Dose Escalation Study of Intravenous Estramustine Phosphate in Combination with Paclitaxel and Carboplatin in Patients with Advanced Prostate Cancer

William Kevin Kelly, Andrew X. Zhu, Howard Scher, Tracey Curley, Mary Fallon, Susan Slovin, Lawrence Schwartz, Steve Larson, William Tong, Beryl Hartley-Asp, Cinzia Pellizzoni, and Maurizio Rocchetti

Genitourinary Oncology Service, Division of Solid Tumor, Department of Medicine [W. K. K., H. S., S. S.], Department of Nursing [T. C.], Department of Radiology [L. S.], Division of Epidemiology and Biostatistics [M. F.], Department of Pharmacology [W. T.], and Department of Nuclear Medicine [S. L.], Memorial Sloan Kettering Cancer Center, New York, New York; 10021; Department of Medicine, Joan and Sanford Weill Medical College of Cornell University, New York, New York [W. K. K., S. S.]; Hematology-Oncology, Massachusetts General Hospital, Dana-Farber/Partners Cancer, Boston, Massachusetts [A. X. Z.]; and Pharmacia Corporation, Peapack, New Jersey [B. H-A., C. P., M. R.]

ABSTRACT

Purpose: The purpose is to determine a safe weekly dose of i.v. estramustine phosphate (EMP) to combine with weekly paclitaxel and monthly carboplatin in patients with advanced prostate cancer.

Experimental Design: Patients with advanced prostate cancer (castrate and noncastrate) were administered escalating doses of weekly 1-h infusion of i.v. EMP (500–1000–1500 mg/m^2) in combination with weekly paclitaxel (100 mg/m^2 over 1 h) and i.v. carboplatin (area under the curve 1500 mg/m^2). An additional 13 patients were treated with paclitaxel (100 mg/m^2) first, followed by i.v. EMP at 1000 mg/m^2 (cohort 4), and 1500 mg/m^2 (cohort 5). No dose-limiting toxicities were seen, and cohort 5 was determined safe for Phase II studies. Thromboembolic events were observed in 9% of patients (no prophylactic coumadin was used). Plasma concentrations of EMP and metabolites increased proportionally with dose. In all cohorts, there was a slight decrease in EMP and estramustine plasma concentrations between cycles 1 and 2. Although not significant, higher levels of estramustine at cycle 2 were observed in comparison to cycle 1. Decreased clearance of paclitaxel leading to higher than expected paclitaxel plasma concentrations was observed during the first cycle of therapy. Paclitaxel plasma concentrations were lower during cycle 2. In 17 patients with androgen-independent disease, 59% had ≥50% posttherapy decline in PSA and 22% showed measurable disease regression.

Conclusions: The regimen of weekly i.v. EMP in combination with paclitaxel and carboplatin can be safely administered with hepatic toxicity being transient and reversible. Pharmacokinetic results suggest that EMP competitively inhibits the biotransformation of paclitaxel after the first administration. This effect is counterbalanced, after repeated administrations, by a possible induction of the metabolic system caused by EMP. Phase II testing is ongoing to evaluate the efficacy of this combination.

INTRODUCTION

Over the preceding 5 years, we have seen the development of more effective treatment regimens for patients with metastatic prostate cancer; however, the morbidity of the therapy can deter many physicians and patients from treatment. We have previously explored the use of weekly paclitaxel combined with oral EMP and i.v. carboplatin (TEC; Ref. 1). The rationale was based on: (a) the single agent activity profile of carboplatin (2); (b) the observation that weekly paclitaxel and carboplatin are synergistic and platelet sparing (3–5); (c) the known synergy of estramustine and paclitaxel (6); and (d) work suggesting that...

1 The abbreviations used are: EMP, estramustine phosphate; PSA, prostate-specific antigen; CT, computed tomography; MRI, magnetic resonance imaging; DLT, dose-limiting toxicity; KPS, Karnofsky performance status; BSI, bone scan index; AUC, area under the curve; MTD, maximum-tolerated dose; CYP, cytochrome P-450.
Estramustine may increase the intracellular concentration of concomitantly administered drugs by inhibiting p-glycoprotein-catalyzed drug efflux from tumor cells (7). In previous work with the combination of oral EMP with paclitaxel and carboplatin, we showed that 36 of 54 castrate metastatic prostate cancer patients (67%) had ≥50% posttherapy decline in PSA, 45% showing measurable disease regression, and a palliative benefit in the majority of patients who presented with pain (1). Mild to moderate nausea and thromboembolic events, known side effects of EMP, complicated the therapy.

Despite the convenience of the oral formulation of EMP, gastrointestinal and cardiovascular toxicity limit its use in the clinic. After oral dosing, no EMP is present in the systemic circulation, and only the dephosphorylated species of estramustine with the oxidized metabolite, estromustine, and the corresponding hydrolysis products (estradiol, estrone) can be measured in plasma (8). This first-pass formation of metabolites is thought to account, to a considerable extent, for these DLTs. To improve on oral EMP toxicity profile, Hudes et al. (9) performed a Phase I study in which high i.v. doses of EMP were administered weekly. They demonstrated that a high dose of i.v. EMP can be administered safely with a decrease in the gastrointestinal and cardiovascular adverse effects when compared with the oral EMP. In addition, high peak concentrations of active metabolites after i.v. EMP were supposed to provide an advantage over oral EMP in antimicrotubule drug combinations (9).

On the basis of these results and to improve on the safety profile of the TEC regimen, we investigated the use of i.v. weekly EMP in combination with paclitaxel and carboplatin in patients with advanced prostate cancer. The study was conducted in two parts. The first was a dose escalation study to establish a safe dose of i.v. EMP to combine with paclitaxel and carboplatin. This portion of the study included patients with castrate and noncastrate prostate cancer, and the objective was not to see if there was a beneficial effect from the chemotherapy but rather to establish a safe regimen that is feasible in multiple prostate cancer disease states. Once a safe dose was established, Phase II studies were conducted in patients with castrate metastatic disease and noncastrate disease. Here, we are reporting the results of the dose escalation study.

