the major side effects for estramustine, but to a lesser extent than for cisplatin. Methotrexate was less toxic but stomatitis and leukopenia were seen with this agent. This trial did not demonstrate the superiority for any of the three agents tested but methotrexate was advocated for further study due to its best overall response.

Two additional studies included in this subsection combine hormone therapy with a cytotoxic as the comparative arm. The first trial, Anderstrom 1995, evaluated the time to disease progression in HRPC patients randomised to receive either estramustine alone or medroxyprogesterone acetate plus epirubicin (MPA/E). The estimated probability of being free from progression at one year was 17% and 29% for estramustine and MPA/E, respectively. The risk of progression was significantly less with the combination arm (P = 0.013). However, no difference was observed for overall survival, with approximately 40% of patients alive in both arms at 1 year. Significant cardiotoxicity was seen in both groups with heart failure occurring in 9 of 74 patients on estramustine (12%) and 8 of 75 on MPA/E (11%). Nausea and vomiting were more common with estramustine (19% versus 7%). The authors conclude that the combination regime, whilst delaying disease progression has no affect on survival, and that the degree of cardiotoxicity should be considered before treatment.

The second study was a small, placebo controlled, randomised trial from Norway (Tveter 1990), and compared estramustine to low dose epirubicin plus medroxyprogesterone acetate (MPA/E) and epirubicin plus matched placebo (E/P). Epirubicin, either with placebo or in combination with MPA induced a significantly improved pain relief compared to estramustine (P < 0.05). Patients with severe pain on entry and having the greatest analgetic intake (score 3) experienced better palliation than those with moderate pain (score 2). The combination of MPA/E also significantly improved performance status compared to estramustine and E/P (P < 0.05). No toxicity data were reported, although it was stated that no haematological complications occurred in any arm. Low dose epirubicin in combination with MPA provides good palliation for symptomatic metastatic cancer of the prostate.

3. Estramustine plus a cytotoxic agent versus other cytotoxics.

Albrecht and colleagues reported on a randomised phase II study in progressive hormone-escaped metastatic prostate cancer patients, comparing estramustine alone with estramustine plus vinblastine (Albrecht 2004). The main endpoints were PSA response, overall survival and toxicity. The PSA responses were poor with less than 30% of patients in each arm achieving a 50% decrease from baseline. Overall survival was not significantly different between groups and showed no correlation with PSA response. The toxicity of these regimes was substantial and resulted in 40% of patients withdrawing from treatment. Estramustine either alone or in combination was not be recommended for the routine treatment of patients with HRPC.

Oral estramustine in combination with the vinca alkaloid, vinblastine, was compared to vinblastine alone in a randomised trial of 201 patients with HRPC (Hudes 1999). The combination significantly reduced the time to disease progression, and significantly,
more patients in this arm had a reduction in PSA of at least 50% from baseline. However, no difference in overall survival was observed between groups. Nausea, vomiting and leg oedema were significantly greater with the combination schedule. Attempts to assess quality of life and pain response were disappointing due to the limited amount of data that were obtained, thus no reliable conclusion could be drawn from this study on these outcomes.

Soloway and associates (Soloway 1981) evaluated estramustine phosphate and vincristine alone and compared them with a combination of these two agents in previously irradiated men with HRPC. All patients had received at least 2000R to the pelvis and had documented progression after orchidectomy or hormone therapy. Response to therapy was assessed using the National Prostate Cancer Project criteria. The study was poorly reported and limited data were extractable. The median duration of response for those patients responding was not significantly different for estramustine (20 weeks) and vincristine (22 weeks), and was less for the combination arm (13 weeks). Survival, based on evaluable patients, was similar for each arm (Table 01). Anaemia was clinically significant and occurred in all treatment groups (26% to 38%) with nausea and vomiting (42% to 59%) and neurological disturbances (30% to 50%) being prominent. No advantage was found for the combination of these agents compared to single-agent administration.

The same group also investigated single-agent estramustine and cisplatin and compared these with a combination of both drugs, again in previously irradiated men with progressive HRPC (Soloway 1983). This was the fourth randomised study from the National Prostate Cancer Project (NPCP). This had a cross-over, trial design at disease progression, and analysed the data on an intention-to-treat basis and for evaluable patients. The results indicated no significant difference in overall survival or objective progression rates for the three treatment groups. Ninety-two percent of patients had pain on study entry, which improved in 32% receiving estramustine, 36% receiving cisplatin and in 44% for the combination group. Improvements in performance status occurred in 5%, 7% and 12%, respectively, with no statistically significant differences. The main side effects were nausea and vomiting for all groups (62% to 88%) and accompanying anorexia (75% to 95%). The side effects were severe in 29% of those patients receiving the combination compared to 12% and 14% for estramustine and cisplatin, respectively. An additive effect of the combination on objective response rates was suggested but the evidence was not compelling.

One hundred and sixty-three patients with HRPC were randomised to either estramustine plus paclitaxel or paclitaxel alone in a recent phase II study (Berry 2004). This study was undertaken to determine the response rates and safety of these regimes in patients with progressive disease. Partial responses were seen in 37 patients receiving the combination and in 22 patients on estramustine alone. These respective response rates were significantly different (47% versus 27%, P < 0.001) although the median durations were similar (115.1 months versus 115.5 months). Overall survival was also improved with the combination regime and was marginally statistically significant (P = 0.049). The main adverse events observed with estramustine/paclitaxel combination and paclitaxel alone schedule were respectively gastrointestinal 20% and 8%, asthenia 15% and 16%, neuropathy 10% and 7%, and neutropenia 6% and 13%. Four patients experienced thromboembolic events with the combination. In terms of response and survival, the combination of the two microtubule inhibitors has shown some encouraging results.

Estramustine was combined with the cytotoxic tubulin-polymerising agent, ixabepilone, in a phase II randomised study (Galsky 2005). Ninety-two patients were randomised to a combination of both agents or to ixabepilone alone. The main outcome of interest was PSA response. In 45 HRPC patients receiving ixabepilone plus estramustine, 31 (69%) had a > 50% decline in PSA in relation to baseline levels, compared to 21 of 44 (48%) for ixabepilone alone. Partial PSA responses were seen in 48% and 32%, respectively, for those patients with measurable disease; however, the majority of these were not confirmed with a CT or MRI scan. Time to PSA progression was short and similar between groups (Table 01). No overall survival data were presented. Grade 3 neutropenia and febrile neutropenia occurred in 29% and 8% for the combination, and 22% and 4% for the patients receiving ixabepilone alone. Peripheral neuropathy was common and was seen in 73% and 67% for the combination and single agent arms, respectively. The study authors advocate further evaluation of ixabepilone, but the conclusions are based mainly on the surrogate marker PSA, and does not present any P values.

The combination of estramustine plus prednimustine was compared to prednimustine alone in HRPC patients who had previously received extensive radiotherapy to the pelvis (Murphy 1979). The rationale for this study (protocol 400) was to evaluate a minimally myelosuppressive regime in patients who had already received myelosuppressive therapy. Pain relief was experienced by 37% of patients in the combination arm and 32% with prednimustine alone. The respective performance status was improved or the patient remained ambulatory in 40% and 37% of cases. Nausea and vomiting were the most common side effects (57% for the combination and 47% for the prednimustine group), although haematological toxicities were reported to be similar in each arm and of minor clinical importance. Six patients (11.5%) on the combination and 11 patients (18%) on prednimustine alone had a white blood counts that decreased to < 3000 per mm³ at some point in their treatment. The overall survival at the end of one year was not significantly different between groups and no reduction in tumour mass (> 50%) was seen in either group. Some palliation of symptoms was seen with these two regimes but no survival advantage was identified.

4. Complex Combination Chemotherapy with Estramustine.
The percentage of patients achieving a PSA response was similar in each arm (12/20 E/E versus 12/18 L/T/D) (Table 01). Changes in performance status (31% improved on E/E versus 41% on L/T/D) and response to pain relief (61% E/E versus 56% L/T/D) were not significantly different between groups. The time to disease progression and overall survival were similar for both regimes. Significant haematological toxicity (80% of patients) and gastrointestinal toxicity (50% of patients) were seen with the chemotherapy arm only (E/E). It was concluded that the combination treatment (L/T/D) may offer a safer alternative to chemotherapy in this clinical setting.

In a Japanese study, Akaza et al (Akaza 1988) evaluated estramustine in combination with peplomycin and doxorubicin, and compared this regime to 5-fluorouracil plus peplomycin plus doxorubicin in a subgroup of patients with HRPC. This trial reported two groups of patients: previously untreated patients and 44 patients who were anti-androgen treatment refractory. The latter group was randomised to the above schedules and is discussed below. The primary outcome of interest was tumour response, categorised according to primary lesion response and osteoblastic lesion response. Overall survival was also determined. No patient had a complete objective response to either regime, and only three cases receiving 5-fluorouracil, peplomycin and doxorubicin achieved a partial response with respect to the primary lesion. Only one patient in the study, from the same group, achieved a partial response with regard to bone metastases evaluation. In the comparison of survival times, there was no significant difference between the two groups. The dose of estramustine was not reported, nor were any toxicity data or quality of life data. The results of this study suggest that the combination of agents used have poor efficacy and survival rates in HRPC patients.

Finally, in a recent randomised, multicentre, phase II study, estramustine was a component in a multi-agent comparison (Miklikan 2003). Patients with progressive androgen-independent prostate cancer were randomised to alternating regimens of estramustine/vinblastine and ketoconazole/doxorubicin (EV/KD) or a combination of estramustine/paclitaxel/etoposide (EPE). As expected, these intensive cytotoxic regimens were difficult to deliver and toxic. Thromboembolic events with estramustine were seen in 27% of patients, which included deep vein thrombosis and pulmonary oedema. Grade 4 toxicities occurred with both regimens and included stomatitis, sensory neuropathy, supraventricular tachycardia, neutropenia, and febrile neutropenia. There were nine early deaths (13%), four by complications of neutropenia, four by rapid disease progression, and one myocardial infarction. Neither response rates (47% EV/KD, 36% EPE) nor survival times differed significantly between treatment groups. Not surprisingly, neither regimen was recommended for further evaluation.

**Cyclophosphamide**

Cyclophosphamide is a prodrug that requires hepatic metabolism for conversion to an active alkylating agent with properties similar to those of mustine. It is used as a single agent and in combination chemotherapy for a number of leukaemias and lymphomas as well as solid tumours such as prostate cancer. The present review identified 10 randomised trials using cyclophosphamide for HRPC. In six of these trials, cyclophosphamide was used as a single agent (Scott 1976; Chlebowski 1978; Loening 1981; Muss 1981; Kasimis 1985; Saxman 1992). In two trials it was combined with another cytotoxic (Page 1985; Murphy 1988), and in two other trials it was combined with several agents (Herr 1982; Graham 1986). The clinical data for these studies are summarised in Table 02.

The first randomised trial to evaluate cyclophosphamide as a single agent was that of the National Prostate Cancer Project (NPCP protocol 100, Scott 1976). Cyclophosphamide was compared to 5-fluorouracil or standard palliative therapy in patients with stage D prostate cancer. All had disease progression and had failed to respond or had relapsed following hormone therapy. The proportion of patients responding was greater for both chemotherapy arms and were 46%, 36% and 19% for cyclophosphamide, 5-fluorouracil and standard therapy, respectively (see table of ‘Included studies’ for response definitions). The difference was statistically different for cyclophosphamide compared to standard therapy (P < 0.02). The survival of responding patients on the chemotherapy arms was longer than for responding patients on standard therapy. However, the survival data were presented by response group, and it was not possible to derive a summary statistic for this study.

The efficacy of single agent cyclophosphamide was compared, in a very small trial, with the combination of cyclophosphamide plus doxorubicin and 5-fluorouracil, for the treatment of advanced metastatic prostate cancer (Chlebowski 1978). Similar numbers of patients receiving cyclophosphamide alone achieved an objective response (NPCP criteria) compared to the combination arm (53% versus 50%). Overall survival was not significantly different between the two groups, although those patients responding to cyclophosphamide alone survived significantly longer than non-responders (P < 0.01), but this was not the case in the combination arm. Nausea and vomiting were the most common toxicities of clinical significance (grade not given) and were observed in approximately 60% of patient in both regimes. One patient in each arm had severe granulocytopenia but there were no treatment-related deaths. Single agent cyclophosphamide appeared equivalent to the combination with doxorubicin and 5-fluorouracil in the advanced cancer patients.

Another randomised study evaluated single agent cyclophosphamide. This time it was compared to methyl-CCNU alone or hy-
droxyurea alone in patients with relapsing clinical stage D prostate cancer (Loening 1981). Objective responses (NPCP criteria) evaluated 12 weeks after therapy initiation, were 35% for cyclophosphamide, 15% for hydroxyurea and 30% for methyl-CCNU; these were not significantly different statistically. The respective values for disease progression were 65%, 86%, and 70%. Performance status was improved in 18% of patients on hydroxyurea compared to 12% and 4% for cyclophosphamide and methyl-CCNU, respectively. Pain relief was improved in 20% of patients in each arm. None of the treatment comparisons were significantly different.

A very small, randomised, study compared cyclophosphamide alone or in combination with methotrexate and 5-fluorouracil in advanced cancer prostate cancer patients (Muss 1981). Response rates, using NPCP criteria, were 53% with single agent cyclophosphamide and 54% in patients receiving the combination chemotherapy. For both treatment arms, the responding patients had a significantly longer survival compared to non-responders (P = 0.002). However, there was no significant difference in duration of response (P = 0.76) nor overall survival (P = 0.39) for patients in either arm. This study aimed to recruit 50 patients to detect a 20% difference in response rates, but was closed early due to a lack of significant benefit of the combination regimen.

Preliminary results of a randomised, crossover trial were reported by Kasimis and colleagues (Kasimis 1985), comparing cyclophosphamide with a combination regimen of 5-fluorouracil plus doxorubicin plus mitomycin C. This was another small study with primary objectives of response (NPCP criteria) and toxicity. No survival data were available. There was no significant difference in the overall objective response rates between groups (P = 0.72), however, the median time to disease progression was significantly longer with the combination arm (P = 0.007). Twenty-five percent of patients on cyclophosphamide alone and 64% receiving the combination chemotherapy achieved a 'remarkable' relief of pain (P <0.01), and was associated with a reduction in analgesic consumption and an improved performance status. One of 15 patients receiving the combination treatment died of sepsis due to neutropenia and febrile neutropenia developed in 35% of patients, compared to 5% with cyclophosphamide alone (75% and 56%, respectively) compared to the combination (43% nausea only). No follow-up publication of this trial has been identified.

The Hoosier Oncology Group randomised patients with advanced prostate cancer to cyclophosphamide alone or combined with doxorubicin plus methotrexate (CAM) to determine whether a survival advantage could be achieved with the combination therapy (Saxman 1992). There were no complete responses to chemotherapy and only 2% and 6% of patients achieved a partial response to cyclophosphamide alone and the combination regimen, respectively. Overall progression occurred in 57% of patients and was not significantly prolonged with CAM (P = 0.07). Overall survival, on an intention-to-treat basis, was very similar for each treatment group (P = 0.7) suggesting that the combination chemotherapy was of minimal value to the majority of patients.

Two randomised trials combined cyclophosphamide with another cytotoxic agent as one of the comparative arms. The first evaluated cyclophosphamide plus 5-fluorouracil against doxorubicin plus lomustine in a small group of patients with hormone-refractory prostate cancer (Page 1985). Objective response rates (partial response plus stable disease - NPCP criteria) occurred in 52% and 71% of patients, respectively (P = 0.17), whereas subjective response rates (see table of 'Included studies' for definitions) were observed in 48% and 82% of patients (P = 0.03). This was not translated into a significant difference in overall survival between groups (P = 0.46). Major toxic effects were myelosuppression, nausea and vomiting which were of similar frequency and severity in each group. The combination may have had superior palliative activity but no survival advantage.

