Phase II Trial of Paclitaxel, Estramustine, Etoposide, and Carboplatin in the Treatment of Patients with Hormone-Refractory Prostate Carcinoma

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BACKGROUND. Preclinical data suggest that the combination of intravenous (i.v.) paclitaxel, carboplatin, oral etoposide, and oral estramustine (TEEC) has significant activity in patients with advanced, hormone-refractory prostate carcinoma. The authors conducted this clinical trial to evaluate the addition of carboplatin to the three-drug combination of paclitaxel, estramustine, and etoposide (TEE).

METHODS. Twenty patients with carcinoma of the prostate that was progressing despite hormone therapy were enrolled on this Phase II trial. Patients were treated with oral estramustine, 280 mg three times daily, and oral etoposide, 50 mg/m^2, once daily on Days 1–7, with i.v. paclitaxel, 135 mg/m^2, over 1 hour followed by carboplatin (area under the curve, 5) on Day 2 of each 21-day treatment cycle. Patients were evaluated for response after three cycles, and three additional cycles were given to responding or stable patients.

RESULTS. Nineteen patients were evaluable for response, and 12 patients had measurable disease at baseline. The measurable response rate was 58% (7 of 12 patients; 95% confidence interval [95% CI], 28–85%), and all of those were partial responses. Eleven patients had decreases > 50% from their baseline prostate specific antigen levels during therapy, for a response rate of 58% (95% CI, 34–80%) by this criterion. The median time to disease progression was 5.5 months, with a median survival of 14.2 months. Major toxicities included Grade (according to version 2 of the National Cancer Institute Common Toxicity Criteria) 4 neutropenia in 4 patients, Grade 4 thrombocytopenia in 4 patients, and anemia ≥ Grade 3 in 4 patients. One patient had a deep vein thrombosis.

CONCLUSIONS. The combination of TEEC was active in patients with hormone-refractory prostate carcinoma. The regimen was tolerable, with primarily hematologic toxicity. The addition of carboplatin to TEE did not appear to add to the efficacy of the three-drug combination of antimicrotubule agents. *Cancer* 2003;98: 269–76. © 2003 American Cancer Society.

KEYWORDS: hormone-refractory prostate carcinoma, clinical trial, paclitaxel, estramustine, etoposide, carboplatin.

Adenocarcinoma of the prostate continues to be a major cause of morbidity and mortality in men. Although hormone therapy initially is highly effective in treating symptoms and lowering prostate specific antigen (PSA) levels, the median length of response in men with metastatic disease is in the range of 18–24 months.[1] Recent studies have demonstrated that estramustine-based regimens have significant activity in patients with advanced prostate carcinoma, although a positive impact on overall survival has yet to be demonstrated.[2–5]

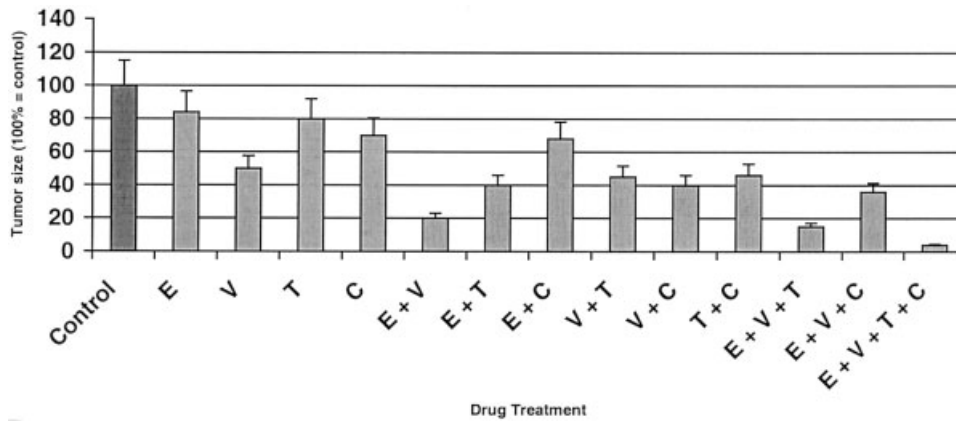Estramustine phosphate, a combination of estradiol and nitrogen