PATIENTS AND METHODS

Patient Eligibility and Evaluation

Patients with histologically confirmed androgen-dependent and androgen-independent prostate cancer were considered for the study. Androgen-dependent patients included: patients with locally advanced adenocarcinoma of the prostate with an estimated 3-year PSA relapse-free survival of <25% (T1a, N0, M0, or Gleason grade ≥ 7 and serum PSA ≥ 20 ng/ml; Ref. 10); patients with local relapse after radiation therapy or radical prostatectomy with measurable disease on CT or MRI scan; and patients with poor risk metastatic disease (bone scan showing ≥20 osseous lesions or visceral metastatic disease). Patients with small cell or neuroendocrine carcinoma of the prostate were also eligible. Androgen-dependent patients who fit one of the above inclusion criteria were eligible for the study if they had been on androgen ablation for <3 months.

Androgen-independent patients must have had documentation of progressive disease after the discontinuation of an anti-androgen, castrate levels of testosterone (<30 ng/ml), a life expectancy of >3 months, and no more than one prior course of chemotherapy (patients could have had one previous EMP- or taxane-based regimen), palliative radiotherapy, or radioisotope therapy. Disease progression was defined as the presence of at least one of the following events: (a) a rising PSA of ≥50% from baseline on three successive occasions; (b) new metastatic lesions on bone scan; or (c) a >25% increase in a bidimensionally measurable tumor mass. Patients who had not undergone surgical castration were continued on luteinizing hormone-releasing hormone agonists.

All patients had a KPS ≥ 70%, WBC ≥ 3500 cells/mm³, granulocytes ≥ 1500 cells/mm³, platelet count ≥ 120,000 cells/mm³, hemoglobin ≥ 8.0 g/dl, serum creatinine ≤ 2.0 mg/dl, and a baseline serum glutamic-oxaloacetic transaminase < 1.5 × the institutional normal. Patients must not have undergone major surgery, radiation therapy, chemotherapy, or immunotherapy within 4 weeks before entry. Patients could not have radioisotope therapy within 8 weeks before entry. Individuals were excluded if they had New York Heart Association class III or IV heart disease, history of ventricular arrhythmias, history of bleeding disorder, peripheral neuropathy (grade 3 or 4), central nervous system disease, active infection, insulin-dependent diabetes mellitus, or the presence of brain metastases. The Institutional Review Board approved the protocol and written informed consent was required for all patients.

The pretreatment evaluation included a complete history and physical examination with a baseline KPS. Laboratory studies included an automated blood and platelet count, serum electrolytes, comprehensive screening profile (alkaline phosphatase, lactate dehydrogenase, aspartate transaminase, blood urea nitrogen, creatinine, calcium, phosphorus, uric acid, total protein, albumin, total bilirubin, and electrolytes), testosterone level, serum acid phosphatase, and PSA. Imaging studies included an abdominal and pelvic CT or MRI scan, bone scan, and chest radiograph. All patients had a baseline electrocardiogram, and additional cardiac work-up was undertaken if the patient had a history, symptoms, or electrocardiogram changes consistent with coronary artery disease congestive heart failure. Patients with unstable coronary artery disease were not permitted in the study.

Patients obtained a weekly automated blood and platelet count before chemotherapy, and a comprehensive screening profile, acid phosphatase, and PSA were repeated every 2 weeks while on the study. Measurable disease, when present, as well as radionuclide bone scans were reevaluated at 12-week intervals.

Evaluation of Response

All patients registered were eligible for assessment of toxicity and response if they received any treatment. Toxicities were graded on the Common Toxicity Criteria from the Cancer Therapy Evaluation Program (version 2) of the National Cancer Institute (Bethesda, MD). Outcomes were assessed independently using CT or MRI scans for measurable lesions, radionuclide bone scans, and posttherapy changes in serum PSA. No overall response category was given (11). In patients with measurable disease, standard Phase II response criteria (12) were used, and radiographs were reviewed independently, with the
reviewer (L. S.) blinded to the clinical outcome. All radionuclide bone scans were reviewed independently, with the reviewer (S. L.) blinded to the clinical outcomes. The bone scans were assessed by visual comparison and scored using the BSI (13, 14). Posttherapy changes in bone scans were classified as: improvement (visual improvement in discrete osseous lesions and >10% decrease in the BSI); stable (no new osseous lesions and no more than ±10% change from the baseline BSI), and progression (any new lesion or >10% increase in the BSI).

Baseline serum PSA (Tandem-E, Hybritech, upper limit of normal range 4.0 ng/ml) was defined as the PSA within 2 weeks of initiating therapy, and changes from baseline were assessed from this level. Baseline serum PSA had to be ≥ 4 ng/ml to assess for posttherapy changes in PSA. Posttherapy changes in serum PSA were reported on the basis of the degree of change from baseline, ≥80% and ≥50% confirmed by a minimum of three consecutive values two or more weeks apart. PSA progression was defined as three consecutive increases in serum PSA to >50% above baseline or nadir serum PSA. Stable serum PSA included patients without serum PSA progression but who had <50% decline in the baseline serum PSA.

The time to progression was calculated from the start of the therapy to the off study date defined by the criteria for progression based on PSA, measurable or osseous disease, or removal from the study because of toxicity or death. The date of PSA progression was defined as the date that the first PSA rise could be confirmed by two sequential rises in the serum PSA, 2 or more weeks apart.

**Treatment**

**Dose Escalation Phase.** EMP for injection is available as a lyophilized powder of the meglumine salt in vials of 300-mg EMP (information provided by the manufacturer, Pharmacia Corporation). All patients received the i.v. EMP as a 1-h constant rate infusion administered into a central vein via a permanent venous access device such as a mediport or Hickman catheter. The protocol initially explored three different dose levels of i.v. EMP (500, 1000, and 1500 mg/m²) given weekly. Because the maximal concentrations of the two main metabolites, estramustine and estromustine, occur ~1–3 h after the start of the EMP 1-h infusion, patients were observed for the next 2 h before the administration of the weekly 1-h infusion of paclitaxel. Immediately after the completion of the paclitaxel infusion, carboplatin was administered i.v. over 30 min. Paclitaxel was administered i.v. over 1 h at 100 mg/m² weekly. The dose of carboplatin was based on the Calvert formula (15) with the target AUC of 6 mg/ml (up to a maximum of 1000 mg) every 4 weeks.

To investigate whether the order of drug administration has an effect on paclitaxel plasma concentration, improves the transient liver dysfunction observed in cohorts 1–3, and decreases the overall drug administration time, two additional cohorts of patients were added to the study. In dose levels 4 and 5 (1000 and 1500 mg/m² of i.v. estramustine, respectively), paclitaxel was given over 1 h immediately followed by the estromustine over 1 h. There was not a 2-h delay between paclitaxel and estramustine in dose levels 4 and 5. The dose of paclitaxel (100 mg/m²) and carboplatin (AUC = 6) remained constant. The regimen was planned to give weekly therapy without a treatment break. Four weeks of therapy was considered to be one cycle.