The second randomised trial combined cyclophosphamide with doxorubicin, and compared this regime to single agent methotrexate, and a combined arm of cyclophosphamide plus 5-fluorouracil plus cisplatin (Murphy 1988). Myelosuppression was of similar frequency and severity across all three arms (anaemia 32% to 34%, WBC 28% to 42%, platelets 4% to 14%). Nausea and vomiting was less prevalent with methotrexate than with the other two arms (P < 0.02). There were no complete regressions and only one partial regression on the methotrexate arm. Survival analysis indicated that 105 of 152 patients had died (69%) with no significant difference between regimens. Also progression-free survival data showed that 84% of patients had failed, again with no significant difference between these treatments. These data do not provide encouragement to further investigate these regimens.

Cyclophosphamide was combined with two other cytotoxic agents as a comparative arm in a small randomised trial reported by Herr (Herr 1982). Forty patients with HRPC were randomised to receive either cyclophosphamide plus methotrexate plus 5-fluorouracil or chloroethyl-CCNU alone (20 patients in each arm). Response to treatment was poor with only three partial responses achieved in the combination arm. The proportion of patients classified as having disease progression was 65% and 70% for the combination and chloroethyl-CCNU, respectively. Overall survival was not significantly different between the two treatment groups. These regimen appear to be minimally effective in endocrine resistant advanced prostate cancer.

Finally, one randomised trial, in which cyclophosphamide was combined with three other agents, was published by the Emory University Clinic Atlanta, Georgia (Graham 1986). In this study cyclophosphamide was combined with methotrexate, 5-fluorouracil and prednisone, and was compared with another multi-agent arm comprising methotrexate, 5-fluorouracil, prednisone, vincristine and melphalan. The description of the toxicities associated with each arm was limited but indicated that gastrointestinal
and haematological complications were most common and equivalent in each group. Response rates were equal for each of the two groups (37% versus 36%). Overall survival was not significantly different for patients receiving either of these complex multi-agent regimens.

5-Fluorouracil

5-Fluorouracil is an antimitabolite that is indicated for the palliation of a variety of carcinomas both alone and in combination with other agents. The literature search identified four relevant randomised trials that reported on the use of 5-fluorouracil in the treatment HRPC patients (Table 03). Three studies used single agent 5-fluorouracil (Smalley 1981; Daliani 1995; Breul 1997), whereas one combined 5-fluorouracil with oxaliplatin (Droz 2003).

The South Eastern Cancer Study Group evaluated single agent 5-fluorouracil and the combination of 5-fluorouracil plus cyclophosphamide and doxorubicin in both HRPC patients and in patients with advanced bladder cancer (Smalley 1981). This review was only concerned with the prostate cancer group. There appeared to be no significant difference in overall survival for the prostate cancer patients receiving either treatment for evaluable patients or on an intention-to-treat basis. The majority of those receiving the combination regime experienced nausea and vomiting after each dose. Although the granulocyte count decreased below \(<1500/\text{mm}^3\) following combination chemotherapy, a rebound occurred within 4 days and was rarely of clinical significance. Patients with prostate cancer were evaluated for response using either placental alkaline phosphatase levels or the NPCP criteria for objective response. However, the data presented varied according to the method of measurement making it difficult to summarise the response results.

When 5-fluorouracil was combined with interferon-\(\alpha\) minimal anti-tumour activity was reported (Daliani 1995). In this small phase II trial there was no significant difference in the extent or duration of response, nor in overall survival for either treatment group. Both regimes induced significant toxicity, principally mucositis and neurotoxicity and three treatment-related deaths occurred in the 5-fluorouracil alone arm. The authors conclude that these regimes are inactive in prostate cancer and should not be tested in further trials.

Monotherapy with 5-fluorouracil was compared to 5-fluorouracil plus folic acid in a small German prospective randomised study (Breul 1997). Pain, assessed by scoring the intensity and frequency, was not completely alleviated in any patient; however, 78% on 5-fluorouracil alone and 58% on the combination experienced mild to moderate pain relief. Side effects were mainly gastrointestinal (stomatitis and diarrhoea) and were more common in the combination arm (grades 1 to 4, 11 versus 5). Haematological toxicities (leukopenia and thrombocytopenia) were more frequent with the 5-fluorouracil monotherapy (grades 1 to 4, 15 versus 9). There was no statistically significant difference between the two arms in terms of time to disease progression and overall survival. Clinical response did not always correlate with PSA response with some patients experiencing increasing pain and a deterioration of performance status with decreasing PSA levels, whilst others had increasing PSA levels and good a clinical response.

The benefit of adding 5-fluorouracil to oxaliplatin was evaluated in a recent small phase II randomised trial (Droz 2003). Twenty-six patients received oxaliplatin alone and 28 received oxaliplatin plus 5-fluorouracil. There were no complete responses in either treatment arm (assessed by pain, performance status, weight gain, and PSA levels), although 11% and 19% had a PSA partial response (Table 03) to single agent oxaliplatin and the 5-fluorouracil combination, respectively. No difference in overall survival was observed between the two groups. Respective grade 3 and 4 toxicities for oxaliplatin and oxaliplatin plus 5-fluorouracil include anaemia (19% versus 32%), stomatitis (0% versus 4%), asthenia (4% versus 7%) and neurotoxicity (4% versus 11%). Based on objective response rates and clinical benefit (12% and 39%) further study using the combination is warranted.

Doxorubicin

Doxorubicin (Adriamycin) is a cytotoxic antibiotic that forms stable complexes with DNA and interferes with the synthesis of nucleic acids. It has shown clinical activity in many malignancies such as acute leukaemias, lymphomas, paediatric malignancies as well as adult solid tumours especially breast and lung carcinomas. It has also been evaluated for activity in men with advanced prostate cancer.

Six randomised trials using doxorubicin in HRPC patients are included in this section (Table 04). In three trials doxorubicin was used as a single agent (Torti 1985; Francini 1993; Leaf 2003). In two trials it was combined with another agent (Rangel 1992; Millikan 2001), and in one trial it was combined with two other cytotoxics (Laurie 1992).

The first trial was very small, with 37 patients with HRPC randomised to receive either doxorubicin or doxorubicin plus cisplatin (Torti 1985). Tumour response was assessed using the NCOG criteria which requires a 75% reduction in the primary tumour to be classified as a partial response. Using this definition, 20% responded in the doxorubicin arm and 14% in the combination arm. Twenty-seven percent of patients in the doxorubicin alone arm achieved some pain relief (NCOG Pain Status Scale) compared to 40% when combined with cisplatin. Toxicity was severe, particularly with the combination regimen where thrombocytopenia was dose limiting. Nausea and vomiting were common in both groups and dose limiting in patients on both arms. Time to disease progression and overall survival were similar for both treatment groups (Table 04).

Another small randomised trial compared single agent doxorubicin with epirubicin, testing the hypothesis that weekly epirubicin
would have less side effects and decreased cardiotoxicity than doxorubicin (Francini 1993). The main adverse effects were cardiotoxicity and myelosuppression but were less frequent with epirubicin. Cardiotoxicity occurred in 11% of patients in the epirubicin arm and 48% in the doxorubicin arm. Grade 2 to 3 leukopenia was 18% and 52%, respectively, and grade 2 to 3 anaemia was 16% and 57%. After 24 months of follow up, overall survival was significantly improved with epirubicin compared to doxorubicin ($P = 0.042$). Response, which included an assessment of pain and performance status, was 20% for epirubicin and 15% for doxorubicin. These data suggest that epirubicin is as effective as doxorubicin in terms of palliation but with fewer side effects.

A phase II, multicentre, randomised study, set up by the Eastern Cooperative Oncology Group (ECOG), was designed to evaluate doxorubicin as a single agent compared with doxorubicin combined with diethylstilbestrol (DES) in men with HRPC (Leaf 2003). This trial was initiated in 1983 but not published until 2003. There appears to be no clinical advantage, in terms of response for patients treated with doxorubicin alone compared to those receiving the combination (21% versus 24%, $P = 0.70$). The combination arm was more toxic, with 7% of patients experiencing severe cardiotoxicity (7% versus 1%) and thrombosis with pulmonary embolism (7% versus 0%). The addition of DES to doxorubicin did not improve overall survival in these patients and it was concluded that there was no clinical benefit with the combination regimen.

Single agent doxorubicin given weekly and combined with prednisone was compared to prednisone alone in a randomised study of 110 patients with HRPC (Rangel 1992). A significant number of patients receiving the combination achieved a subjective response ($P = 0.01$) and had evidence of stable disease ($P = 0.02$). However, overall survival was not improved by the addition of doxorubicin to prednisone ($P = 0.26$). The weekly regime of doxorubicin was well tolerated although cardiotoxicity was noted in approximately 15% of patients. Weekly doxorubicin, although of subjective benefit, did not provide a substantive advantage to these patients.

A phase II randomised study, initiated by the MD Anderson Cancer Centre, was set up to define response rates and survival of men with HRPC receiving either doxorubicin plus ketoconazole or ketoconazole alone (Millikan 2001). All patients had progressive disease despite castrate levels of testosterone. Patients with metastatic disease involving the long bones or viscera fared significantly worse than those with disease confined to the axial skeleton. Both regimens were associated with grade 3–4 toxicities including haematological (mainly doxorubicin arm), anorexia, nausea with vomiting, stomatitis and fatigue (mainly doxorubicin arm). Additionally, patients who had a PSA response, had an improved survival. Nevertheless, there was no significant difference in overall survival or time to disease progression. Neither regimen was recommended for further assessment in a phase III trial setting.

Laurie et al (Laurie 1992) reported on a randomised trial in which combination chemotherapy with doxorubicin, 5-fluorouracil and mitomycin C was compared to sequential therapy with the same agents given at full dose. One hundred and forty-five patients with advanced metastatic prostate cancer with progressive disease following hormone therapy were recruited with primary trial endpoints of response rates and survival. In the sequential arm, mitomycin C was given first followed by doxorubicin when disease progression occurred and then 5-fluorouracil. Objective responses were seen in 10/72 (14%) of patient receiving the combination schedule and 13/72 (18%) in the sequential chemotherapy arm. The median duration of response was 209 days for the combination arm, 219 days for responders to mitomycin (as measured from the initiation of therapy), and 119 days for responders to doxorubicin. When the study terminated, 141 patients had died and there was no significant difference in overall survival between the two groups ($P = 0.25$). Myelosuppression was the major toxicity in both arms with severe leukopenia and thrombocytopenia observed in 64% and 21% of patients randomised to the combination and sequential chemotherapy, respectively. The corresponding values for patients responding to mitomycin C, doxorubicin and 5-fluorouracil alone were 7% and 14%, 52% and 30%, and 75% and 25%. These data suggest that the schedules used in this study are of minor clinical importance for the treatment of HRPC.

**Mitoxantrone**

Mitoxantrone, an anthracenedione structurally similar to doxorubicin, was synthesized in the 1970s, and has been used to treat leukaemias, non-Hodgkin's lymphoma, breast cancer, and to a lesser extent, advanced prostate cancer. The exact mechanism of action is unknown but includes intercalation with DNA to cause inter/intrastrand cross-linking. It also causes DNA strand breaks through binding with the phosphate backbone of DNA. Mitoxantrone is cell cycle phase-nonspecific.

Three randomised trials using mitoxantrone in HRPC patients have been included in this section (Table 05). In one trial mitoxantrone was combined with hydrocortisone as one of the comparative arms (Kantoff 1999), and in two trials mitoxantrone was combined with prednisone (Tannock 1996; Berry 2002).

Kantoff et al combined mitoxantrone with hydrocortisone and compared this combination with hydrocortisone alone (Kantoff 1999). Although patients receiving the combination had a small but statistically significant delay in time to disease progression ($P = 0.02$), there was no difference in overall survival. There was an indication of a better quality of life in the combination arm based on emotional state ($P = 0.04$), family disruption ($P = 0.02$), and two pain criteria (frequency $P = 0.06$ and severity $P = 0.03$), although symptom distress, sexual and urological function favoured the hydrocortisone alone arm. Grade 3–4 cardiotoxicity was found in 5% of patients receiving mitoxantrone, in addition, haematological toxicity was significantly greater in this treatment group.
The palliative activity of mitoxantrone combined with prednisone was evaluated in a Canadian randomised trial (Tannock 1996). Compared to prednisone alone, the palliative response, as measured by a 2 point decrease in a 6-point pain intensity scale, was significantly in favour of the combination (29% versus 12%, P = 0.01). Responding patients generally had an improvement in quality-of-life scales. The major toxicities were associated with mitoxantrone and include grade 3/4 neutropenia (7%), nausea and vomiting, alopecia (24%) and cardiotoxicity (66%). Although a significant palliative response was seen with the combination, there was no difference in overall survival.

A similar study, comparing mitoxantrone plus prednisone with prednisone alone, was undertaken in asymptomatic men with HRPC, with time to treatment failure as the primary endpoint (Berry 2002). At a median follow up of 22 months, the combination regime significantly delayed the time to disease progression (P = 0.018) and increased the number of patients achieving a > 50% decrease in PSA levels (P = 0.007). However, as with the previous study, there was no significant difference in overall survival.

**Docetaxel**

Docetaxel (Taxetere) is a semi-synthetic analogue of taxol (Paclitaxel) which is derived from the bark of the Pacific yew tree. Docetaxel is used for the treatment of certain forms of breast cancer, lung cancer and prostate cancer. It kills tumour cells by disrupting the function of cellular microtubules, which are essential structures for cell morphology and division and, therefore, survival. Four randomised studies of docetaxel for advanced prostate cancer have been included in this section with a summary of the trial data described in Table 06.

Single-agent docetaxel was compared to the combination of docetaxel plus thalidomide in a randomised phase II trial of 75 patients with androgen independent prostate cancer (Dahut 2004). Thalidomide (α-N-[p-halimido] glutamide) was initially developed as a sedative about 30 years ago but induced foetal limb malformation (dysmelia) and was withdrawn from the market. However, the rationale for investigating this agent is that prostate cancer tissue is highly vascularised compared to the adjacent benign tissue, as shown by microvessel density studies, and thalidomide has anti-angiogenic activity (reduces blood vessel formation). It has also been reported that thalidomide has activity in androgen independent prostate cancer (Figg 2001). In the present study patients received either weekly docetaxel alone or in combination with daily thalidomide. After a median follow up of 26.4 months, more patients on the combination arm had a PSA response (difference between arms of 16%) and experienced a greater delay in progression-free interval (difference between medians 2.2 months) and had an improved overall survival (median difference 25.3 months). Although these results are encouraging there was no statistical significance observed. Grade 3 haematological toxicity was seen in less than 4% of patients in each arm. Other side effects were common (20% to 80%) and included grade 1-2 gastrointestinal toxicity, fatigue, oedema, sensory disturbances, pleural effusion and depressed consciousness. Thromboembolic events with thalidomide were of concern and anti-coagulant therapy (heparin) was given prophylactically after 12 of 43 patients in the combined group developed either vein thrombosis (n = 9) or transient ischaemic attack or shock (n = 9). Thalidomide did not alter the pharmacokinetics of docetaxel with the respective area under the curve. The plasma clearance for the single agent was 1062 ng/h/mL and 34.8 L/h/m², and 1168 ng.h/mL and 29.3 L/h/m² for the combination arm.