FIGURE 1. The effect of drug treatment on the growth of subcutaneously implanted Mat-LyLu cells. One million cells were injected on Day 0. Animals were killed and tumors were excised on Day 14. Combinations of agents demonstrated a wide range of activity. The combination of estramustine (E), etoposide (V), paclitaxel (T), and carboplatin (C) inhibited tumor growth by 96% compared with the next best combination of estramustine, etoposide, and paclitaxel (85% inhibition; $P < 0.05$). Bars indicate standard errors.

mustard, has demonstrated effectiveness in several models of prostate carcinoma and has synergy with other antimicrotubule agents.[6] Estramustine exerts its cytotoxicity by binding directly both microtubule-associated proteins and tubulin.[7] Preclinical models reveal that estramustine acts synergistically with etoposide at low levels in the Mat-LyLu (MLL) subline of Dunning rat prostate adenocarcinoma cells and in an in vivo model.[8] Three Phase II studies have demonstrated that the combination of estramustine and etoposide has a soft tissue response rate of 40–50%, with at least 50% of patients showing decreases $\geq$ 50% in PSA levels compared with baseline levels.[9–11] The addition of estramustine to the vinca alkaloid, vinblastine, has shown synergistic effects on antimitotic activity in vitro.[12,13] Three Phase II studies have demonstrated that the combination has a soft tissue response rate of 15–40%, with 40–60% of patients showing decreases $\geq$ 50% in PSA levels compared with baseline levels.[14–16] With the development of the taxanes and their ability to stabilize microtubules irreversibly, in vitro studies again demonstrated a synergistic effect when paclitaxel was used in combination with estramustine on the DU145 prostate carcinoma cell line.[17] The synergistic effect was seen with both wild type and estramustine-resistant sublines of DU145. A Phase II trial combining estramustine and a 96-hour infusion of paclitaxel demonstrated that 4 of 9 patients with measurable disease had a response, and > 50% of patients had decreases $\geq$ 50% in PSA levels compared with baseline levels.[6]

Given the potential effectiveness of estramustine in prostate carcinoma and its synergy with other antimicrotubule agents, we conducted a Phase II trial of intravenous (i.v.) paclitaxel, oral estramustine, and oral etoposide (TEE) in 37 patients with hormone-refractory prostate carcinoma (HRPC).[2] A response rate of 45% (10 of 22 patients) was demonstrated in patients with measurable disease. In addition, 65% of

patients had decreases $\geq$ 50% from their baseline PSA levels. The therapy was tolerated well, with leukopenia and anemia as the major toxicities. Serial measurements of quality of life using the Functional Assessment of Cancer Therapy-Prostate instrument showed no significant change during therapy.

Based on these data, this three-drug combination of antimicrotubule agents clearly has activity in HRPC. Unfortunately, all of the patients eventually had disease progression, and most died of their prostate carcinoma. The activity of this regimen, however, makes it a good starting point for the exploration of additional combinations that may capitalize on synergistic interactions between the agents. Although carboplatin has little or no evidence of activity as a single agent in patients with prostate carcinoma,[18] platinum compounds are synergistic when combined with taxanes in other tumor types.[19–21] Experiments using these agents in vitro against the rat prostate carcinoma cell line MLL and the human prostate carcinoma cell line PC-3 demonstrated significant additive effects between the agents. The most significant growth inhibition was seen when all four agents were used together (data not shown). These data prompted us to perform preclinical in vivo testing of the agents alone and in combination to determine their effect on prostate carcinoma cell growth. The results of these experiments are shown in Figure 1. All of the agents inhibited MLL cell growth significantly compared with control, with etoposide demonstrating the most single-agent activity ($P < 0.001$). The combination of estramustine and etoposide inhibited tumor growth by 80% compared with control ($P < 0.001$). The addition of paclitaxel to these two drugs resulted in growth inhibition of 85% compared with control. Adding carboplatin to this combination inhibited tumor growth by 96%, which is significant compared with the next best combination of estramustine, etoposide, and paclitaxel ($P < 0.05$). Similar observations led investigators at Memorial