A standard dose escalation scheme was used in this study. The DLT was defined as grade 3 or 4 thrombocytopenia or neutropenia lasting ≥ 2 weeks or any grade 3 or 4 gastrointestinal or neurological toxicity occurring during the first cycle of therapy. The dose was escalated every 4 weeks if DLT was not encountered. Three to 6 patients were entered on each dose level starting at dose level 1. If 1 of 3 patients at a given dose level experienced a DLT, 3 additional patients were treated at the same dose level. Dose escalation continued if only 1 of 6 patients experienced a DLT. If 2 or 3 of the first 3 patients experienced DLT, or ≥2 of 6 patients experienced DLT at a given dose level, the MTD was determined to be the preceding dose level. The MTD or recommended Phase II dose is that with an observed incidence of DLT in no more than 1 of 6 patients. If ≤3 patients were treated at a dose under consideration as the MTD, additional patients up to a total of 6 were entered to confirm the MTD.

Preliminary included dexamethasone (20 mg p.o.) 12 and 6 h before the paclitaxel week 1, dexamethasone (8 mg p.o.) 12 h and then 6 h before paclitaxel on week 2, and dexamethasone (8 mg p.o.) 6 h before paclitaxel on weeks 3 through the end of the study. If a patient had a reaction when the dexamethasone was tapered, this patient continued with dexamethasone (20 mg p.o.) 12 and 6 h before paclitaxel. Diphenhydramine hydrochloride (50 mg i.v.) and cimetidine (300 mg i.v.) or ranitidine (50 mg i.v.) were given before the paclitaxel. All patients received appropriate antiemetics as indicated.

**Dose Modifications.** On the day of treatment, the chemotherapy was withheld if the total WBC was <3.0 cells/m³ or if the platelets were <100,000 cells/m³. Therapy was resumed once WBC were ≥ 3.0 cells/m³ and platelets were ≥ 100,000 cells/m³. If patients had WBC < 3.0 cells/m³, then the subsequent weekly dose of paclitaxel was reduced by 10 mg/m². If platelets were < 100,000 cells/m³, then the subsequent monthly carboplatin dose was reduced by 25%. For grade 3 or 4 nonhematological toxicity, the chemotherapy was withheld until these toxicities resolved to grade 0 or 1. In addition, the subsequent weekly dose of paclitaxel was reduced by 10 mg/m², and the EMP was reduced by 50% (later in the study, the decrease was to 250 mg/m²). If patients had 100,000 cells/m³, then the subsequent monthly carboplatin dose was reduced by 25%. For grade 3 or 4 nonhematological toxicity, the chemotherapy was withheld until these toxicities resolved to grade 0 or 1. In addition, the subsequent weekly dose of paclitaxel was reduced by 10 mg/m², and the EMP was reduced by 50% (later in the study, the decrease was to 250 mg/m³). There was no change for the monthly carboplatin dose for grade 3 or 4 nonhematological toxicity. If patients required greater than three dose reductions or a delay in the next weekly dose of therapy of > 3 weeks, the patient was withdrawn from the study.

**Pharmacokinetics.** Pharmacokinetic evaluation was performed during the first and second cycles of the study at the first week of therapy. To be consistent with previous studies, in all cohorts, blood samples for the determination of paclitaxel levels were drawn at baseline (before paclitaxel administration), 30, 60, 90, and 120 min and at 18 h after the initiation of paclitaxel infusion. Blood samples for the determination of EMP and metabolites were drawn: at baseline (time 0); at 2 h before the paclitaxel infusion; and approximately at 21 and 168 h after the start of EMP infusion in cohorts 1–3. They were drawn at baseline (time 0), at 2 h, and approximately at 20 and 168 h after the start of i.v. EMP infusion in cohorts 4 and 5.

Plasma, stored at −20°C until analysis, was analyzed for
paclitaxel by reverse-phase high-performance liquid chromatography, according to previously published methods (16). Pharmacokinetic analysis of paclitaxel was performed by noncompartamental methods, and AUC-time curve estimation used the linear trapezoidal rule with extrapolation to infinite time using WinNonLin version 3.1.

To evaluate further the abnormal findings in the increased levels of paclitaxel during the first cycle of therapy, the metabolites of paclitaxel (3′-p-hydroxypaclitaxel and 6β-hydroxypaclitaxel), using stored plasma from patients treated in cohorts 3 and 5, were analyzed a posteriori (i.v. EMP was 1500 mg/m^2 for both cohorts). Paclitaxel metabolites were analyzed based on the method by Schellen et al. (17), with modification for the metabolite using a Prospekt-2 (Spark-Holland)-automated sample processor interface with an Agilent LC/MS, model 1100 LC/MSD-SL. The plasma sample was filtered through a 0.45-μm filter and placed into the auto sampler. The Prospekt-2 made use of a C18-HS solid phase extraction cartridge, which was prepared by passing acetonitrile and water through the cartridge. The auto sampler picked up 50 μl of the plasma and the Prospekt-2 loaded the plasma onto the solid phase extraction cartridge, which had been washed with water, then 20% methanol/water. The Prospekt-2 then switched the mobile phase stream of 65% acetonitrile/35% of 0.1% formic acid at a flow rate of 0.4 ml/min through the solid phase extraction onto the Hypersil C18 3-μm 4.6 × 30 mm column. This was then monitored by mass spectrometry in atmospheric pressure chemical ionization-positive mode, single ion monitoring of 519 for paclitaxel and 3-hydroxytaxol, 525 for 6-hydroxytaxol. The retention times for 3-hydroxy, 6-hydroxy, and paclitaxel were 3.4, 5.6, and 7.3 min, respectively. The detection limit for paclitaxel is 7.5 ng/ml, linear to 1000 ng/ml. Because the metabolites (Gentest, Woburn, MA) are not available in large quantity, the standard curve of paclitaxel was used for the metabolites to obtain their relative amounts in plasma. The levels of EMP and its metabolites were determined in human plasma using a LC-MS-MS method with a quantitation limit of ~10 ng/ml for EMP and 2.5 ng/ml for estramustine and estro-mustine. Briefly, acetonitrile (200 μl) containing 1% acetic acid was added to human plasma (100 μl). The mixture was vortex mixed and centrifuged for 3 min at 21,000 × g. An aliquot (200 μl) was transferred to autosampler vials, and 75 μl were injected into the high-performance liquid chromatography. The compounds were separated using a Zorbax SB C18 4.6 × 150 mm, a 5-m (Hewlett Packard) analytical column and eluted in gradient conditions with a mobile phase containing acetonitrile and 2 mM ammonium acetate buffer (pH 6.8). Mass spectrometry detection was performed using a PE-Sciex API 3000 instrument in the positive ion mode. The instrument was equipped with an ion spray interface.