A three-arm, prospective, phase II, randomised study was designed to evaluate 2 schedules of docetaxel (70 mg/m² and 35 mg/m²) plus estramustine and prednisone versus mitoxantrone plus prednisone in hormone refractory prostate cancer patients (Oudard 2005). The respective proportion of patients with a PSA decline of > 50% and the time to disease progression were significantly greater and significantly longer for patients receiving docetaxel (P < 0.00001 in both cases). Although the median overall survival was greater for the docetaxel arms, it was not significantly different between regimens. Multivariate analysis of prognostic variables suggested a significant association between survival and ECOG performance status (P = 0.0001) and baseline haemoglobin (P = 0.006). The pain index, as assessed by the McGill questionnaire, was not significantly different between the three arms, although there was an improvement in the 70mg/m² and 35 mg/m² docetaxel arms compared to the mitoxantrone arm (40% and 29% versus 17%, respectively). However, a significant improvement in ECOG performance status was seen with docetaxel (60% and 48% versus 28%, respectively). Grade 3-4 granulocytopenia was the most common toxicity in the 70mg/m² docetaxel and mitoxantrone arms (37% and 48%, respectively) although this was not observed with the lower dose of docetaxel. Gastrointestinal toxicity (grade 3-4) occurred in 0% to 7% of patients and was not clinically significant. Thrombosis caused by estramustine, was seen in 7% in both the docetaxel arms despite anti-coagulant therapy. The authors suggest that further studies on the combination of docetaxel are warranted.

Overall survival was the primary endpoint in a randomised trial comparing mitoxantrone plus prednisone (considered to be the standard palliative therapy) with 2 schedules of docetaxel plus prednisone in 1006 men with HRPC (Tannock 2004). Docetaxel was administered using a weekly or a three-weekly schedule. When compared to the mitoxantrone arm, the hazard ratios for death in the three weekly docetaxel arm was 0.76 (95% CI 0.62 to 0.94, P = 0.009) and that for the weekly schedule was 0.91 (95% CI 0.75 to 1.11, P = 0.36). This indicates a statistically significant improvement in overall survival with the three-weekly docetaxel regime with a 24% reduction in the risk of death. In addition, a significant reduction in pain was observed in patients receiving the three weekly docetaxel regimen compared to the mitoxantrone arm (35% versus 22%, P = 0.01) but not with the weekly schedule (31%), although the median duration of pain response (3.5 to 5.6...
months) was not significantly different between groups. Also the quality of life assessment showed a significant improvement with the three weekly schedule of docetaxel than among those treated with mitoxantrone (22% versus 13%, P = 0.009). Grade 3/4 neutropenia was significantly more common with the three weekly docetaxel (32%) than for those patients receiving weekly docetaxel or mitoxantrone (2% and 22%), although the frequency of febrile neutropenia was less than 4% in all arms. Nausea and vomiting were common with all regimens (38% to 42%) and diarrhoea was significantly more frequent with both docetaxel schedules. Discontinuation of treatment with docetaxel was due to fatigue, musculoskeletal events, nail changes, sensory neuropathy, and infection whereas for mitoxantrone cardiac dysfunction was the major reason.

In a fourth randomised trial compared mitoxantrone plus prednisone with docetaxel plus estramustine in patients with HRPC with overall survival as the primary endpoint (Petrylak 2004). The results indicated a significant improvement in overall survival, median time to disease progression, and the percentage of patients achieving a PSA response for the docetaxel - estramustine arm. However, this regime was significantly more toxic in terms of gastrointestinal side effects (P = 0.001), nausea and vomiting (P = 0.001), infection (P = 0.004), metabolic toxicity (P < 0.001) and neurological dysfunction (P = 0.001). It should also be noted that there was no significant difference in pain relief between the two groups as assessed by the patients.

**Vinorelbine**

Vinorelbine is a cytotoxic anti-cancer agent classified as a vinca alkaloid, which are derived from the Jamaican Periwinkle. This compound is a semi-synthetic vinca alkaloid and inhibits tumour cell growth by disrupting the function of microtubules, but by a different mechanism from that of docetaxel. One randomised phase III trial has investigated the efficacy of vinorelbine in patients with HRPC, in which vinorelbine was combined with hydrocortisone and compared to hydrocortisone plus placebo (Abratt 2004). The primary end point of this study was progression-free survival (PFS) and was reported to be significantly in favour of the vinorelbine arm (P = 0.007). The median PFS was 3.7 months (95% CI 2.8 to 4.3) for vinorelbine and 2.8 months (95% CI 2.2 to 3.5) for the placebo group with respective PFS rates at 6 months of 33.2% and 22.8%. At a median follow up of 24 months, the overall survival was virtually the same for both groups; the survival curves were superimposable (median 14.7 months, vinorelbine versus 15.2 months for placebo). This is despite significantly better PSA responses with vinorelbine (30.1% versus 19.2%, P = 0.01). The mean score for quality of life, including a global score of quality, a functional scale and a symptom scale, showed no significant changes between the two treatment arms. Grade 3-4 neutropenia was seen in 26% of patients receiving vinorelbine compared to 0% for placebo. Anaemia, thrombocytopenia, infection, vomiting, fatigue, alopecia and neurotoxicity were all more frequently experienced in patients randomised to vinorelbine. It was suggested that vinorelbine has a role in treating HRPC patients who have failed taxane therapy, but the poor overall survival data suggest a minimum clinical advantage for these elderly men.

**DISCUSSION**

In Europe, the estimated number of deaths from metastatic prostate cancer for the year 1998 was 56,035 (WHO 2004), whilst the calculated figure for the United States of America was 37,000 (Landis 1998). During the latter stages of this disease, greater than 80% of patients experience progressive pain associated with bone metastases, and which can impact considerably on the patients’ quality of life. These tragic statistics have motivated extensive clinical research into this condition, in particular, the palliative use of systemic chemotherapy. The present review identified over 100 randomised trials of chemotherapy in advanced prostate cancer, 47 of which were eligible for inclusion. It is surprising, that even with this large number of trials, few compared the same chemotherapeutic regimes and, therefore, the conclusions drawn from the trial data are based on quantitative description rather than from more robust meta-analytical summaries.

Not all trials reported the primary review outcome of overall survival, because either the trials were designed as a phase II study, where safety and response were the main objectives (Galsky 2005), or where the follow-up times were insufficient (Kasimis 1985) . In other trials overall survival data were poorly reported (De Kernion 1988; Murphy 1977; Scott 1976). For those trials where data were available and categorised under estramustine (Table 01), the median overall survival averaged 11.9 months (range 5.0 to 23.5) and was not significantly different from the respective comparative arms (5.0 to 18 months), although the addition of estramustine to paclitaxel improved overall survival with marginal significance (Berry 2004). For the other drug categories of cyclophosphamide, 5-fluorouracil, doxorubicin and mitoxantrone, the average median overall survival times (months) were, respectively, 8.3, 8.3, 10.1, and 15.8, and were not significantly different from the comparative treatment group in any trial. A noticeable observation from the data was the median overall survival times reported for trials evaluating docetaxel in HRPC patients (Table 06). When used as a single agent, the median survival time was reported as 14.7 months (Dahut 2004; Table 06), and 28.9 months with the addition of thalidomide. This is considerably longer than for all the previously described drugs. In the three other randomised studies in the docetaxel group, the median overall survival for treatment arms receiving docetaxel averaged 18.2 months and was significantly longer than the combination of prednisone plus mitoxantrone, in two trials (Petrylak 2004; Tannock 2004); the latter combination was regarded until recently as the standard therapy for HRPC in the USA. In the study reported by Tannock et al (Tannock 2004), only the three weekly docetaxel regime, and not
the weekly regime, significantly improved survival. Based on the survival data from the randomised studies in this review, treatment regimes containing docetaxel appear to provide a significant survival advantage compared to other chemotherapeutic regimes. However, the absolute differences in median survival times were relatively small (< 2.5 months), which from a patient’s point of view, may be considered of marginal benefit.

The quality of the included studies varied considerably, with some studies having poor standards of reporting. Although all the early studies were randomised, the assessment of chemotherapy for metastatic prostate cancer was hampered by the use of poor response criteria. In the 1970s the National Prostate Cancer Project (NPCP) pioneered the development of objective response criteria based, in part on measurable lesions and included complete response, partial response, objectively stable and objective progression (Scott 1975a; Scott 1976). A number of the older randomised trials used the NPCP criteria and accordingly no patient had a complete response to any chemotherapeutic regime tested, and between 2% to 7% had partial regressions. The mean response for stable disease with trials evaluating estramustine was 27% (De Kernion 1988; Eloam 1991; Loening 1983; Murphy 1977; Murphy 1979; Soloway 1981; Soloway 1983); for cyclophosphamide it was 41% (Chlebowski 1978; Herr 1982; Kasimis 1985; Loening 1981; Murphy 1988; Muss 1981; Scott 1976), and for a 5-fluorouracil it was 48%. The majority of patients had objective progression with respective mean values of 68%, 52% and 52%. These data suggest that early chemotherapy regimes for patients with HRPC were ineffective in terms of tumour response. However, the assessment of objective response in advanced prostate cancer is a major subject for debate, and the early studies have been criticised for a number of reasons. Osteoblastic lesions are often the only manifestation of disseminated disease and accurately assessing response to chemotherapy using these lesions is difficult. In many of the studies, a significant proportion of patients had measurable disease for purposes of assessment, which suggests that they had very advanced or atypical disease and were, therefore, unlikely to experience a significant response to chemotherapy. In addition, the inclusion of stable disease as a category of response is controversial, as it could be a phase in the natural history of the disease itself, rather than the effect of chemotherapy (Beedassy 1999). Furthermore, tumour markers, such alkaline phosphatase, and acid phosphatase were included in assessment criteria (De Kernion 1988; Eloam 1991; Loening 1981; Murphy 1977; Murphy 1988; Saxman 1992; Scott 1976; Smalley 1981; Soloway 1981; Soloway 1983), which are, by contemporary standards, considered unreliable.

Most of the more recent studies included PSA in the assessment of response to chemotherapy (see Tables 1 to 6), and, although some agents such as suramin and retinoic acid may directly modulate expression of PSA (Petrylak 1999), it is considered to be the most reliable marker available for prostate cancer. Although the exact magnitude of the PSA decline that constitutes a clinical benefit is controversial, a commonly expressed variable of response is the proportion of patients achieving a > 50% reduction in PSA from baseline for at least two consecutive measurements over a 4-week period. For the randomised trials that reported the percentage of patients with a > 50% decline in PSA, the mean values for regimes containing estramustine, 5-fluorouracil, doxorubicin, mitoxantrone, and docetaxel were, respectively, 48%, 20%, 50% (one study only), 33% and 52%. Estramustine, mitoxantrone and docetaxel all appear to give similarly high PSA responses; however, the comparisons are not definitive as a variable number of other agents were combined with each drug. The clinical value of PSA as a surrogate marker for all outcomes is not clear. In one trial, a decrease in PSA one month after chemotherapy with estramustine correlated significantly with cancer-specific survival (Iversen 1997), whereas one study reported that PSA correlated poorly with clinical response, with some patients exhibiting a rise in PSA and a good response whilst others had a falling PSA but a worsening of pain and performance status (Breul 1997). However, in overall terms, the percentage of patients with a > 50% fall in PSA for all the trials combined and all interventions, correlated significantly with the corresponding median overall survival data (Spearman’s rank correlation 0.735, P = 0.01), suggesting that the greater the proportion of patients with a PSA response the longer the median overall survival.

Over 80% of the patients included in this review presented with osseous metastases. The most distressing complication associated with bone involvement is pain, which may manifest as tonic background pain which is a deep non-specific ache increasing in intensity as the disease progresses, incident pain on movement (alloodynia) which renders the patients virtually immobile, and spontaneous pain which may be severe (Urch 2004). Thirteen of the included trials reported that 25% to 100% of patients had bone pain on study entry (mean 81% ± 21%), whereas one trial recruited asymptomatic men (Betty 2002). The effectiveness of chemotherapy on pain relief was poorly reported, with 17 studies not assessing pain response, and in 15 studies, pain relief was incorporated into the response definition and was not discernible as a distinct parameter. A number of drugs, either as single agents or in combination, were shown to be effective in reducing pain, with 5-fluorouracil (Breul 1997), estramustine plus etoposide (Dimopoulos 2004), estramustine and epirubicin as single agents (Eloma 1991) inducing pain relief in 62% to 76% of patients. Other regimes, such as single agents hydroxyurea, methly-CCNU, and cyclophosphamide (Loening 1981), methotrexate and cisplatin (Loening 1983), estramustine plus prednisone (Murphy 1988), prednisone alone (Murphy 1988), the combination of docetaxel plus estramustine plus prednisone (Oudard 2005), and estramustine alone (Soloway 1981), induced pain relief in 22% to 40% of patients. However, it is difficult to make comparisons between agents, because of the variation in pain definitions, type of patients recruited, time of assessment, and study designs. In one study, where pain assessment was the primary outcome of interest, mitoxantrone plus...
prednisone was significantly better than prednisone alone (Tannock 1996). Furthermore, in a subsequent study, docetaxel plus prednisone (three weekly) was found to induce significantly more pain relief than mitoxantrone plus prednisone (Tannock 2004).

Myelosuppression was a major toxicity induced by most of the chemotherapeutic agents assessed in this review. Grade 3 or 4 myelosuppression was reported in 8% to 35% of patients receiving estramustine (Smalley 1981; Dimopoulos 2004; Hudes 1999; Millikan 2003; Galsky 2005), 8% to 20% for cyclophosphamide (Chlebowski 1978; Saxman 1992; 0% to 32% for 5-fluorouracil (Breul 1997; Droz 2003), 6% to 57% for doxorubicin (Francini 1993; Torti 1985), 6% to 70% for mitoxantrone (Kantoff 1999; Berry 2002), and 2% to 32% for docetaxel (Petrylak 2004; Tannock 2004). Significant gastrointestinal toxicity was also reported in the majority of trials with nausea and vomiting experienced by 8% to 75% of patients receiving estramustine, 46% to 75% with cyclophosphamide, 2% to 9% with doxorubicin, and 0% to 60% for docetaxel. For mitoxantrone, nausea and vomiting were seen in 5% to 38% of patients (Tannock 2004; Berry 2002), and was reported to be tolerable in one study (Kantoff 1999), and severe after 5 cycles in another (Tannock 1996). There were no data extractable from trials containing 5-fluorouracil regimes; although Smalley et al (Smalley 1981) reported that vomiting occurred for several hours after each dose. Mucositis was particularly noticeable with 5-fluorouracil and doxorubicin containing regimes (Daliani 1995; Droz 2003; Rangel 1992; Millikan 2001). Cardiotoxicity was reported for all agents in 10% to 14% of patients, except for 5-fluorouracil whereas neutrotoxicity was only observed with estramustine (10% to 73%), 5-fluorouracil (11% to 80%) and docetaxel (24% to 48%). Alopecia was also extensively seen, with up to 100% of patients developing this toxicity with cyclophosphamide (Chlebowski 1978) and 5-fluorouracil (Smalley 1981). Treatment was stopped due to unacceptable toxicity in 10% to 40% receiving estramustine (Newling 1993; Johansson 1991; Akaza 1988), 17% for doxorubicin (Francini 1993), 3% for mitoxantrone (Tannock 2004) and 4% to 11% for docetaxel (Oudard 2005; Petrylak 2004; Tannock 2004). In addition, the number of treatment related deaths for each agent group were 4% to 7% for estramustine (Albrecht 2004; Akaza 1988), 3% for cyclophosphamide (Kasimis 1985; Saxman 1992), 1% to 8% for 5-fluorouracil (Breul 1997; Daliani 1995), 0.7% to 1% for doxorubicin (Leaf 2003; Millikan 2001), and 0.3% for docetaxel (Tannock 2004). The evidence from these trials indicates that chemotherapy is associated with substantial toxicity and that it places great demand on men with HRPC, who are often elderly. It is, therefore, essential that patients make a well-informed decision to undergo chemotherapy, making a balanced judgement on the risks and benefits of this treatment.

HRPC patients are generally elderly men with co-morbid conditions and many will have received several previous stressful clinical procedures and treatments. Chemotherapy, as an additional avenue of therapy, with its accompanying side effects, may be a daunting prospect for these men. Quality of life assessment is, therefore, of great importance when chemotherapy is to be considered for this population. It is surprising that only four randomised trials, out of the 47 included in this review, were designed to assess quality of life during chemotherapy (Berry 2004; Ablit 2004; Tannock 1996; Tannock 2004). Tannock and colleagues (Tannock 1996) used the Prostate Cancer Specific Quality of Life Instrument and two EORTC assessment protocols and reported an improvement with mitoxantrone/prednisone compared to prednisone alone. This was significant for overall well being. In a separate study, the same author (Tannock 2004) reported a significant improvement in quality of life (FACT-P questionnaire) with docetaxel plus prednisone compared to mitoxantrone plus prednisone, despite the increased toxicity of the docetaxel regime.

Finally, this review concentrated on assessing the effectiveness of systemic chemotheraphy for HRPC patients rather than hormone naive patients or those with hormone sensitive disease. It is, therefore, important that the included studies clearly defined the patient populations recruited for chemotherapy. There is no universally accepted definition of HRPC, but the general description of progressive disease despite hormonal therapy, was widely adopted. Another important consideration is that chemotherapy should not be initiated too soon following hormone therapy, because a clinical response due to anti-androgen withdrawal would confound the evaluation of chemotherapy (Small 1997). Thirty percent of studies stated that chemotherapy was started between 4 to 6 weeks following discontinuation of hormone therapy. Better reporting of patient characteristics and trial design would improve trial quality, and aid comparisons between studies.

**AUTHORS’ CONCLUSIONS**

**Implications for practice**

Ideally a chemotherapeutic regime for patients with HRPC should be efficacious, improve survival, palliate symptoms, be non-toxic and improve quality of life compared to best standard of care. None of the regimes described in this review fulfilled all these criteria. However, the study by Tannock et al (Tannock 2004) using a three weekly regime of docetaxel plus continuous prednisone provides encouraging results compared to mitoxantrone plus prednisone (FDA approved as the palliative treatment of choice for HRPC). It was a very large, randomised study and the three weekly docetaxel regime significantly improved survival, pain relief and quality of life. At the present time this probably represents the best chemotherapeutic regime available for men with HRPC. The increase in survival with this regime is important because it confirms that HRPC is chemosensitive and that this regime may induce a change in the natural history of this disease. These data will motivate further studies to develop improved chemotherapeutic regimes for men with HRPC.
Implications for research

Men with symptomatic HRPC are a difficult group of patients for the clinician to treat and are not always candidates for chemotherapy. However, the improvement in chemotherapy over the last decade should continue to provide a viable option for the management of this disease. However, the clinical benefits of chemotherapy can only be tested against patients without such treatment in a randomised trial, and should be further evaluated against best standards of palliative care, involving radiotherapy, bisphosphonates and radioisotopes. Better reporting of trial data should be emphasised in new studies, such as more precise patient characteristics, including the type of pain experienced. Quality of life assessment should be an essential component in any studies of chemotherapy in HRPC. In addition more studies in less advanced prostate cancer, either as first line for newly diagnosed disease, or concurrent with hormone therapy, should be encouraged.

It is unclear how long chemotherapy, if initiated, should continue, and additional studies should be designed to address this issue. In the absence of any definitive data, it seems reasonable to continue until disease progression occurs or side effects determine treatment cessation. In addition, new studies should determine if second-line chemotherapy with perhaps estramustine plus docetaxel, has any benefit in patients relapsing from docetaxel plus prednisone.

Active research should continue to evaluate new agents in men with HRPC. In the present review, thalidomide although problematic with thromboembolic events, produced impressive synergistic activity with docetaxel and should be explored in phase III studies (Vordos 2004). The epothilones, which are a new class of microtubule inhibitors, warrant clinical evaluation in randomised trials, following a study demonstrating a significant PSA response in up to 92% of patients with HRPC. In addition, chemotherapy in combination with other active biological agents such as suramin, cell-cycle inhibitors and immune therapy may lead to encouraging approaches. It is also important to continue basic research to unravel the molecular and genetic complexities of HRPC to direct future targeted chemotherapy.

Potential conflict of interest

None

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None

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- National Collaborating Centre for Cancer, Cardiff UK
- Velindre NHS Trust, Cardiff UK
- Minneapolis VA Centre for Chronic Disease Outcomes Research USA

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References to studies included in this review

Abratt 2004 (published data only)

Akaza 1988

Albrecht 2004 (published data only)

Anderstrom 1995 (published data only)

Berry 2002 (published data only)

Berry 2004 (published data only)
Chemotherapy for hormone-refractory prostate cancer (Review)

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Breul 1997  {[published data only]}

Chlebowski 1988  {[published data only]}

Dahut 2004  {[published data only]}

Daliani 1995  {[published data only]}

De Kernion 1988  {[published data only]}

Dimopoulos 2004  {[published data only]}

Droz 2003  {[published data only]}

Elomaa 1991  {[published data only]}

Francini 1993  {[published data only]}

Galsky 2005  {[published data only]}

Graham 1986  {[published data only]}

Herr 1982  {[published data only]}

Hudes 1999  {[published data only]}

Iversen 1997  {[published data only]}

Johansson 1991  {[published data only]}

Kantoff 1999  {[published data only]}

Kasimis 1985  {[published data only]}

Laurie 1992  {[published data only]}

Leaf 2003  {[published data only]}

Loening 1981  {[published data only]}
Chemotherapy for hormone-refractory prostate cancer (Review)

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Loening 1983 [published data only]

Millikan 2001 [published data only]

Millikan 2003 [published data only]

Murphy 1977 [published data only]

Murphy 1979 [published data only]

Murphy 1988 [published data only]

Muss 1981 [published data only]

Newling 1993 [published data only]

Oudard 2005 [published data only]

Page 1985 [published data only]

Petrylak 2004 [published data only]

Rangel 1992 [published data only]

Saxman 1992 [published data only]

Scott 1976 [published data only]

Smalley 1981 [published data only]

Soloway 1981 [published data only]

Soloway 1983 [published data only]

Tannock 1996 [published data only]
Tannock IF, Osoba D, Stockler MR, Ernst DS, Neville AJ, Moore MJ, Armitage GR, Wilson JF, Venner PM, Coppin CM, Murphy KC. Chemotherapy with mitoxantrone plus prednisone or prednisone

**Tannock 2004 [published data only]**

**Torti 1985 [published data only]**

**Tveter 1990 [published data only]**

**References to studies excluded from this review**

**Ahles 2004**

**Akaza 1993**

**Alfthan 1983**

**Andersson 1980**

**Benson 1983**

**Boel 1999**

**Burns-Cox 2002**

**Datta 1997**

**Dawson 2000**

**De Reijke 1999**

**DeWys 1983**

**Edsmyr 1978**

**Ernst 2003**

**Falsaperla 2005**

**Figg 2001**

**Fontana 1998**

Chemotherapy for hormone-refractory prostate cancer (Review)

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Fossa 2000

Fossa 2001

Gibbons 1976

Gibbons 1983

Hedlund 1996

Heidenreich 2004

Hervonen 2002

Huben 1988

Janknegt 1997


Johansson 1987

Johansson 1988

Nakamura 1997

Kuriyama 2001

Kurimoto 1999

Kuriyama 2001

Kylmala 1997

Lundgren 1995
Manni 1986a

Manni 1986b

Matsuda 1995

Miyake 1996

Murphy 1986

Newling 1990

Noguchi 2004

Osborne 1990

Patel 1990

Pienta 2003

Pummer 1991

Ruff 1989

Sakai 1999

Schmidt 1976

Schmidt 1979

Scott 1975a

Scott 1975b

Small 2000

Small 2002

Smith 1986

Stephens 1984

Sumiyoshi 1999

Takenaka 2001

Vahlensieck 1985

Van Poppel 2003

Walczak 2003

Wang 2000

Additional references
Beedassy 1999

Bubley 1999

Catalona 1999

Goktas 1999

Hudes 1992

Hudes 1995

Landis 1998

Petrylak 1999

Pienta 1994

Small 1997

Smith 1999

Urch 2004

Vordos 2004

WHO 2004

Woolam 2000
Yagoda 1993

Zelefsky 2003

*Indicates the major publication for the study

T A B L E S

Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Abratt 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>To determine if intravenous vinorelbine (VLB) in combination with hydrocortisone increases progression free survival compared to hydrocortisone alone in HRPC patients. Randomised phase III trial. Method not stated. ITT analysis. Quality score: 1/1/1</td>
</tr>
<tr>
<td>Participants</td>
<td>451 patients with metastatic prostate cancer, progressive after primary hormone therapy. All had failed prior androgen deprivation with castrate levels of testosterone. (progressive disease = either objective evidence of disease progression (new lesions) or symptomatic (decreased performance status, weight loss) with increased PSA.</td>
</tr>
<tr>
<td>Interventions</td>
<td>VLB i.v.30 mg/sqm on days 1 &amp; 8, 3 week cycle, plus hydrocortisone 40mg/day, n = 206, versus hydrocortisone 40mg/day, n = 208.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Progression free survival = time from randomisation to progression or death. PSA response: Complete = normalisation ≤0.2 ng/ml for 6 weeks. Partial = ≥50% decrease in PSA for 6 weeks. Clinical response rates = positive response in pain, analgesic consumption or performance status for ≥ 9 weeks. Overall survival. Quality of life - EORTC QLQ C30 questionnaire.</td>
</tr>
</tbody>
</table>

Notes
Allocation concealment B – Unclear

Study Akaza 1988

Methods
To investigate the efficacy of estramustine in combination chemotherapy in a) HRPC patients and b) previously untreated stage C or D prostate cancer patients. Prospective randomised trial - method sealed envelope and telephone. No concealment. Quality score: 2/0/1

Participants
44 patients enrolled, 26 evaluable. 2 groups: untreated prostate cancer (106) and HRPC patients (44). Only latter group considered. HRPC = stage C or D prostate cancer patients resistant to anti-androgen therapy.
Interventions | Estramustine 4 capsules/day (dose not given) plus peplomycin i.m. 5mg twice weekly to 80mg, plus doxorubicin 30-50mg 3-4 times per 3-weeks (i.v.)
| n = 22
| versus
| 5-Fluorouracil orally 300-400mg three times per day, plus peplomycin plus doxorubicin n = 14.

Outcomes | Tumour response:
| a. primary lesion
| b. bone lesion
| 2. prostatic acid phosphatase.
| response
| 3. overall evaluation.
| 4. overall survival.

Notes
Allocation concealment A – Adequate

---

**Study** | **Albrecht 2004**
---|---
Methods | To determine PSA response rate and toxicity of estramustine alone or combined with vinblastine in HRPC patients. Randomised phase II trial - continuing to a phase III if toxicity acceptable). Central registration randomisation and data collection. Quality score: 2/0/1
Participants | 92 patients recruited, 90 evaluable. Patients had metastatic prostate cancer with progressive disease despite sustained previous hormone therapy.
Interventions | Estramustine phosphate orally 10mg/kg/day continuous n= 45.
| versus
| estramustine plus vinblastine iv 4mg/sqm weekly for 6 weeks then every 8 weeks n=45
Outcomes | Overall response rate (PSA):
| Complete - PSA normal (<4ng/ml).
| partial - PSA decreased by 50%.
| Progression- 50% increase in PSA from nadir.
| Stable - no response or progression.
| Overall - best response at 8 weeks.
Notes
Allocation concealment A – Adequate

---

**Study** | **Anderstrom 1995**
---|---
Methods | To compare the time to progression in HRPC patients receiving either estramustine or medroxyprogesterone acetate (MPA) plus epirubicin. A prospective randomised trial. Method not stated. Quality score: 1/0/1
Participants | 149 HRPC patients recruited, 145 evaluable. All had disease progression following orchidectomy or estrogen.
Interventions | Estramustine 12mg/kg/day orally (n=72).
| versus
| MPA 500mg twice daily orally and continuous plus epirubicin i.v. 20mg/sqm/m/week to a total of 100mg/sqm (n= 73)
Outcomes | Tumour progression - defined as: 25% or more increase in measurable lesion volume, obvious cancer related decrease in performance status, significant increase in existing lesions or new ones on bone scan.
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Berry 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>To compare time to treatment failure with mitoxantrone plus prednisone against prednisone alone in asymptomatic men with HRPC. A multicentre phase III, open label, randomised trial. No cross over. No method stated. Quality score: 1/0/1</td>
</tr>
<tr>
<td>Participants</td>
<td>119 men with asymptomatic HRPC. Eligibility included at least 4 weeks since androgen ablation therapy, systemic corticosteroids, radiotherapy or surgery.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Mitoxantrone 12mg/sqm iv every 3 weeks x6 cycles plus prednisone 4 mg twice daily, n = 56 versus prednisone as above, n = 63.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Time to treatment failure - disease progression, time to toxicity or death, time to initiation of alternative therapy. PSA: response = 50% reduction in PSA. Objective response. Time to progression (progression defined as increase in PSA (x2 or more), 25% increase in number of bone lesions on scan, or 25% increase in size of soft tissue lesions). Survival</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Study</th>
<th>Berry 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>To determine the response rates and safety of paclitaxel with and without estramustine. Open label phase II randomised trial. ITT analysis. Method not stated. Quality score: 1/0/1</td>
</tr>
<tr>
<td>Participants</td>
<td>166 patients with metastatic hormone refractory prostate cancer. All had progressive disease defined as a &gt; 25% increase in measurable lesions or a &gt; 25% increase in new bone lesions, or a doubling of PSA plus additional evidence of bone metastases. At least 4 weeks elapsed from anti-androgen therapy</td>
</tr>
<tr>
<td>Interventions</td>
<td>28 day cycles of paclitaxel 100mg/sqm i.v. on days 2, 9 &amp; 16, plus estramustine 280mg orally x3 per day, days 1 to 3, 8 to 10, 15, and 17, n= 79. versus paclitaxel 100mg/sqm days 1, 8, 15 and 17, n = 84</td>
</tr>
<tr>
<td>Outcomes</td>
<td>PSA response (objective = &gt;50% decrease for 4 weeks, with stable disease or improved performance status). Performance status. Survival - calculated from first day of treatment to death. Toxicity - NCI common toxicity criteria 2.0. Response: NPCP criteria. Disease progression.</td>
</tr>
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<tr>
<th>Study</th>
<th>Breul 1997</th>
</tr>
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<tbody>
<tr>
<td>Methods</td>
<td>To evaluate the effect of 5-Fluorouracil (5-FU) monotherapy or combined with folic acid in patients with HRPC.</td>
</tr>
</tbody>
</table>

Notes
- Allocation concealment: B – Unclear
### Characteristics of included studies (Continued)

Prospective randomised phase II study.  
Method not stated.  
Quality score:  
1/0/1

<table>
<thead>
<tr>
<th>Participants</th>
<th>50 patients with progressive prostate cancer following anti-androgen therapy. All had tumour related pain. Stratified by performance status.</th>
</tr>
</thead>
</table>
| Interventions | 5-FU 600 mg/sqm 60 min infusion, n = 25  
versus  
5-FU as above plus folinic acid 400mg/sqm 30 min infusion, n = 24.  
In both groups chemotherapy continued for 5days in a 21 day interval for 2 cycles. |
| Outcomes     | Pain - scored by intensity and frequency.  
Toxicity.  
PSA response - 50% decrease over 4 weeks.  
Time to progression (progression defined as pain exceeding initial value). |
| Notes        | Allocation concealment B – Unclear |

<table>
<thead>
<tr>
<th>Study</th>
<th>Chlebowski 1978</th>
</tr>
</thead>
</table>
| Methods      | To compare the efficacy of cyclophosphamide with the combination of cyclophosphamide, 5-fluorouracil and doxorubicin in patients with advanced adenocarcinoma of the prostate.  
Randomised, prospective trial. Randomisation by central statistical analytical centre.  
Quality score:  
1/0/1 |
| Participants | 27 men with histologically diagnosed metastatic adenocarcinoma of the prostate resistant to hormone manipulation. Expected survival of 60 days.  
No prior chemotherapy.  
Estrogen therapy stopped at least 2 weeks before study entry. |
| Interventions| Cyclophosphamide 800mg/sqm i.v. day 1 n = 15,  
versus  
cyclophosphamide 200mg/sqm orally day 3-6, every 3 weeks plus  
5-fluorouracil 500mg/sqm i.v. days 1, 8,  
plus  
Adriamycin 50mg/sqm i.v. day. n = 12, every 4 weeks |
| Outcomes     | Survival - from initiation of chemotherapy until death.  
Objective response - NPCP response criteria. |
| Notes        | Allocation concealment A – Adequate |

<table>
<thead>
<tr>
<th>Study</th>
<th>Dahut 2004</th>
</tr>
</thead>
</table>
| Methods      | To compare the efficacy of docetaxel plus thalidomide in patients with androgen independent prostate cancer.  
Open label randomised phase II trial (2:1 randomisation ratio). Method by randomised blocks - no stratification.  
Quality score:  
2/0/1 |
| Participants | 75 patients with androgen independent prostate cancer. All had elevated and rising PSA with testosterone < 50-ng/ml, and/or new bone lesions and/or enlargement of soft tissue lesions. All had metastatic disease and failed to benefit from combined androgen blockade and anti-androgen withdrawal. |
| Interventions| Docetaxel 30mg/sqm i.v. (30 min) weekly x 3, 1 week rest (i.e. 4 week cycle), n = 25, |
Characteristics of included studies (Continued)

versus
docetaxel as above plus thalidomide 200mg orally each day, n=50.
All received 8mg dexamethasone 12 and 1hour before docetaxel.