The AUC was used to assess whether the 3′-p-hydroxy-paclitaxel and 6β-hydroxy-paclitaxel profile were different between the two cycles. The AUC was calculated per subject, per cycle, using values recorded at times 30, 60, 90, 120, and 1080 min after administration of the drug. The difference in the AUC between cycles for each subject was computed and compared using the paired t test.

**Duration of Therapy.** Patients could receive a maximum of six cycles of therapy. However, patients with locally advanced androgen-dependent prostate cancer were considered for radical prostatectomy or radiotherapy after four cycles of therapy. Patients were prohibited from having any concomitant radiation or radioisotope therapy while on the protocol.

**Ancillary Medications.** All patients previously on luteinizing hormone-releasing hormone analogs were maintained on these medications. Patients with androgen-dependent disease received a concomitant luteinizing hormone-releasing hormone agonist while on the study.

**RESULTS**

**Patient Characteristics**

A total of 32 patients, 15 with androgen-dependent and 17 with androgen-independent disease, were treated (Table 1). The median age was 60 years (range, 49–71 years) for the androgen-dependent disease and 66 years (range, 56–76 years) for the androgen-independent disease. The median KPS was 90% for both groups. For the androgen-dependent group, there were 3 patients with bone disease only and 3 patients with soft tissue disease only, 5 patients with both bone and soft tissue disease, and 4 patients with only localized prostate cancer. For the androgen-independent group, 7 patients had bone disease only, 2 patients had soft tissue disease only, and 8 patients had both bone and soft tissue disease. The majority of the patients in the androgen-independent group were treated with 2 or more prior hormonal manipulations (82%), and 29% of the patients received prior chemotherapy or immunotherapy. The median baseline serum PSA for androgen-dependent disease and androgen-independent disease was 9.4 ng/ml (range, 0.17–797.9 ng/ml) and 235.35 ng/ml (range, 14.72–820.2 ng/ml), respectively. The remainder of the biochemical parameters are listed in Table 1. Although small cell and neuroendocrine tumors of the prostate were eligible for the study, all patients entered had documented adenocarcinoma of the prostate.

**Dose Escalation and Adverse Events**

In the five cohorts of patients, 418 doses of i.v. EMP were administered. In the first cycle of therapy 128 doses of i.v. EMP were planned, and 31 doses were held. Twenty-eight of 31 (90%) doses of i.v. EMP were withheld secondary to toxicity. The median duration of treatment was 4 months but ranged from 1 to 6 months.

**Adverse Events during Cycle 1 of Therapy**

**Cohort 1 (500 mg/m^2 EMP).** Three patients were initially entered; one patient was withheld for 3 weeks for prolonged thrombocytopenia and then taken off study. The patient with prolonged thrombocytopenia did not recover his platelet count to >100,000 cells/mm^3, and it was suspected that he had prostatic cancer involvement of the bone marrow. No bone marrow biopsy or aspirate was performed to confirm bone marrow involvement. Three additional patients were added, and no DLTs were seen.

**Cohort 2 (1000 mg/m^2 EMP).** Eight patients were treated at this dose level. One patient was removed after the first dose of therapy, secondary to a severe allergic reaction to the paclitaxel with skin desquamation, 6 patients were entered as per protocol, and 1 additional patient was added after Institu-
tional Review Board approval for therapeutic exception to expand this cohort by one patient. The later patient fit all entry criteria for the protocol. Seven patients completed 4 weeks of therapy with 1 patient having a grade 3 transaminase elevation and leukopenia for 2 weeks (DLT). One additional patient developed elevated transaminases, but this was attributed to the concomitant botanicals that he started during therapy. Before entering this study, the patient had been taking several botanicals and had abnormal transaminases. These botanicals were discontinued with normalization of his liver function tests. After starting the chemotherapy, the patient started back on his alternative medications on his own and developed severe transaminase elevation. The botanicals were discontinued again, and the patient was rechallenged without additional transaminase elevation. It was determined that this dose level was safe, and the dose was escalated.

Cohort 3 (1500 mg/m$^2$ EMP). Of the first 3 patients, 1 patient developed grade 3 leukopenia and hepatic dysfunction, and the cohort was expanded. Two additional patients were treated and 1 developed grade 3 transaminase elevation associated with severe nausea. Additional accrual to this cohort was discontinued. A preliminary pharmacokinetic analysis of the data from patients enrolled in the 3 cohorts showed abnormally high peak plasma concentrations of paclitaxel, suggesting decreased metabolism of the drug. The initial protocol built in a 2-h lapse between the administration of i.v. EMP and paclitaxel to allow the EMP metabolites, estramustine and estromustine, to reach maximal concentrations. Because the order of the drug administration may have had a role in decreasing the metabolism of paclitaxel, the protocol was amended to reverse the order of administration of i.v. EMP and paclitaxel. The next two cohorts (cohort 4 and 5) explored giving the paclitaxel first, followed by the i.v. EMP and then the carboplatin.

Cohort 4 (1000 mg/m$^2$ EMP after Paclitaxel). Seven patients were entered on this dose level. One patient developed a central venous catheter thrombosis complicated by catheter infection and sepsis without neutropenia after the first dose of chemotherapy. The thrombosis and infection were not felt to be related to the study drugs but rather a complication of the venous catheter. This patient was taken off the study and replaced. No other DLTs were seen.

Cohort 5 (1500 mg/m$^2$ EMP after Paclitaxel). Six patients were treated, and 3 patients had grade 3 leukopenia that recovered in <1 week. No other grade 3 or 4 leukopenia or other grade 3 or 4 toxicity was seen in the remainder of patients. This dose level and order was determined to be safe and was selected for the Phase II studies.

### Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>A.</th>
<th>Androgen dependent (n = 15)</th>
<th>Androgen independent (n = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone disease only</td>
<td>3</td>
<td>Bone disease only</td>
</tr>
<tr>
<td>Soft tissue disease only</td>
<td>3</td>
<td>Soft tissue disease only</td>
</tr>
<tr>
<td>Localized disease only</td>
<td>4</td>
<td>Bone and soft tissue</td>
</tr>
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<td>Median age, years</td>
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<td>Median age, years</td>
</tr>
<tr>
<td>Range</td>
<td>49–71</td>
<td>Range</td>
</tr>
<tr>
<td>Median KPS</td>
<td>90</td>
<td>Median KPS</td>
</tr>
<tr>
<td>Range</td>
<td>80–100</td>
<td>Range</td>
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<tr>
<th>B.</th>
<th>Androgen dependent</th>
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</tr>
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<tbody>
<tr>
<td>Prostatectomy</td>
<td>1</td>
<td>Prostatectomy</td>
</tr>
<tr>
<td>None</td>
<td>14</td>
<td>None</td>
</tr>
<tr>
<td>Radiation</td>
<td>9</td>
<td>Radiation</td>
</tr>
<tr>
<td>None</td>
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</tr>
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</tr>
<tr>
<td>None</td>
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<td>None</td>
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<tr>
<th>C.</th>
<th>Baseline biochemical parameters</th>
<th>Medians (range)</th>
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<tr>
<td>Hemoglobin</td>
<td>14.9 (10.7–16.5)</td>
<td>13 (9.6–15.8)</td>
</tr>
<tr>
<td>Aspartate aminotransferase</td>
<td>23 (14–47)</td>
<td>21 (12.0–37.0)</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1 (0.7–1.3)</td>
<td>1 (0.8–1.9)</td>
</tr>
<tr>
<td>Acid phosphate</td>
<td>2.2 (0.6–27.8)</td>
<td>11 (1.3–95.6)</td>
</tr>
<tr>
<td>PSA</td>
<td>9.4 (17–797.9)</td>
<td>235.35 (14.72–820.2)</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>76 (48–288)</td>
<td>130 (50–975)</td>
</tr>
</tbody>
</table>

* Number of patients (n = 32).
The results of the previously reported study of oral EMP, paclitaxel (100 mg/m²), and carboplatin (AUC = 6) (1).

### Overall Adverse Events

There was a cumulative effect from the therapy manifested as increased fatigue and malaise, but patients remained functional with minimal impact on performance status (Table 2). This could be attributed to the hypophosphatemia that occurred in 63% of the patients. However, phosphorous replacement did not substantially improve the patients’ symptoms. Leukopenia was seen in 28% of the patients, but there were no neutropenic fevers requiring hospitalization. Low-grade (≤2) transaminitis was commonly seen in patients and usually occurred during the first 2–3 weeks of treatment. This was transient, with normalization of the values within 1–2 weeks, but it did require the dose of i.v. EMP to be withheld. It was uncommon to see elevation of transaminases after the first cycle of therapy. Although the cohorts were small, there was a trend to increase in the frequency of grade 1 and 2 transaminitis with the higher doses of i.v. EMP (1500 mg/m²). There was no relationship found between other concomitant medications (except in 1 patient who was taking multiple botanicals) that the patients were taking and incidence of hepatic dysfunction.

Three patients (9%) developed deep venous thrombosis, 3 developed central catheter thrombosis (9%), and 2 patients had catheter-related infections requiring hospitalization and antibiotics. One patient did have transient cardiac ischemia that was treated medically without additional complication, but he was removed from the study. No pulmonary embolisms or cerebral vascular accidents were seen.

Chronic nail changes and sloughing of the nails were commonly seen in patients who had three or more cycles of therapy. Low-grade neurosensory changes occurred in 7% (23%) of patients.

### Pharmacokinetic Evaluation

#### Paclitaxel Plasma Concentrations

Pharmacokinetic evaluation was performed during the first cycle of treatment. Midway through the first cohort of patients, the study was amended to perform pharmacokinetics during the second cycle of therapy. Consequently, only 1 patient from cohort 1 had paclitaxel pharmacokinetic data for cycle 2. The mean ± SDs for the maximum plasma paclitaxel concentration (\(C_{\text{max}}\)), paclitaxel

### Table 2  Adverse events

<table>
<thead>
<tr>
<th>Grade</th>
<th>0</th>
<th>1+</th>
<th>2+</th>
<th>3+</th>
<th>4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac/thromboembolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombosis/lower Extremity</td>
<td>28 (88%)</td>
<td>0 (0%)</td>
<td>1 (3%)</td>
<td>3 (9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Thrombosis/media-port</td>
<td>29 (91%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Catheter-related infection</td>
<td>30 (94%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Anemia</td>
<td>7 (22%)</td>
<td>11 (34%)</td>
<td>13 (41%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>7 (22%)</td>
<td>4 (12%)</td>
<td>12 (38%)</td>
<td>9 (28%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Thrombocytopenia</td>
<td>11 (34%)</td>
<td>18 (57%)</td>
<td>1 (3%)</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>2 (6%)</td>
<td>3 (10%)</td>
<td>21 (66%)</td>
<td>6 (19%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>6 (19%)</td>
<td>2 (6%)</td>
<td>3 (9%)</td>
<td>20 (63%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>14 (44%)</td>
<td>16 (50%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>9 (28%)</td>
<td>19 (60%)</td>
<td>1 (3%)</td>
<td>3 (9%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Liver toxicity (bilirubin)</td>
<td>22 (68%)</td>
<td>4 (13%)</td>
<td>5 (16%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Liver toxicity (aspartate aminotransferase)</td>
<td>11 (34%)</td>
<td>13 (41%)</td>
<td>4 (13%)</td>
<td>4 (12%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Liver toxicity (alanine aminotransferase)</td>
<td>23 (72%)</td>
<td>18 (60%)</td>
<td>1 (3%)</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (31%)</td>
<td>15 (47%)</td>
<td>7 (22%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24 (75%)</td>
<td>2 (6%)</td>
<td>4 (13%)</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (6%)</td>
<td>20 (63%)</td>
<td>10 (31%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Neurosensory</td>
<td>7 (23%)</td>
<td>23 (71%)</td>
<td>0 (0%)</td>
<td>2 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Skin rash/urticaria</td>
<td>23 (71%)</td>
<td>7 (23%)</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