Outcomes
PSA response = decrease of 50% for 2 consecutive values 4 weeks apart.
Time to progression.
Toxicity - NCI Common Toxicity criteria (version 2).

Notes
Allocation concealment A – Adequate

Study: Daliani 1995

Methods
To evaluate the relative anti tumour activity and tolerance of 5-fluorouracil (5-FU) versus 5-fluorouracil plus alpha interferon in metastatic prostate cancer.
Prospective randomised trial. Method unclear.
Quality score: 1/0/1

Participants
51 patients with disseminated and unresectable metastatic prostate cancer. All had prior hormone therapy.
HRPC defined as - castrate testosterone levels and evidence of tumour progression (new sites or increase in size of metastases on scan, decrease in performance status, new soft tissue lesions.

Interventions
5-FU 750 mg/sqm iv continuous infusion for 5 days, week 1, 7 days later bolus given weekly for 2-5 weeks repeated every 6 weeks, n = 23,
versus
5-FU 600mg/sqm 5 day infusion week 1, then bolus weekly for 2-5 weeks, plus interferon alpha 10m/U daily x 5 in week 1, then 3 times/week for week 2, n = 28

Outcomes
Response:
Complete - disappearance of all evidence of tumour on scan, symptom-free.
Partial - 50% decrease in measurable lesions for 4 weeks.
Quality of Life - functional living index questionnaire

Notes
Allocation concealment B – Unclear

Study: De Kernion 1988

Methods
To assess and compare the efficacy of estramustine and flutamide in HRPC patients.
Randomised trial No method stated.
Quality score: 1/0/1

Participants
220 patients with disseminated hormone resistant prostate cancer. All had failed to respond to orchidectomy.

Interventions
Estramustine phosphate 600mg/sqm orally in 3 divided doses n=109
versus
flutamide 0.25g 3 times per day orally, n = 111

Outcomes
Response: NPCP criteria.
Toxicity.
Disease progression.
Survival.

Notes
Allocation concealment B – Unclear

Study: Dimopoulos 2004

Methods
To evaluate estramustine plus etoposide with a combination of lanreotide, triptorelin and dexamethasone.
### Characteristics of included studies (Continued)

Phase II randomised study (method not stated). Not ITT analysis.

**Quality score:**
1/0/1

<table>
<thead>
<tr>
<th>Participants</th>
<th>40 patients with metastatic prostate cancer that was progressing despite androgen deprivation. No prior chemotherapy.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Oral estramustine phosphate 140 mg x 3 per day plus etoposide 100mg oral for 21 days. Repeated every 28 days, n= 20. versus somatostain analog (lanreotide) 30mg im every 2 weeks plus dexamethasone 4mg tapered to 1mg plus androgen ablation with orchidectomy or an LHRH analog triptorelin 3.75 mg im monthly. n= 18</td>
</tr>
<tr>
<td>Outcomes</td>
<td>PSA response rates (decrease of 50% or greater). Time to progression: progression defined as a PSA increase of &gt;50% from nadir, or deterioration of bone metastases and measurable disease on scan or CT. Overall survival - from study entry until death. Toxicity.</td>
</tr>
<tr>
<td>Notes</td>
<td>Allocation concealment A – Adequate</td>
</tr>
</tbody>
</table>

### Study

**Droz 2003**

**Methods**
To evaluate oxaliplatin with and without 5-fluorouracil in advanced HRPC. Randomised multicentre phase II study. Method not stated.

**Quality score:**
1/0/1

**Participants**
54 patients with confirmed metastatic prostate cancer who had failed anti - androgen therapy with either orchidectomy or LHRH analogs. All had achieved castrate testosterone levels <30ng/ml.

**Interventions**
Oxaliplatin 130 mg/sqm 2 h infusion every 3 weeks, n = 26, versus oxaliplatin 130mg/sqm 2 h infusion plus 5-fluorouracil 1g/sqm/day days 1-4 every 3 weeks, n = 28

**Outcomes**
Clinical response - pain intensity and frequency, -performance status, - weight change, - PSA levels. Time to progression: from first treatment to objective evidence of tumour progression. Survival: measured from initial treatment until death. Overall best response: (WHO criteria) assessed by measurable and evaluable lesions and PSA levels (CR = PSA 4ng/ml) Toxicity - NCI criteria.

**Notes**
Allocation concealment B – Unclear

### Study

**Elomaa 1991**

**Methods**
To compare the effects and toxicity of estramustine and low-dose epirubicin in patients with HRPC. Prospective randomised trial. No method given.

**Quality score:**
1/0/0.

**Participants**
41 patients with hormone refractory metastatic prostate cancer. All had relapsed after hormone therapy. Mean age 70 (58-93) estramustine, 66 (48-81) epirubicin.

**Interventions**
Estramustine 280 mg twice daily (n=20)
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Oncis 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>To test whether a weekly schedule of epirubicin could reduce toxicity compared to doxorubicin in patients with HRPC. Randomised trial (ratio 2:1). No method stated. Quality score: 1/0/1</td>
</tr>
<tr>
<td>Participants</td>
<td>72 patients with advanced prostatic adenocarcinoma who had relapsed after hormone therapy. All had bone metastases.</td>
</tr>
<tr>
<td>Interventions</td>
<td>epirubicin 30mg/sqm iv weekly, n= 48, versus doxorubicin 25 mg/sqm iv weekly, n= 24. Both schedules continued until disease progression or major side-effects.</td>
</tr>
<tr>
<td>Notes</td>
<td>Allocation concealment B – Unclear</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Galsky 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>To evaluate the anti-tumour activity and safety of ixabepilone with and without estramustine. Multi-institutional phase II randomised trial. Method of randomisation - permuted block, allocation via clinical trials office. Quality score: 2/0/1</td>
</tr>
<tr>
<td>Participants</td>
<td>92 chemotherapy naive patients with proven adenocarcinoma of the prostate. All had progressive disease despite castration (&lt; 50ng/ml). &gt; 66% had more than 3 hormone manipulations.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Estramustine phosphate 280mg/sqm orally x 3/day for 5 days plus ixabepilone 35 mg/sqm 3 hr iv infusion day 2. n= 45 versus ixabepilone 35mg/sqm every 3 weeks n = 47. Pre-medication with ranitidine. Treatment continued until progression.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Proportion of patients achieving PSA response (50% decrease). Progression - defined as a. 3 consecutive rises in PSA b. new lesions on bone scan. c. new or progression on measurable disease on CT or MRI scans.</td>
</tr>
<tr>
<td>Notes</td>
<td>Allocation concealment A – Adequate</td>
</tr>
</tbody>
</table>

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Chemotherapy for hormone-refractory prostate cancer (Review)

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### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Graham 1986</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To investigate the relative efficacy of cyclophosphamide and melphalan containing combination in hormonally unresponsive prostatic carcinoma. Randomised trial weighted A:B, 1:2. Quality score: 1/0/1</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>66 patients with stage D2 prostatic cancer. All had hormonally unresponsive disease. 58 evaluable. Initial weekly then monthly followup.</td>
</tr>
</tbody>
</table>
| **Interventions** | Group A: n = 39  
Prednisone 40mg/day x 7 - taper to 10mg/day orally, plus  
methotrexate 10 mg twice daily orally, plus  
vincristine 1mg for 4 weeks every 4th month, plus  
melphalan 2mg orally.  
versus  
Group B: n=19  
methotrexate as above, plus 5-fluorouracil 400 mg/sqm , plus prednisone 40mg orally tapered to 10mg. |
| **Outcomes** | Response:  
Objective - 10% decrease in alk. phos. or 10% increase in weight.  
Stable - significant and sustained trend towards normalisation.  
Survival.  
Toxicity. |
| **Notes**     | Allocation concealment B – Unclear |

<table>
<thead>
<tr>
<th>Study</th>
<th>Herr 1982</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To study the effect of cyclophosphamide plus methotrexate plus 5-fluorouracil combination compared to single agent chloroethly - cyclohexane- nitrosourea CCNU. Prospective randomised trial with cross over at disease progression. Allocation method not stated. Quality score: 1/0/1</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>40 patients with metastatic prostatic carcinoma. All had progressive disease after failing hormone therapy (progression = deterioration in weight, symptoms (bone pain), and performance status, new lesions or &gt; 25% increase of measurable lesions. All patients evaluable and a minimum follow up of 2 yrs or until death.</td>
</tr>
</tbody>
</table>
| **Interventions** | Cyclophosphamide 75 mg/sqm orally days 1 & 14, plus  
methotrexate 45 mg/sqm days 1 & 8, plus  
5-fluorouracil 500mg/sqm days 1 & 8 - each repeated 3 weekly, n= 20,  
versus  
CCNU 130 mg/sqm orally every 6 weeks n = 20. |
| **Outcomes** | Response defined by NPCP criteria.  
- Objective  
- Stable  
- Subjective  
Duration of response. |
| **Notes**     | Allocation concealment B – Unclear |
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
</table>
| **Hudes 1999**   | To compare estramustine plus vinblastine with vinblastine alone in patients with HRPC.  
                   | Randomised trial. Treatment was assigned by stratified permuted block and central randomisation through Hoosier Oncology Group office. ITT analysis used.  
                   | Quality score: 2/0/1                                                         | Estramustine 600mg/sqm orally days 1-42 every 8 weeks, plus vinblastine 4mg/sqm i.v. bolus weekly for 6 weeks then 2 weeks off, n = 100  
                   | versus vinblastine as above n = 101                                         | Overall survival.  
                   | Toxicity (NCI criteria)                                                      | Disease progression - progressive disease = increase in size of palpable or radiographic tumour, increasing PSA or a combination of both with or without worsening symptoms.  
                   | Notes                                                                       | Notes                                                                                                                                |
| **Iversen 1997** | To investigate the potential benefits of adding estramustine to standard palliative therapy.  
                   | Randomised double-blind, placebo controlled, parallel group, multicentre trial.  
                   | Randomisation by local block method.  
                   | Quality score: 2/2/1                                                         | Estramustine phosphate (500mg/day) plus standard Palliative therapy (n = 61)  
                   | versus placebo (matched capsules) plus standard palliative therapy (n = 68)  
                   | Time to subjective progression.  
                   | Disease progression defined as: increased score (based on performance status, pain, analgesic use, glucocorticoids and radiotherapy).  
                   | Toxicity.  
                   | Objective response.  
                   | Subjective response.  
                   | Overall survival.  
                   | Cancer specific survival.                                                     | Notes                                                                                                                                |
| **Johansson 1991** | To compare the safety, palliation and survival of estramustine with medroxyprogesterone acetate in patients with HRPC.  
                   | Quality score:                                                              | Notes                                                                                                                                | Allocation concealment A – Adequate                                       |
Characteristics of included studies (Continued)

1/0/1. Randomised trial - method not stated. Cross over design on disease progression.

<table>
<thead>
<tr>
<th>Participants</th>
<th>105 patients recruited, 102 eligible. All had progressive metastatic prostate cancer following orchidectomy, oestrogens or flutamide. Skeletal metastases were most common (50/51 Estra, 49/51 MPA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interventions</td>
<td>Estramustine 280mg orally twice daily (n = 51) versus MPA 1000mg i.m. daily for 15 days then weekly (n = 51)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Disease progression = volume increase of 25% for measurable tumour, or increase in extent of existing bone lesions on scans, or new lesions, or worsened performance status. Progression-free survival = time until progression or death.</td>
</tr>
<tr>
<td>Notes</td>
<td>Allocation concealment B – Unclear</td>
</tr>
</tbody>
</table>

**Study**  
**Kantoff 1999**

**Methods**  
To demonstrate a survival advantage of mitoxantrone plus hydrocortisone compared to hydrocortisone alone in patients with HRPC. Randomised trial, method not stated. Stratified by performance status, disease status and number of prior endocrine therapies. Quality score: 1/0/1

**Participants**  
242 men with HRPC and prior endocrine manipulation and documented progressive disease. Anti-androgen withdrawal required before entry. No crossover at disease progression.

**Interventions**  
Mitoxantrone 14mg iv every 3 weeks, plus hydrocortisone 30mg orally (morning) and 10mg evening, n= 110, versus hydrocortisone alone as above, n=123.

**Outcomes**  
Survival (randomisation to death).  
Time to progression - from randomisation until following: worsening of performance status, new lesions on bone scan, or increased PSA by 100% of baseline).  
Time to treatment failure = time to following: progression, unacceptable toxicity, refusal to continue.  
Response: Complete - disappearance of disease + normal PSA, Partial - (measurable) > 50% decrease or >80% decrease in PSA, (assessable) >80% decrease in PSA for 6 weeks.  
Quality of life - pain - 22 item questionnaire (Functional living Index Cancer) to provide Global assessment.

**Notes**  
Allocation concealment B – Unclear

**Study**  
**Kasimis 1985**

**Methods**  
To compare single agent cyclophosphamide with 5-fluorouracil plus doxorubicin plus mitomycin C in patients with HRPC. Randomised, cross-over trial. Method by sealed envelope. Quality score: 1/0/1.

**Participants**  
31 patients with histologically confirmed metastatic adenocarcinoma of the prostate who had failed prior hormone therapy. All had symptomatic progressive disease.

**Interventions**  
cyclophosphamide 1.1g/sqm i.v bolus every 21 days, n= 16, versus
**Characteristics of included studies (Continued)**

<table>
<thead>
<tr>
<th>5-fluorouracil 600mg/sqm 24 h infusion days 1-5, 28-32, plus doxorubicin 30mg/sqm iv 20 min infusion days 1 &amp; 28 (not to exceed 550mg/sqm), plus mitomycin C 10mg/sqm iv bolus day 1. 56 day cycle. n = 15.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Response NPCP criteria. Time to progression.</td>
</tr>
<tr>
<td>Notes</td>
<td>Allocation concealment A – Adequate</td>
</tr>
</tbody>
</table>

**Study: Laurie 1992**

<table>
<thead>
<tr>
<th>Methods</th>
<th>To evaluate the clinical value of 5-fluorouracil plus doxorubicin plus mitomycin C (FAM) combination chemotherapy and compare with sequential administration of each drug given at full dose. Randomised clinical trial. Method not stated. Quality score: 1/0/1.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>145 patients with histologically proven advanced prostate cancer with progressive disease despite hormone therapy. All had measurable or assessable disease. Stratified by ECOG performance status (0 or 1 versus 2 or 3), non-osseous metastases and acid phosphatase levels.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Combination: 5-fluorouracil 600 mg/sqm day 1 &amp; 8, plus doxorubicin 30 mg/sqm day 1, plus mitomycin C 10 mg/sqm day 1, cycle repeated 4-5 weeks, n = 70, versus Sequential: mitomycin C 12.5 mg/sqm day 1 every 4 weeks, doxorubicin 50 mg/sqm day 1 every 3-4 weeks, 5-fluorouracil 500mg/sqm days 1-5 every 5 weeks, n = 72.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Objective tumour response: Complete - disappearance of all evidence of disease. Partial - 50% decrease in lesions, recalcification of osseous lesions. Progression - &gt;25% increase in tumour mass (perpendicular diameter), new lesions. Survival.</td>
</tr>
<tr>
<td>Notes</td>
<td>Allocation concealment B – Unclear</td>
</tr>
</tbody>
</table>

**Study: Leaf 2003**

<table>
<thead>
<tr>
<th>Methods</th>
<th>To evaluate whether a combination of doxorubicin and diethylstilbestrol (DES) is superior to doxorubicin alone in HRPC. Randomised phase II trial (ECOG). Stratified by disease measurability, performance status and degree of weight loss. No method stated. Quality score: 1/0/1.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>188 entered, 150 eligible. Patients with histologically confirmed adenocarcinoma of the prostate with progressive metastatic disease following treatment with orchidectomy and/or estrogen therapy.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Doxorubicin 50 mg/sqm in every 3 weeks (max 500 mg/sqm), n = 76, versus Doxorubicin as above plus DES 1g iv daily x 5, then 1g iv twice weekly for 4 cycles (12 weeks), n = 74.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Response: complete- disappearance of all measurable tumour (1month).</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

- Partial- 50% decrease in tumour size (1 month).
- Progression- increase >25% in tumour mass or new lesions.
- Toxicity.
- Failure-free survival.
- Overall survival
  (time from registration to date of any cause of death).

### Study  | Loening 1981
---|---
**Methods** | To evaluate single agents cyclophosphamide, methyl - CCNU, and hydroxyurea in patients with advanced prostate cancer. Randomised trial. Method not stated. Cross-over design. Quality score: 1/0/1

**Participants** | 125 participants with histologically confirmed relapsing clinical stage D prostate cancer. All had distant metastases.

**Interventions** | Cyclophosphamide 1 g/sqm iv every 3 weeks, n = 47, versus Methyl CCNU 175 m/sqm orally every 6 weeks, n = 38, versus Hydroxyurea 3 g/sqm orally every day in 3 divided doses, n = 40

**Outcomes** | Objective response: (NPCP criteria):
- Complete,
- Partial regression,
- Stable disease,
- progression.

Subjective response:
- pain,
- performance status.

### Study  | Loening 1983
---|---
**Methods** | To compare estramustine with methotrexate and cisplatin in HRPC patients. Randomised trial - method not stated. Not ITT analysis. Quality score: 1/0/1

**Participants** | 189 patients with advanced prostate cancer demonstrating clinical progression having failed or never responded to orchidectomy or hormone therapy.

**Interventions** | Oral estramustine phosphate 600mg/sqm/day in 3 divided doses, n=63 versus i.v. methotrexate 40mg/sqm da 1, 60 mg/sqm day 8 then weekly., n=67 versus iv cisplatin 60mg/sqm +pre- and post infusion hydration days 1, 4, 21 & 24 - then monthly, n=59.

**Outcomes** | Objective and subjective responses -NPCP criteria.
- Toxicity.
- Overall survival.
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Millikan 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To define response rates and toxicities of doxorubicin plus ketoconazole versus ketoconazole alone in HRPC. Randomised phase II trial. Method not stated. Quality score: 1/0/1</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>89 patients with histologically confirmed adenocarcinoma of the prostate. 91% had bone metastases and all had progressive disease with castrate levels of testosterone (&lt;50 ng/dl). All were off anti androgen therapy for at least 4 weeks prior to registration.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Ketoconazole 400mg orally twice daily (1 hour before and after eating, with ascorbic acid), n= 45, versus ketoconazole as above plus doxorubicin 20 mg/sqm i.v.every week - max dose of 400mg/sqm, n= 44. All received hydrocortisone.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Response: ( for measurable disease) = decrease PSA by 80% for 8 weeks with stable symptoms, or 50% decrease in measurable lesions. Progression: any of the following - 25% increase in PSA above nadir, new lesions on bone scan, worsening symptoms. Time to progression. Toxicity - NCI criteria. Survival.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Millikan 2003</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To compare two multi-component chemotherapy regimens in patients with androgen independent prostate cancer. Randomised, multicentre, phase II trial. Method not stated. Quality score; 1/0/1</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>75 patients with metastatic, androgen independent prostate cancer that was progressive despite castrate levels of testosterone (&lt; 4ng/dL).</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Ketoconazole orally 400mgx3/day for 7days, plus doxorubicin 20 mg/sqm on day 1 (KA) alternating with vinblastine 4mg/sqm day 1 plus estramustine orally 140mg x3/day for 7days (VE) KA/VE alternated for 6 weeks then weeks 7 &amp; 8 rest, n = 37, versus paclitaxel 135mg/sqm day 2, estramustine orally 280mg x3/day for 2 weeks, etoposide orally 50mg x2/day for 2 weeks (EPE) cycle repeated every 21 days, n = 38.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Response: PSA - &gt; 50% reduction and 80% reduction from baseline at 8 weeks., tumour- 50% reduction in measurable nodal or visceral lesions. Time to progression - measured from protocol registration. Toxicity - NCI criteria. Survival.</td>
</tr>
</tbody>
</table>

### Notes

- Allocation concealment B – Unclear
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Method</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Murphy 1977</strong></td>
<td>To compare estramustine with streptozotocin and standard therapy in HRPC patients previously treated with radiotherapy. Randomised trial. Method by centralised statistics Office. Cross-over design (estramustine and streptozotocin on disease progression). Quality score: 2/0/1</td>
<td>105 patients with advanced metastatic hormone refractory prostate cancer. All had extensive prior pelvic radiotherapy (at least 2000R)</td>
<td>Estramustine 600mg/sqm orally, daily in 3 divided doses (n = 46). Streptozotocin 500mg/sqm i.v. daily x 5every 6 weeks (n = 38). Standard therapy - any non-chemotherapy treatment e.g. prednisone, phosphorus 32, chlorotrianisene, diethylstibestrol.</td>
<td>Quality score: 2/0/1</td>
<td></td>
</tr>
<tr>
<td><strong>Murphy 1979</strong></td>
<td>To evaluate estramustine plus prednimustine versus prednimustine alone in advanced metastatic prostate cancer patients receiving prior irradiation. Randomised trial - method not stated. Quality score: 1/0/1</td>
<td>135 patients with confirmed metastatic prostate cancer who had failed hormone therapy and had progressive disease.</td>
<td>Estramustine 600mg/sqm orally, daily in 3 divided doses plus prednimustine 30mg orally daily in 3 divided doses for 6 or every 7 days (n = 54) versus Prednimustine as above ( n= 62)</td>
<td>Objective response. Pain relief. Toxicity. Survival.</td>
<td>Allocation concealment A – Adequate</td>
</tr>
<tr>
<td><strong>Murphy 1988</strong></td>
<td>To evaluate single agent methotrexate with cyclophosphamide combination chemotherapy in HRPC patients. NCPC group prospective randomised trial (protocol 1500). Method not stated. Quality score: 1/0/1</td>
<td>180 patients (119 eligible) with advanced hormone refractory carcinoma of the prostate.</td>
<td></td>
<td></td>
<td>Allocation concealment B – Unclear</td>
</tr>
</tbody>
</table>

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Chemotherapy for hormone-refractory prostate cancer (Review)  
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Characteristics of included studies (Continued)

Interventions
Cyclophosphamide 500 mg/sqm iv day 1 every 3 weeks plus
doxorubicin 50 mg/sqm iv day 1 every 3 weeks n= 60,
versus
methotrexate 40 mg/sqm iv day 1, 60 mg/sqm day 8 every 2 weeks n= 63,
versus
cyclophosphamide as above plus
cisplatin 50 mg/sqm pre/post hydration every 3 weeks plus
5-fluorouracil 500mg/sqm iv day 1 then every 21 days n = 57.

Outcomes
NPCP response criteria used.
Progression-free survival.
Overall survival.
Toxicity.

Notes
Allocation concealment B – Unclear

Study Muss 1981

Methods
To compare cyclophosphamide as a single agent or in combination with 5-fluorouracil plus methotrexate in
advanced prostate cancer.
Randomised trial. No method stated.
Quality score: 1/0/1

Participants
40 patients (32 eligible) with metastatic carcinoma of the prostate with progressive disease following endocrine
manipulations. Approx. 80% were symptomatic.

Interventions
Cyclophosphamide 750 mg/sqm iv every 3 weeks, n = 21,
versus
cyclophosphamide 500mg/sqm iv plus
methotrexate 10 mg/sqm iv plus
5-fluorouracil 500mg/sqm iv every 3 weeks. n = 19.

Outcomes
Response NPCP criteria (stable disease = no change in bone or other lesions for 3 months, no progression
of symptoms.
Duration of response (time to progression).
Survival.

Notes
Allocation concealment B – Unclear

Study Newling 1993

Methods
To compare estramustine with mitomycin C for the treatment of hormone resistant metastatic prostate
cancer. Prospective, multi-centre, phase II randomised trial. Method not stated.
Quality score: 1/0/1

Participants
171 patients with progressive metastatic prostate cancer following hormone therapy. Patients were mainly
symptomatic - 80% had pain on entry.

Interventions
Estramustine phosphate 500-700mg/day orally, n = 82,
versus
mitomycin C 15mg/sq m,
2 -hour iv infusion every 6 weeks, n = 79.

Outcomes
Disease progression. Duration of survival.
Objective progression: new hotspots on bone scan (persistent), new soft tissue or visceral lesions, 25% increase
of measurable lesions.
### Characteristics of included studies (Continued)

**Subjective response:**
decrease WHO performance status by 2 levels or levels 3-4, increase pain score.

**Notes**
Allocation concealment B – Unclear

<table>
<thead>
<tr>
<th>Study</th>
<th>Oudard 2005</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To evaluate the PSA response of 2 docetaxel - estramustine - prednisone (DEP) regimes and mitoxantrone plus prednisone (MP) in advanced prostate cancer. Multicentre (24) randomised phase II trial. Randomisation by central office. In failed patients crossover from docetaxel to mitoxantrone and vice versa. ITT analysis. Quality score: 2/0/1</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>130 patients with progressive, metastatic prostate cancer despite androgen deprivation.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
</tbody>
</table>
- D = 70mg/sqm 1 hour infusion on day 2 every 21 days, plus  
- E = 280mg orally twice daily days 1-5 and 8-12 (total 840 mg), plus  
- P = 10mg/day, n = 44, versus  
- D = 35mg/sqm 30min infusion days 2 & 9 every 21 days, plus E & P as above, n = 44, versus  
- M = 12 mg/sqm every 3 weeks (30 min infusion), plus P as above, n= 42.  
Oral warfarin 2mg/d on DEP arm. |
| **Outcomes** | PSA response.  
Clinical response - pain index (McGill questionnaire), ECOG performance status.  
Toxicity - NCI common toxicity criteria version 1.  
Time to PSA progression - date from randomisation to progression (>25% increase in PSA from baseline or >50% increase from nadir for 3 successive values 3 weeks apart).  
Overall survival - study entry to death or last follow-up. |
| **Notes** | Allocation concealment A – Adequate |

<table>
<thead>
<tr>
<th>Study</th>
<th>Page 1985</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To compare the efficacy of cyclophosphamide / 5-fluorouracil combination with doxorubicin plus lomustine. Prospective randomised trial. Allocation by sealed envelope. Quality score: 2/0/1</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>51 patients with proven metastatic prostate carcinoma with progressive disease following orchidectomy or estrogen therapy (stopped at least 4 weeks before entering study). 4 patients not evaluable.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
</tr>
</tbody>
</table>
- Cyclophosphamide 500 mg/sqm iv day 1 every 4 weeks plus  
- 5-fluorouracil 500 mg/sqm days 1 & 8 every 4 weeks versus  
- doxorubicin 45 mg/sqm iv days 1 (max 450 mg/sqm) every 3 weeks plus lomustine 40 mg/sqm orally on day 1 every 3 weeks.  
Treatment continued until disease progression. |
| **Outcomes** | Objective response: NPCP criteria used. Subjective response: graded 0 - 3 (based on pain response, prostatism and leg edema). Complete response CR - disappearance of symptoms. Partial - one grade less than CR. Stable disease - change by less than one grade. Progression - increase by one grade. |
### Characteristics of included studies (Continued)

**Notes**

**Allocation concealment** A – Adequate

<table>
<thead>
<tr>
<th>Study</th>
<th>Petrylak 2004</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To determine whether docetaxel plus estramustine improves survival compared to mitoxantrone plus prednisone in androgen independent prostate cancer. (SWOG 99-16). Prospective randomised phase III trial. Method not stated. Quality score: 1/0/1.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>770 men (674 eligible) with histologically confirmed metastatic, hormone independent, prostate cancer. All had progressive disease (determined from bidimensional measurable lesions, evaluable progression e.g. by bone scans, increased PSA above baseline on 2 samples 7 days apart. Androgen ablation discontinued 4-6 weeks prior to registration.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Docetaxel 60mg/sqm days 2 and 6, plus Estramustine 280 mg/sqm days 1-5, n = 386, versus mitoxantrone 12mg/sqm day 1 plus prednisone 5 mg twice daily, n = 384.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Overall survival. Progression free survival - progression = 25% increase in PSA (to at least 5ng/ml above baseline confirmed 4 weeks later). Objective response - sum of bi-dimentional measurements of metastatic lesions. PSA response (50% decrease). Toxicity.</td>
</tr>
</tbody>
</table>

**Notes**

**Allocation concealment** B – Unclear

<table>
<thead>
<tr>
<th>Study</th>
<th>Rangel 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To compare doxorubicin plus prednisone with prednisone alone in HRPC. Randomised trial. Method not stated. Quality score: 1/0/1</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>111 patients with stage D1 prostate cancer progressive after androgen deprivation therapy.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Doxorubicin 20 mg/sqm iv weekly (10 min infusion) - max dose 700 mg/sqm, plus prednisone 5 mg orally twice daily, n = 59, versus prednisone as above, n = 51</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Response: Objective - assessed by serum markers and bone scan. Subjective - weight, appetite and analgesic use. Overall survival. Time to progression (progression = new bone lesions on scan or increased pain or decreased performance).</td>
</tr>
</tbody>
</table>

**Notes**

**Allocation concealment** B – Unclear

<table>
<thead>
<tr>
<th>Study</th>
<th>Saxman 1992</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To determine whether the addition of doxorubicin and methotrexate to a cyclophosphamide regimen improves survival in advanced prostate cancer.</td>
</tr>
</tbody>
</table>
Characteristics of included studies (Continued)

Randomised trial. Method by centralised biostatistical office. Stratified by performance status (KPS 80-100 and 50 - 70). No crossover. ITT analysis. Quality score: 2/0/1

Participants 103 patients (99 evaluable) with hormone refractory metastatic prostate cancer. 69% evaluable disease, 31% measurable disease.