### Table 3  Pharmacokinetic parameters of paclitaxel for cycles 1 and 2

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Cohort</th>
<th>n</th>
<th>Mean i.v. EMP dose (mg/m²)</th>
<th>Mean paclitaxel dose (mg/m²)</th>
<th>Mean (C_{\text{max}}) (µg/ml)</th>
<th>Mean (C_{1\text{hAUC}}) (µg x h/ml)</th>
<th>Mean AUC (µg x h/ml)</th>
<th>Mean (V_{\text{max}}) (liter/h/m²)</th>
<th>Mean CI (liter/h/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>6</td>
<td>500</td>
<td>100</td>
<td>4.9 ± 1.1</td>
<td>0.035 ± 0.02</td>
<td>10.0 ± 1.9</td>
<td>21.3 ± 5.4</td>
<td>10.3 ± 2.2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>1000</td>
<td>100</td>
<td>3.8 ± 0.8</td>
<td>0.062 ± 0.02</td>
<td>9.1 ± 1.7</td>
<td>31.8 ± 5.0</td>
<td>11.3 ± 2.2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1500</td>
<td>100</td>
<td>3.4 ± 1.0</td>
<td>0.065 ± 0.03</td>
<td>8.9 ± 2.2</td>
<td>39.0 ± 1.8</td>
<td>11.7 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>1000</td>
<td>100</td>
<td>4.0 ± 1.1</td>
<td>0.051 ± 0.02</td>
<td>9.5 ± 2.3</td>
<td>26.4 ± 5.5</td>
<td>11.1 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>1500</td>
<td>100</td>
<td>3.5 ± 1.1</td>
<td>0.048 ± 0.03</td>
<td>8.0 ± 1.9</td>
<td>40.6 ± 13.0</td>
<td>12.9 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>2*</td>
<td>100</td>
<td>90</td>
<td>2.0</td>
<td>0.023</td>
<td>4.5</td>
<td>53.7</td>
<td>22.3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>2*</td>
<td>917</td>
<td>93</td>
<td>2.5 ± 0.5</td>
<td>0.025 ± 0.01</td>
<td>4.9 ± 0.9</td>
<td>55.6 ± 20.1</td>
<td>19.3 ± 3.2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>1200</td>
<td>92</td>
<td>3.4 ± 1.2</td>
<td>0.046 ± 0.02</td>
<td>6.7 ± 1.1</td>
<td>47.8 ± 35.0</td>
<td>13.9 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>1000</td>
<td>92</td>
<td>2.8 ± 0.7</td>
<td>0.028 ± 0.01</td>
<td>5.2 ± 1.0</td>
<td>45.9 ± 14.5</td>
<td>18.1 ± 2.7</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>1500</td>
<td>92</td>
<td>2.6 ± 1.0</td>
<td>0.044 ± 0.01</td>
<td>5.0 ± 1.2</td>
<td>78.1 ± 27.0</td>
<td>19.5 ± 6.8</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>*Oral</td>
<td>3</td>
<td>10 mg/kg</td>
<td>100</td>
<td>2.33 ± 0.43</td>
<td>0.026 ± 0.005</td>
<td>5.19 ± 0.46</td>
<td>41.8 ± 18.3</td>
<td>18.8 ± 1.66</td>
</tr>
</tbody>
</table>

* Dose of EMP/paclitaxel adjusted as per protocol.

+ The results of the previously reported study of oral EMP, paclitaxel (100 mg/m²), and carboplatin (AUC = 6) (1).
taxel concentration at 18 h ($C_{18\,h}$), AUC, volume of distribution ($V_{dss}$), and total clearance ($Cl$) are listed in Table 3. During the first cycle of therapy, the $C_{\text{max}}$, $C_{18\,h}$, and AUC for paclitaxel varied minimally as the various doses of i.v. EMP. Reversing the order of administering paclitaxel and EMP also did not have a substantial effect on these parameters. However, the $C_{\text{max}}$, $C_{18\,h}$, and AUC tended to be higher in patients who were treated with the i.v. formulation of EMP when compared with patients who were treated with the oral EMP in combination with the same fixed doses of paclitaxel and carboplatin (1). During cycle 2, $C_{\text{max}}$, $C_{18\,h}$, AUC, and Cl were similar to the values found in the oral study (Table 3). To understand better the rationale for the variations of plasma concentration during cycles 1 and 2, plasma samples from 5 of 11 patients from cohorts 3 and 5 were retrospectively evaluated for the active metabolites of paclitaxel. (Six of these 11 patients had insufficient plasma to perform the analysis.) It was suspected that any changes in the metabolites would be detected in these two cohorts because both received the highest doses of i.v. EMP. Fig. 1 shows the mean plasma concentration versus time profiles for cycle 1 and 2 for (a) paclitaxel, (b) $3'-p$-hydroxy-paclitaxel, and (c) $6a$-hydroxy-paclitaxel. Both metabolites showed a decline after the first cycle of therapy, but the decrease was greater for the levels of $6a$-hydroxy-paclitaxel. Paired test applied to the AUC data of $6a$-hydroxy-paclitaxel available for patients both at cycles 1 and 2 ($n = 5$) confirmed a significant statistical difference between the two cycles ($P < 0.01$).

**EMP and Metabolite Plasma Levels.** The pharmacokinetics of EMP and metabolites after i.v. EMP administration has been extensively evaluated by Hudes et al. (9). On the basis of these studies, a limited plasma sampling strategy for EMP and metabolites was used here for a monitoring of plasma levels. The mean ± SD plasma levels of EMP and its metabolites estramustine and estromustine at 2 h, between 20 and 21 h, and 168 h after the first weekly treatment at cycles 1 and 2 are summarized in Table 4. There was a rapid decline in the plasma concentration of EMP, but clinically relevant concentrations of the drug were still measured at 20–21 h postinfusion. Estramustine and estromustine showed detectable levels before subsequent administration, as well as before the second cycle of treatment in accordance with the long terminal half-life measured in the Phase I study by Hudes et al. (9). In cycle 1, plasma concentrations of EMP and metabolites increased proportionally with dose. In all cohorts, there was a minimal increase in EMP and estramustine plasma concentrations between cycles 1 and 2. Although not significant, higher levels of estromustine at cycle 2 were observed in comparison to cycle 1. At cycle 2, a minimal decrease in EMP plasma concentrations compared with cycle 1 was observed at 20–21 h.