Interventions Cyclophosphamide 1g/sqm iv bolus every 3 weeks, (800mg/sqm for previously irradiated patients) n = 53, versus Cyclophosphamide 500mg/sqm iv bolus every 3 weeks (400 for RT patients) plus doxorubicin 50 mg/sqm iv bolus every 3 weeks (max 450mg/sqm) plus methotrexate 40mg/sqm iv bolus every 3 weeks (32mg/sqm for RT patients) n = 50

Outcomes Response for measurable disease:
Complete response = disappearance of measurable lesions.
Partial = >50% decrease in sum of measurable lesions.
Progression = >25% increase in sum of all measurable lesions or deterioration in symptoms (10% weight loss, 20% decrease in performance status).
Evaluable disease:
Progression = new lesions or deterioration in symptoms.
Stable disease = absence of new lesions or symptoms of disease for 3 months.

Notes Allocation concealment A – Adequate

Study Scott 1976

Methods To determine the efficacy of cyclophosphamide versus 5-fluorouracil versus standard therapy. Randomised trial - NPCP protocol 100. Randomisation by centralised statistics Office. Cross-over design. Quality score: 2/0/1

Participants 125 patients with stage D prostate cancer and progressive disease following hormone or ablative therapy. 110 patients were eligible.

Interventions Cyclophosphamide 1g/sqm i.v. every 3 weeks x 4 n = 41, versus 5-Fluorouracil 600mg/sqm i.v. weekly x 12 n = 33, versus Standard therapy - any palliative treatment apart from chemotherapy n= 36.

Outcomes Objective response:
complete -
a) absence of any detectable soft tissue tumour,
b) normalisation of acid phosphatase,
c) re-calcification of all osteolytic lesions,
d) no evidence of progression.
Partial - 50% decrease in tumour volume, b) & c) as above.
Stable - < 25% increase in any measurable lesion and b) above.
Progression -any of the following: a) significant deterioration in symptoms and performance status. b) new lesions c) increase in size of existing lesions.

Notes Allocation concealment A – Adequate
Characteristics of included studies *(Continued)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Smalley 1981</th>
<th>Soloway 1981</th>
<th>Soloway 1983</th>
</tr>
</thead>
</table>
| **Methods** | **To evaluate 5-Fluorouracil (5-FU) monotherapy compared to 5-FU with cyclophosphamide (cycloP) plus doxorubicin (Dox) in patients with bladder cancer and prostate cancer (only concerned with the latter). Randomised phase II trial. Method by centralised telephone.**
| **Participants** | 101 patients with advanced metastatic prostate cancer refractory to either estrogen therapy and/or orchidectomy. | 121 patients with histologically confirmed advanced, metastatic, prostate cancer with disease progression following orchidectomy and hormone therapy. 90 patients were evaluable. All received previous pelvic radiation. | 149 patients with histologically confirmed cancer of the prostate with distant metastases which was clinically progressing. All had failed or never responded to orchidectomy or hormone therapy. 92% had pain on entry. |
| **Interventions** | 5-FU 600mg/sqm iv weekly every 3 weeks, n = 32, versus 5-FU 500mg/sqm iv plus cycloP 500mg/sqm plus Dox 50mg/sqm all cycled every 3 weeks, n = 39. | Estramustine phosphate 600mg/sqm daily in 3 divided doses n = 38, versus vincristine 1mg/sqm iv every 2 weeks n= 42, versus estramustine plus vincristine as above, n= 41 | Estramustine phosphate 600mg/sqm orally per day in 3 divided doses, n = 50, |
| **Outcomes** | Response - Placental alkaline phosphatase levels and/or NPCP criteria. Progression - clinical evidence including pain, decreased performance status and weight associated with X-ray evidence of skeletal metastases. | Objective and subjective response (NPCP criteria). Toxicity. Survival. | |
| **Notes** | Allocation concealment A – Adequate | Allocation concealment B – Unclear | |

*Chemotherapy for hormone-refractory prostate cancer (Review)*

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### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Tannock 1996</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To compare mitoxantrone plus low dose prednisone with prednisone alone as palliative therapy in HRPC patients. Multicentre randomised trial. Method not stated. Quality score: 1/0/1</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>161 patients from 11 Canadian Institutes. All had metastatic prostate cancer with pain and disease progression despite standard hormone therapy. Life expectancy of 3 months.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Mitoxantrone 12 mg/sqm iv every 3 weeks, plus prednisone 5 mg twice daily, n = 80 versus prednisone as above, n = 81. Prochlorperazine as anti-emetic.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Pain: response defined as a 2 point decrease in pain as assessed by a 6 point scale with no increase in analgesic use (McGill-Melzack pain questionnaire). Analgesic use. Survival. Quality of life: linear analog scale, self assessment scales and prostate cancer specific QOL instrument. Progression: increase in pain score &gt; 1, or increase in analgesic score &gt; 2.3%</td>
</tr>
</tbody>
</table>

### Notes
- Allocation concealment A – Adequate

### Study | Tannock 2004
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>To determine if docetaxel plus prednisone improves overall survival as compared to mitoxantrone and prednisone. Multicentre (24) randomised phase III trial. Randomisation centralised using the stratified permuted block allocation. ITT analysis. Quality score: 2/0/1</td>
</tr>
</tbody>
</table>
| **Participants** | 1006 patients with confirmed prostate cancer and clinical or radiological evidence of metastatic disease. All had progression during hormone therapy. (progression = increased PSA on 3 consecutive measurements at

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versus cisplatin 60 mg/sqm iv with pre- and post- hydration, on days 1 and 21, repeated monthly, n = 51, versus estramustine plus cisplatin as above, n = 48.

Outcomes
- **Response**: NPCP criteria:
  - **Objective resp -**
    - Complete resp: complete disappearance of tumour, no new lesions.
    - Partial resp: normalisation of alkaline phosphatase.
  - Stable: no new lesion, or measurable lesion increase > 25%, decreased alk phos, no worsening of bone lesions, no worsening of hepatomegaly by > 30%, no significant worsening of cancer-related symptoms eg weight and performance status.
  - **Objective progression** - any of the following: significant decrease in weight or performance status, new lesions, increase in measurable lesions, recurring anaemia or development of ureteral obstruction.

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**Notes**
- Allocation concealment A – Adequate

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Chemotherapy for hormone-refractory prostate cancer (Review)

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Characteristics of included studies (Continued)

least one week apart or findings on physical examination or imaging studies). At least 4 weeks elapsed between anti-androgen therapy and enrolment. Performance status at least 60%.

Interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Torti 1985</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>To evaluate doxorubicin alone compared to doxorubicin plus cisplatin in HRPC. Randomised trial. Method not stated. Quality score: 1/0/1</td>
</tr>
<tr>
<td>Participants</td>
<td>37 patients with HRPC relapsed following, or failed to respond, to hormone therapy. Required adequate renal, hepatic and marrow function. Performance status ≥40.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Doxorubicin 60 mg/sqm 20 min i.v. infusion every 3 weeks, n = 20, versus doxorubicin (as above) plus cisplatin 80 and 60mg/sqm (pts with limited and extensive radiotherapy). 24 hour infusion every 3 weeks, n=17.</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Response NCOG criteria; Complete: disappearance of all tumour. Partial: 75% reduction in tumour mass or 50% reduction in other soft tissue metastases without evidence of progression on scan or X-ray, or pain assessment. Progression: new lesions on scan, 25% increase in measurable lesions, 20% increase in pain or 25% reduction in performance status.</td>
</tr>
</tbody>
</table>

Notes

Allocation concealment A – Adequate

Study

<table>
<thead>
<tr>
<th>Study</th>
<th>Tveter 1990</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>To compare estramustine with epirubicin plus MPA and epirubicin plus placebo. 3 arm, placebo controlled, randomised trial. No method given. Epirubicin arms were blind. Quality score: 1/1/1</td>
</tr>
<tr>
<td>Participants</td>
<td>79 patients with metastatic prostate cancer and progressive disease following standard hormone therapy. All had symptomatic disease. 8 weeks elapsed between castration and enrolment.</td>
</tr>
</tbody>
</table>
Interventions

Estramustine phosphate orally 280 mg twice daily, n = 25
versus
epirubicin 20mg iv weekly, plus medroxyprogesterone acetate (MPA) 500mg twice weekly, n = 24
versus
epirubicin 20mg iv weekly plus matched placebo twice daily, n = 30.

Outcomes

Pain Score:
0. no pain
1. slight, no analgesics.
2. moderate, mild analgesics.
3. severe, strong analgesics.

Performance status:
1. No symptoms
2. mild symptoms, ambulatory.
3. Bedridden < 50% of day.
4. Bedridden > 50% of day.
4. Confined to bed.

Time to progression - interval from treatment start to progression or death.

Notes

Allocation concealment B – Unclear

Characteristics of excluded studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahles 2004</td>
<td>Dose-escalation study with Suramin - not a cytotoxic agent.</td>
</tr>
<tr>
<td>Akaza 1993</td>
<td>Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>Alfhan 1983</td>
<td>Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>Andersson 1980</td>
<td>Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>Benson 1983</td>
<td>Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>Boel 1999</td>
<td>Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>Burns-Cox 2002</td>
<td>Randomised trial but not chemotherapy.</td>
</tr>
<tr>
<td>Datta 1997</td>
<td>Randomised but not chemotherapy.</td>
</tr>
<tr>
<td>Dawson 2000</td>
<td>Randomised trial but not chemotherapy.</td>
</tr>
<tr>
<td>De Reijke 1999</td>
<td>Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>DeWys 1983</td>
<td>Not all patients recruited were HRPC.</td>
</tr>
<tr>
<td>Edsmyr 1978</td>
<td>Patients recruited were not HRPC. Previous report of Alfhan1983.</td>
</tr>
<tr>
<td>Ernst 2003</td>
<td>Although a randomised trial with chemotherapy, the main aim was to determine the efficacy of the bisphosphonate, clodronate, combined with chemotherapy.</td>
</tr>
<tr>
<td>Falsaperla 2005</td>
<td>A randomised trial of a non-chemotherapeutic agent - ellagic acid.</td>
</tr>
<tr>
<td>Fontana 1998</td>
<td>Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>Fossa 2000</td>
<td>Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>Fossa 2001</td>
<td>Randomised trial but not chemotherapy.</td>
</tr>
<tr>
<td>Year</td>
<td>Study Description</td>
</tr>
<tr>
<td>--------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>1983</td>
<td>Gibbons  Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1996</td>
<td>Hedlund Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>2004</td>
<td>Heidenreich Randomised trial comparing two different formulations of doxorubicin.</td>
</tr>
<tr>
<td>2002</td>
<td>Hervonen Randomised trial but dose finding study.</td>
</tr>
<tr>
<td>1983</td>
<td>Huben Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1997</td>
<td>Janknegt Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1987</td>
<td>Johansson Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1988</td>
<td>Johansson Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1977</td>
<td>Johnson Review of randomised trials - not primary study</td>
</tr>
<tr>
<td>1988</td>
<td>Kitahara Not all patients recruited were HRPC.</td>
</tr>
<tr>
<td>1996</td>
<td>Komatus Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>2001</td>
<td>Kuriyama Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1997</td>
<td>Kylmala Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1995</td>
<td>Lundgren Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1986a</td>
<td>Manni Treatment method unclear.</td>
</tr>
<tr>
<td>1986b</td>
<td>Manni Early report of Manni 1986</td>
</tr>
<tr>
<td>1995</td>
<td>Matsuda Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1996</td>
<td>Miyake Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1986</td>
<td>Murphy Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1990</td>
<td>Newling Same study as Newling 1993.</td>
</tr>
<tr>
<td>2004</td>
<td>Noguchi Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1990</td>
<td>Osborne Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1990</td>
<td>Patel Randomised trial but not chemotherapy.</td>
</tr>
<tr>
<td>2003</td>
<td>Pienta Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1991</td>
<td>Pummer Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1989</td>
<td>Ruff Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1999</td>
<td>Sakai Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1979</td>
<td>Schmidt Unclear from this paper (or the one cross-referenced) whether patients were hormone refractory.</td>
</tr>
<tr>
<td>1975a</td>
<td>Scott Previous report of Scott 1976.</td>
</tr>
<tr>
<td>2000</td>
<td>Small Randomised trial of suramin - not a cytotoxic agent.</td>
</tr>
<tr>
<td>2002</td>
<td>Small Randomised dose escalation study of suramin.</td>
</tr>
<tr>
<td>1986</td>
<td>Smith Randomised study but unclear if patients were hormone refractory.</td>
</tr>
<tr>
<td>1984</td>
<td>Stephens Not all patient hormone refractory.</td>
</tr>
<tr>
<td>1999</td>
<td>Sumiyoshi Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>2001</td>
<td>Takenaka Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1985</td>
<td>Vahlensieck Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>1993</td>
<td>Van Poppel Randomised trial but patients recruited were not HRPC.</td>
</tr>
<tr>
<td>2003</td>
<td>Walczak Describes E1899 ongoing randomised trial. No data reported.</td>
</tr>
<tr>
<td>2000</td>
<td>Wang Randomised trial but patients recruited were not HRPC.</td>
</tr>
</tbody>
</table>
### ADDITIONAL TABLES

#### Table 01. Estramustine: Overall survival (months), PSA Response, Disease Progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Patients</th>
<th>Overall survival</th>
<th>PSA 50% decline</th>
<th>Time To Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Subsection 1.</strong> Estramustine vs BSC or Hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iversen 1997</td>
<td>1. Estramustine plus standard therapy</td>
<td>61</td>
<td>median 9.4 mths</td>
<td>37%</td>
<td>median 4.6 months</td>
</tr>
<tr>
<td></td>
<td>2. Placebo plus standard therapy.</td>
<td>68</td>
<td>5.0</td>
<td>2%</td>
<td>5.0</td>
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<tr>
<td>De Kernion 1988</td>
<td>1. Estramustine</td>
<td>109</td>
<td>not reported</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>2. Flutamide</td>
<td>111</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Johanssen 1991</td>
<td>1. Estramustine</td>
<td>52</td>
<td>8.3</td>
<td>not reported</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>2. Medroxyprogesterone acetate</td>
<td>53</td>
<td>11.6</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>Murphy 1977</td>
<td>1. Estramustine</td>
<td>46</td>
<td>data not extractable</td>
<td>not reported</td>
<td>11.3 (mean)</td>
</tr>
<tr>
<td></td>
<td>2. Streptozotocin</td>
<td>38</td>
<td></td>
<td>8.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Standard therapy</td>
<td>21</td>
<td></td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td><strong>Subsection 2.</strong> Estramustine versus Single Cytotoxic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elomaa 1991</td>
<td>1. Estramustine</td>
<td>20</td>
<td>15.0</td>
<td>not reported</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td>2. Epirubicin low-dose</td>
<td>21</td>
<td>15.0</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Newling 1993</td>
<td>1. Estramustine</td>
<td>82</td>
<td>10.0</td>
<td>not reported</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>2. Mitomycin C</td>
<td>79</td>
<td>10.0</td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td>Loening 1983</td>
<td>1. Estramustine</td>
<td>63</td>
<td>10.8</td>
<td>not reported</td>
<td>66% at 12 weeks</td>
</tr>
<tr>
<td></td>
<td>2. Methotrexate</td>
<td>67</td>
<td>11.5</td>
<td>59%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Cisplatin</td>
<td>59</td>
<td>10.0</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>Anderstrom 1995</td>
<td>1. Estramustine</td>
<td>74</td>
<td>9.5</td>
<td>not reported</td>
<td>4.4</td>
</tr>
<tr>
<td></td>
<td>2. MPA + Epirubicin</td>
<td>75</td>
<td>11.5</td>
<td>7.7</td>
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</tr>
<tr>
<td>Tveter 1990</td>
<td>1. Estramustine</td>
<td>25</td>
<td>not reported</td>
<td>not reported</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>2. Epirubicin + medroxyprogesterone acetate</td>
<td>24</td>
<td></td>
<td>5.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. Epirubicin + placebo</td>
<td>30</td>
<td></td>
<td>3.0</td>
<td></td>
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<tr>
<td><strong>Subsection 3.</strong> Estramustine versus Estra + Cytotoxic</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Albrecht 2004</td>
<td>1. Estramustine</td>
<td>45</td>
<td>12.7</td>
<td>28.9%</td>
<td>6.8</td>
</tr>
<tr>
<td>Study</td>
<td>Treatment 1</td>
<td>Treatment 2</td>
<td>OS (months)</td>
<td>PR (%)</td>
<td>CR (%)</td>
</tr>
<tr>
<td>--------------</td>
<td>------------------------------------</td>
<td>------------------------------------</td>
<td>-------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Hudes 1999</td>
<td>Estramustine + vinblastine</td>
<td>100</td>
<td>11.9</td>
<td>25*</td>
<td>3.7*</td>
</tr>
<tr>
<td></td>
<td>Estramustine + vinblastine (VinB)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vinblastine</td>
<td>101</td>
<td>9.2</td>
<td>3.0</td>
<td>2.2</td>
</tr>
<tr>
<td>Soloway 1981</td>
<td>Estramustine</td>
<td>38</td>
<td>mean 8.9</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>Vincristine</td>
<td>42</td>
<td>9.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Estramustine + Vincristine</td>
<td>41</td>
<td>7.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soloway 1983</td>
<td>Estramustine</td>
<td>50</td>
<td>5.2</td>
<td>not reported</td>
<td>82%</td>
</tr>
<tr>
<td></td>
<td>Cisplatin</td>
<td>51</td>
<td>7.0</td>
<td></td>
<td>67%</td>
</tr>
<tr>
<td></td>
<td>Estramustine + Cisplatin</td>
<td>48</td>
<td>7.0</td>
<td></td>
<td>79%</td>
</tr>
<tr>
<td>Berry 2004</td>
<td>Estramustine + Paclitaxel</td>
<td>79</td>
<td>16.1*</td>
<td>47%</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>84</td>
<td>13.1</td>
<td>27%</td>
<td>4.3</td>
</tr>
<tr>
<td>Galsky 2005</td>
<td>Estramustine + ixabepilone</td>
<td>45</td>
<td>not reported</td>
<td>69%</td>
<td>5.2</td>
</tr>
<tr>
<td></td>
<td>Ixabepilone</td>
<td>47</td>
<td>48%</td>
<td></td>
<td>4.4</td>
</tr>
<tr>
<td>Murphy 1979</td>
<td>Estramustine + Prednimustine</td>
<td>54</td>
<td>12.3</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>Prednimustine</td>
<td>62</td>
<td>12.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subsection 4.</td>
<td>Complex Combinations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimopoulos 2004</td>
<td>Estramustine + Etoposide</td>
<td>20</td>
<td>18.8</td>
<td>60%</td>
<td>6.0</td>
</tr>
<tr>
<td></td>
<td>Lanreotide + Cisplatin + Dexamethasone</td>
<td>18</td>
<td>18.0</td>
<td>66%</td>
<td>4.0</td>
</tr>
<tr>
<td>Akaza 1988</td>
<td>Estramustine + peplomycin (peplo)</td>
<td>22</td>
<td>5.5</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>Estramustine + peplo + doxorubicin (Dox)</td>
<td>22</td>
<td>7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Millikan 2003</td>
<td>Estramustine/VinB alternating ketoconazole/Dox</td>
<td>37</td>
<td>23.5</td>
<td>56%</td>
<td>data not extractable</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel/etoposide</td>
<td>38</td>
<td>17.0</td>
<td>41%</td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant p < 0.05
### Table 02. Cyclophosphamide -Median Overall survival, PSA Response, Disease Progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Patients</th>
<th>Median Survival</th>
<th>PSA Response %</th>
<th>Progression - median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scott 1976</td>
<td>1. Cyclophosphamide (CycloP)</td>
<td>41</td>
<td>data not reported</td>
<td>data not reported</td>
<td>53%</td>
</tr>
<tr>
<td></td>
<td>2. 5-Fluorouracil (5FU)</td>
<td>33</td>
<td></td>
<td></td>
<td>63%</td>
</tr>
<tr>
<td></td>
<td>3. Standard therapy</td>
<td>36</td>
<td></td>
<td></td>
<td>81%</td>
</tr>
<tr>
<td>Chlebrowski 1978</td>
<td>1. CycloP</td>
<td>15</td>
<td>7.2 months</td>
<td>data not reported</td>
<td>12.7 months</td>
</tr>
<tr>
<td></td>
<td>2. CycloP + 5FU + Doxorubicin (Dox)</td>
<td>12</td>
<td>8.9</td>
<td>data not reported</td>
<td>5.9</td>
</tr>
<tr>
<td>Loening 1981</td>
<td>1. CycloP</td>
<td>47</td>
<td>10.5</td>
<td>data not reported</td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>2. Methyl-CCNU</td>
<td>38</td>
<td>5.2</td>
<td></td>
<td>3.8</td>
</tr>
<tr>
<td></td>
<td>3. Hydroxyurea (HU)</td>
<td>40</td>
<td>4.8</td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td>Muss 1981</td>
<td>1. CycloP</td>
<td>21</td>
<td>9.3</td>
<td>data not reported</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>2. CycloP + Methotrexate (MTX) +5FU</td>
<td>19</td>
<td>7.1</td>
<td>data not reported</td>
<td>4.5</td>
</tr>
<tr>
<td>Kasimis 1986</td>
<td>1. CycloP + Dox + Mitomycin C (MMC)</td>
<td>16</td>
<td>data not reported</td>
<td>data not reported</td>
<td>1.2*</td>
</tr>
<tr>
<td></td>
<td>2. 5FU + Dox + Mitomycin C (MMC)</td>
<td>15</td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>Saxman 1992</td>
<td>1. CycloP</td>
<td>53</td>
<td>6.5</td>
<td>data not reported</td>
<td>4.2*</td>
</tr>
<tr>
<td></td>
<td>2. CycloP + Dox + MTX</td>
<td>50</td>
<td>8.1</td>
<td>data not reported</td>
<td>6.2</td>
</tr>
<tr>
<td>Page 1985</td>
<td>1. CycloP + 5FU</td>
<td>27</td>
<td>5.8</td>
<td>data not reported</td>
<td>data not reported</td>
</tr>
<tr>
<td></td>
<td>2. Dox + Lomustine</td>
<td>24</td>
<td>9.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Murphy 1988</td>
<td>1. CycloP + Dox</td>
<td>60</td>
<td>10.6</td>
<td>data not reported</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>2. MTX</td>
<td>63</td>
<td>10.6</td>
<td>data not reported</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>3. CycloP + Cisplatin + 5FU</td>
<td>57</td>
<td>10.6</td>
<td>data not reported</td>
<td>4.1</td>
</tr>
<tr>
<td>Herr 1982</td>
<td>1. CycloP + MTX + 5FU</td>
<td>20</td>
<td>6.5</td>
<td>data not reported</td>
<td>65%</td>
</tr>
<tr>
<td></td>
<td>2. Chloroethyl-CCNU</td>
<td>20</td>
<td>6.0</td>
<td>data not reported</td>
<td>70%</td>
</tr>
<tr>
<td>Graham 1986</td>
<td>1. CycloP+MTX+5FU+prednisone (Pred)</td>
<td>39</td>
<td>9.9</td>
<td>data not reported</td>
<td>data not reported</td>
</tr>
<tr>
<td></td>
<td>2. MTX+5FU+Pred+Vincristine+melphalan</td>
<td>19</td>
<td>13.8</td>
<td></td>
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</tr>
</tbody>
</table>

### Table 03. 5-Fluorouracil: Overall Survival, % PSA Response, Disease Progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Patients</th>
<th>Median Survival</th>
<th>PSA Response</th>
<th>Progression - Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smalley 1981</td>
<td>1. 5-Fluorouracil (5FU)</td>
<td>32</td>
<td>8.8</td>
<td>not reported</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>2. 5-FU+cyclophosphamide+doxorubicin</td>
<td>39</td>
<td>6.5</td>
<td>not reported</td>
<td></td>
</tr>
</tbody>
</table>
Table 03. 5-Fluorouracil: Overall Survival, % PSA Response, Disease Progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Patients</th>
<th>Median Survival</th>
<th>PSA Response</th>
<th>Progression - Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daliani 1995</td>
<td>1. 5-FU</td>
<td>23</td>
<td>8.25</td>
<td>12%</td>
<td>not reported</td>
</tr>
<tr>
<td></td>
<td>2. 5-FU + interferon alpha</td>
<td>28</td>
<td>8.25</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Beul 1997</td>
<td>1. 5-FU</td>
<td>25</td>
<td>6.9</td>
<td>33</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>2. 5-FU + Folinic acid</td>
<td>25</td>
<td>4.8</td>
<td>20</td>
<td>4.0</td>
</tr>
<tr>
<td>Droz 2003</td>
<td>1. Oxaliplatin</td>
<td>26</td>
<td>9.4</td>
<td>18</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>2. Oxaliplatin + 5-FU</td>
<td>28</td>
<td>11.4</td>
<td>19</td>
<td>3.4</td>
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</tbody>
</table>

Table 04. Doxorubicin: Overall Survival, PSA Response, Disease Progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Patients</th>
<th>Median Overall Surv</th>
<th>% PSA Response</th>
<th>Disease Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torti 1985</td>
<td>1. Doxorubicin (Dox)</td>
<td>20</td>
<td>12.1 months</td>
<td>Not reported</td>
<td>4.2 median months</td>
</tr>
<tr>
<td></td>
<td>2. Dox + Cisplatin</td>
<td>17</td>
<td>10.8</td>
<td>6.3</td>
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</tr>
<tr>
<td>Francini 1993</td>
<td>1. Dox</td>
<td>24</td>
<td>8.0</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
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<td>2. Epirubicin</td>
<td>48</td>
<td>12.5</td>
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<td></td>
</tr>
<tr>
<td>Leaf 2003</td>
<td>1. Dox</td>
<td>76</td>
<td>7.5</td>
<td>Not reported</td>
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</tr>
<tr>
<td></td>
<td>2. Dox + Diethylstilbestrol</td>
<td>74</td>
<td>9.1</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Rangel 1992</td>
<td>1. Dox + prednisone</td>
<td>59</td>
<td>11.8</td>
<td>Not reported</td>
<td>3.8</td>
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<tr>
<td></td>
<td>2. Prednisone</td>
<td>51</td>
<td>10.0</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Milikan 2001</td>
<td>1. Dox + ketoconazole</td>
<td>44</td>
<td>12.5</td>
<td>50%</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>2. Ketoconazole</td>
<td>45</td>
<td>12.5</td>
<td>40%</td>
<td>3.3</td>
</tr>
<tr>
<td>Laurie 1992</td>
<td>1. fluorouracil+Dox+mitomycin</td>
<td>70</td>
<td>8.7</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
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<td>2. mitomycin-Dox-fluorouracil</td>
<td>72</td>
<td>7.1</td>
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</table>

Table 05. Mitoxantrone: Overall Survival, % PSA Response, Time to Progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Patients</th>
<th>Median Survival</th>
<th>PSA response %</th>
<th>Progression (median)</th>
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</thead>
<tbody>
<tr>
<td>Kantoff 1999</td>
<td>1. Mitoxantrone+hydrocortisone</td>
<td>110</td>
<td>12.3 months</td>
<td>19</td>
<td>3.7 months</td>
</tr>
<tr>
<td></td>
<td>2. Hydrocortisone</td>
<td>123</td>
<td>12.6</td>
<td>14</td>
<td>2.3</td>
</tr>
<tr>
<td>Tannock 1996</td>
<td>1. Mitoxantrone+Prednisone</td>
<td>80</td>
<td>12</td>
<td>31</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>2. Prednisone</td>
<td>81</td>
<td>12</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Berry 2002</td>
<td>1. Mitoxantrone+Prednisone</td>
<td>56</td>
<td>23</td>
<td>48</td>
<td>8.1</td>
</tr>
<tr>
<td></td>
<td>2. Prednisone</td>
<td>63</td>
<td>19</td>
<td>24</td>
<td>4.1</td>
</tr>
</tbody>
</table>
Table 06. Docetaxel: Overall Survival, PSA Response, Disease Progression

<table>
<thead>
<tr>
<th>Study</th>
<th>Interventions</th>
<th>Patients</th>
<th>Median Survival</th>
<th>% PSA Response</th>
<th>Progression (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dahut 2004</td>
<td>1. Docetaxel (Doc)</td>
<td>25</td>
<td>14.7 months</td>
<td>37</td>
<td>3.7</td>
</tr>
<tr>
<td></td>
<td>2. Doc + Thalidomide</td>
<td>50</td>
<td>28.9</td>
<td>53</td>
<td>5.9</td>
</tr>
<tr>
<td>Oudart 2005</td>
<td>1. Doc(70mg)+Estramustine+Prednisone</td>
<td>44</td>
<td>18.6</td>
<td>67*</td>
<td>8.8*</td>
</tr>
<tr>
<td></td>
<td>2. Doc(35mg)+Estramustine+Prednisone</td>
<td>44</td>
<td>18.4</td>
<td>63*</td>
<td>9.3*</td>
</tr>
<tr>
<td></td>
<td>3. Mitoxantrone + Prednisone</td>
<td>42</td>
<td>13.4</td>
<td>18</td>
<td>17.0</td>
</tr>
<tr>
<td>Tannock 2004</td>
<td>1. Doc (3-weekly)+Prednisone</td>
<td>335</td>
<td>18.9*</td>
<td>45*</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>2. Doc (weekly) + Prednisone</td>
<td>334</td>
<td>17.4</td>
<td>48*</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>3. Mitoxantrone + Prednisone</td>
<td>337</td>
<td>16.5</td>
<td>32</td>
<td>56</td>
</tr>
<tr>
<td>Petrylak 2004</td>
<td>1. Doc + Estramustine</td>
<td>386</td>
<td>17.5</td>
<td>50</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>2. Mitoxantrone + Prednisone</td>
<td>384</td>
<td>15.6*</td>
<td>27*</td>
<td>3.2*</td>
</tr>
</tbody>
</table>

* significantly different p <0.05

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**GRAPHS AND OTHER TABLES**

This review has no analyses.

---

**COVER SHEET**

**Title**
Chemotherapy for hormone-refractory prostate cancer

**Authors**
Mike Shelley, Craig Harrison, Bernadette Coles, John Staffurth, Timothy J Wilt, Malcolm D Mason

**Contribution of author(s)**
Mike Shelley: Concept, screen search, quality assessment of studies, data extraction, synthesis of tables and manuscript.
Craig Harrison: Screen search, data extraction, review manuscript.
Bernadette Coles: Developed and executed search strategy, review manuscript.
John Staffurth: Review data and manuscript.
Timothy J Wilt: Review data and manuscript.
Malcolm D Mason: Review data and manuscript.

**Issue protocol first published**
/

**Review first published**
/

**Date of most recent amendment**
10 July 2006

**Date of most recent SUBSTANTIVE amendment**
10 July 2006

**What's New**
Information not supplied by author

**Date new studies sought but none found**
Information not supplied by author