**Posttherapy Outcomes for Patients**

Seventeen patients with androgen-independent disease were eligible for assessment of outcome after therapy. The treatment outcomes for androgen-independent patients are outlined below and in Table 5. Of the 15 androgen-dependent patients, 4 had poor risk locally advanced prostate cancer and subsequently received external beam radiotherapy or radical prostatectomy after they completed four cycles of chemotherapy. The remaining 11 androgen-dependent patients had poor risk metastatic prostate cancer and were continued on androgen ablation after the completion of the chemotherapy. The follow-up for these 15 androgen-dependent patients treated is premature and their outcomes are not available.

**Posttherapy Changes in PSA.** Seventeen androgen-independent patients had elevated PSA before therapy, 10 (59%) had a $\geq 50\%$ posttherapy, and 8 (47%) of those patients had $\geq 80\%$ posttherapy decline in PSA. All patients initially relapsed with a rising PSA, and the median time to progression was 5 months (range, 1–7 months).

**Measurable Disease.** Nine androgen-independent patients had measurable soft tissue disease, 2 (22%) had a partial response, and 5 had stable disease.
Thrombosis with the i.v. EMP compared with 25% of the patients. In contrast, only 9% of the patients developed a deep venous thrombosis with the oral EMP, depending on the use of oral or i.v. EMP. There was an improvement in gastrointestinal symptoms with a decrease in severe nausea (grade 3 or 4) associated with the i.v. EMP compared with the oral EMP study. Similar to the oral EMP study, a quarter of the patients continued with low-grade nausea. In contrast, only 9% of the patients developed a deep venous thrombosis with the i.v. EMP compared with 25% of the patients treated with oral EMP (1). This improvement was offset by the development of central line catheter thrombosis in 3 patients (9%) and catheter-related infection that required hospitalization in an additional 2 patients.

Osteosarcoma. Fifteen androgen-independent patients had metastatic disease to the bone, and 2 patients had improvement in the bone scan with a decrease in the BSI. Nine had stable bone scans throughout the therapy. The changes in the bone scan paralleled the changes in the PSA.

**DISCUSSION**

The current study showed that weekly infusions of i.v. EMP in combination with paclitaxel and carboplatin can be given safely to patients. However, the toxicity profiles did differ depending on the use of oral or i.v. EMP. There was an improvement in gastrointestinal symptoms with a decrease in severe nausea (grade 3 or 4) associated with the i.v. EMP compared with the oral EMP study. Similar to the oral EMP study, a quarter of the patients continued with low-grade nausea. In contrast, only 9% of the patients developed a deep venous thrombosis with the i.v. EMP compared with 25% of the patients treated with oral EMP (1). This improvement was offset by the development of central line catheter thrombosis in 3 patients (9%) and catheter-related infection that required hospitalization in an additional 2 patients.

Transient elevation of the hepatic enzymes (aspartate aminotransferase and alanine aminotransferase) was common with the i.v. administration of estramustine and usually peaked in the first 2–3 weeks of the therapy. Those patients who developed transaminasitis had the i.v. EMP withheld for 1–2 weeks and, subsequently, were restarted on the therapy with minimal hepatic dysfunction or complications. Hepatic toxicity appeared to be related to the dose of i.v. EMP administered, with an increase in frequency of grade 2 liver dysfunction at the higher doses of IV EMP, but the proportion of patients with more severe hepatic dysfunction (grade 3 or 4) did not increase with the dose. There was no relationship between the development of transaminasitis and the order of drug administration or concomitant prescribed medications. However, 1 patient’s hepatic dysfunction was associated with the use of botanicals, underlining the importance of monitoring all supplements that patients take because these may contribute to the toxic effects of therapy.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Analyte</th>
<th>Cohort 1 (500 mg/m² EMP) C₂₀-h (µg/ml) Mean ± SD</th>
<th>Cohort 2 (1000 mg/m² EMP) C₂₀-h (µg/ml) Mean ± SD</th>
<th>Cohort 3 (1500 mg/m² EMP) C₂₀-h (µg/ml) Mean ± SD</th>
<th>Cohort 4 (1000 mg/m² EMP) C₂₀-h (µg/ml) Mean ± SD</th>
<th>Cohort 5 (1500 mg/m² EMP) C₂₀-h (µg/ml) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EMP</td>
<td>0.45 ± 0.24</td>
<td>1.42 ± 0.74</td>
<td>3.16 ± 1.31</td>
<td>0.96 ± 0.41</td>
<td>2.53a</td>
</tr>
<tr>
<td></td>
<td>Estramustine</td>
<td>0.05 ± 0.01</td>
<td>0.13 ± 0.05</td>
<td>0.23 ± 0.08</td>
<td>0.16 ± 0.05</td>
<td>0.37a</td>
</tr>
<tr>
<td></td>
<td>Estramustine</td>
<td>0.16 ± 0.05</td>
<td>0.34 ± 0.09</td>
<td>0.53 ± 0.15</td>
<td>0.40 ± 0.16</td>
<td>0.75a</td>
</tr>
<tr>
<td>2</td>
<td>EMP</td>
<td>0.28 ± 0.09</td>
<td>0.52 ± 0.32b</td>
<td>1.73 ± 1.14b</td>
<td>0.42 ± 0.33</td>
<td>0.97 ± 0.24</td>
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<tr>
<td></td>
<td>Estramustine</td>
<td>0.04 ± 0.01</td>
<td>0.10 ± 0.03b</td>
<td>0.25 ± 0.14b</td>
<td>0.14 ± 0.01</td>
<td>0.25 ± 0.09</td>
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<tr>
<td></td>
<td>Estramustine</td>
<td>0.21 ± 0.01</td>
<td>0.42 ± 0.09b</td>
<td>0.89 ± 0.26b</td>
<td>0.58 ± 0.17</td>
<td>0.92 ± 0.36</td>
</tr>
</tbody>
</table>

a Only 1 patient assessable for drug levels.

b One patient received 500 mg/m² EMP dose. Levels were mediated after normalization to 1500 mg/m² EMP dose.

c One patient received 750 mg/m² EMP dose. Levels were mediated after normalization to 1500 mg/m² EMP dose.

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Analyte</th>
<th>Cohort 1 (500 mg/m² EMP) C₉₀-h (µg/ml) Mean ± SD</th>
<th>Cohort 2 (1000 mg/m² EMP) C₉₀-h (µg/ml) Mean ± SD</th>
<th>Cohort 3 (1500 mg/m² EMP) C₉₀-h (µg/ml) Mean ± SD</th>
<th>Cohort 4 (1000 mg/m² EMP) C₉₀-h (µg/ml) Mean ± SD</th>
<th>Cohort 5 (1500 mg/m² EMP) C₉₀-h (µg/ml) Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Estramustine</td>
<td>0.01 ± 0.003</td>
<td>0.02 (n = 1)</td>
<td>NAb</td>
<td>0.02 ± 0.01</td>
<td>0.04 ± 0.001</td>
</tr>
<tr>
<td></td>
<td>Estramustine</td>
<td>0.05 ± 0.001</td>
<td>0.06 (n = 1)</td>
<td>NAb</td>
<td>0.09 ± 0.06</td>
<td>0.15 ± 0.02</td>
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<td>2</td>
<td>Estramustine</td>
<td>NA</td>
<td>0.02 ± 0.001</td>
<td>0.07 ± 0.06</td>
<td>0.03 ± 0.01</td>
<td>0.04 ± 0.02</td>
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<tr>
<td></td>
<td>Estramustine</td>
<td>NA</td>
<td>0.12 ± 0.01</td>
<td>0.35 ± 0.22</td>
<td>0.28 ± 0.15</td>
<td>0.39 ± 0.30</td>
</tr>
</tbody>
</table>

a Only few patients showed detectable EMP levels at 168-h postdosing, and they were excluded by the calculation of the mean for estramustine and estramustine.

b NA, not available.
Table 5  Patient outcomes for androgen-independent patients

<table>
<thead>
<tr>
<th>A. 17 patients evaluable for PSA response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>≥80%</td>
</tr>
<tr>
<td>≥50%</td>
</tr>
<tr>
<td>Stable</td>
</tr>
<tr>
<td>POD</td>
</tr>
<tr>
<td>Nonassessable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. 15 patients evaluable for bone response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>Improved</td>
</tr>
<tr>
<td>Stable</td>
</tr>
<tr>
<td>POD</td>
</tr>
<tr>
<td>Nonassessable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. 9 patients evaluable for soft tissue response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcome</td>
</tr>
<tr>
<td>PR*</td>
</tr>
<tr>
<td>Stable</td>
</tr>
<tr>
<td>POD</td>
</tr>
<tr>
<td>Nonassessable</td>
</tr>
</tbody>
</table>

*PR, partial response; POD, progression of disease.

Pharmacokinetic analysis revealed that plasma concentrations of EMP and its metabolites at cycle 1 increased proportionally with dose. In all cohorts, there was a slight decrease in EMP and estramustine plasma concentrations between cycles 1 and 2. Although not significant, higher levels of estramustine at cycle 2 were observed in comparison to cycle 1. Accordingly, Hudes et al. (9) observed an increase in EMP clearance after multiple i.v. weekly dosing. Because the effects of the i.v. EMP could alter the pharmacokinetics of paclitaxel, plasma samples for paclitaxel were taken during the first and second cycles of therapy. The sampling time points were identical to the prior Phase I study with oral EMP, paclitaxel, and carboplatin (1). During the first cycle of therapy, there was minimal intracohort variability in plasma paclitaxel pharmacokinetic parameters. Compared with the results from the previous study in which equivalent doses of paclitaxel and carboplatin were given combined with oral EMP, Cmax, and AUC of paclitaxel were 1.5–2 times higher. In cycle 2, the pharmacokinetic parameters, including the AUC, returned to the levels seen in the oral EMP studies. The cause of these changes was not initially clear, but it was known that paclitaxel undergoes oxidative metabolism through the CYP enzymes. Paclitaxel is metabolized by CYP 3A4 and CYP 2C8 to 3′-p-hydroxypaclitaxel and 6α-hydroxyxypaclitaxel, respectively. 3′-p-Hydroxypaclitaxel and 6α-hydroxyxypaclitaxel are additionally metabolized to a common metabolite, 6α,3′-p-dihydroxypaclitaxel by CYP 2C8 and CYP 3A4, respectively (18, 19). CYP 3A4 is known to be involved in the metabolism of EMP (20), and recent in vitro studies indicate that EMP, estramustine, and estramustine (at 100 μM concentration) are able to inhibit CYP-mediated oxidations, especially those of CYP 3A4 (21). Prior studies with oral EMP did show a trend for increased paclitaxel concentrations when oral EMP was combined to paclitaxel, but this seems to be more pronounced with the i.v. EMP because much higher concentrations of EMP and its metabolites were present concomitantly with highest concentrations of paclitaxel. During cycle 2, plasma concentrations of paclitaxel returned to the expected values. These findings suggest that i.v. EMP competitively inhibits the biotransformation of paclitaxel after the first administration. This effect is counterbalanced, after repeated administrations, by possible induction of the metabolic system caused by EMP. To substantiate this hypothesis, the paclitaxel metabolites were studied in two cohorts of patients. The results showed a minimal decrease in 3′-p-hydroxypaclitaxel and substantial decrease in 6α-hydroxyxypaclitaxel during the second cycle of therapy. This would imply that the i.v. EMP initially competed for the CYP 3A4 decreasing the metabolism of paclitaxel and increasing the plasma concentration of paclitaxel. After repeated doses of IV EMP and paclitaxel, there was a marked decrease in the ratio of 6α-hydroxyxypaclitaxel to 3′-p-hydroxypaclitaxel in cycle 2, suggesting an increased metabolism of 6α-hydroxyxypaclitaxel by CYP 3A4. Consistent with these findings are the lower plasma concentrations of EMP during cycle 2 of therapy. The possible induction of CYP 3A by EMP after repeated administration is also supported from the data of a previous study (M. Rocchetti, personal communication) in which an increase in the 6α-hydroxycortisol to cortisol urinary ratio was observed. Modification of paclitaxel metabolism were also observed after repeated administration of prednisolone, an inducer of CYP3A4 (18).

The contribution of carboplatin or other concomitant medications such as the antiemetics or Decadron are unlikely to explain these changes because these agents where given identically in both the oral and i.v. EMP studies. The only difference in these studies was the use of the i.v. formulation of EMP, which appears to have a somewhat important impact on hepatic metabolism of paclitaxel. Petrylak et al. (22) have combined i.v. EMP with weekly docetaxel and have also found increased levels of docetaxel at 24 h after dosing (personal communication and updated abstract ASCO 2002). This would be consistent with our data because also docetaxel is principally metabolized through CYP 3A4.

Antitumor effects were observed in this study with 59% of the patients having a ≥50% posttherapy decline in PSA and 22% of the patients having measurable disease regression. Resolution of osseous lesions on radionuclide scans was also documented. Phase II studies are ongoing to evaluate the efficacy and safety profile of this regimen.

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