Sloan Kettering Cancer Center (MSKCC) to combine carboplatin with paclitaxel, and estramustine with the estramustine given on a 5-day schedule.[22] The overall rate by PSA criteria was 67% in the 56 patients enrolled on that dose escalation study. Based on these data, we conducted the current Phase II trial to assess the benefit of adding carboplatin to i.v. paclitaxel, with a shortened course of oral estramustine and oral etoposide (TEEC). Efficacy and toxicity were the primary endpoints of the study.

MATERIALS AND METHODS
Materials
Estramustine, etoposide, paclitaxel, and carboplatin were obtained the hospital pharmacy. Each was stored according to the manufacturer's recommendations. Estramustine was prepared as a stock solution of 100 mg/mL in 100% ethanol and was stored in a refrigerator.

Cell Cultures
The metastatic MLL prostate carcinoma subline of the Dunning R-3327 rat prostate adenocarcinoma cell line was obtained from Dr. John Isaacs (Johns Hopkins University, Baltimore, MD). The cells were grown and maintained in RPMI-1640 medium containing 10% fetal bovine serum and 1% penicillin-streptomycin.

Animals
Male Copenhagen rats were obtained from Harlan Sprague-Dawley (Indianapolis, IN). Methoxyflurane (Pittman-Moore, Washington Crossing, NJ) was used as inhalational anesthetic for injections.

Experimental Treatments
Animals (minimum, six per group) were injected with 1,000,0000 MLL cells (total volume, 0.1 mL) subcutaneously into the right flank on Day 0 based on a protocol approved by the University of Michigan. Estramustine was given intraperitoneally at a dose of 10 mg/kg on Days 4–13. Etoposide was given at an intraperitoneal dose of 50 mg/kg on Days 4–13. Paclitaxel was given at a dose of 135 mg/M^2 i.v. on Days 4 and 10. Carboplatin was given at a dose of 400 mg/M^2 i.v. on Days 4 and 10. Tumor size was followed by caliper measurement along two axes and by final tumor weight on Day 14, when animals were killed by carbon dioxide inhalation.

Patients
Eligible patients were required to have a histologic diagnosis of adenocarcinoma of the prostate with progressive disease after receiving standard hormone therapy. All patients who were treated previously with an antiandrogen were required to undergo antiandrogen withdrawal. Patients were required to be off all antiandrogens for at least 4 weeks with further evidence of disease progression after cessation of the antiandrogen. Patients also were required to have a performance status of 0, 1, or 2 on the Zubrod scale with a life expectancy $\geq$ 12 weeks and adequate bone marrow (absolute neutrophil count [ANC] $\geq$ 1500/m^3 and platelet count $\geq$ 100,000/m^3), renal function (creatinine $\leq$ 1.5 mg/dL), and hepatic function (bilirubin $\leq$ 1.6 mg/dL and aspartate aminotransferase $\leq$ 3 times the upper limit of normal). Patients were required to have measurable soft tissue disease, or assessable disease manifested as osseous disease with a rising PSA level, or locally advanced disease with a rising PSA level. Patients with any history of recent myocardial infarction or ongoing ischemia requiring antianginal agents, arrhythmia requiring antiarrythmics, or history of ischemic disease with documented compromise of left ventricular function were excluded from this study. Similarly, patients were excluded from the study if they had uncontrolled hypertension, known brain metastases, or spinal cord compression. Patients were required to wait 4 weeks for study entry after the completion of prior chemotherapy, radiation therapy, or a change in hormone therapy. The study was reviewed and approved by the University of Michigan Institutional Review Board. All patients gave written informed consent in accordance with federal, state, and institutional guidelines.

Evaluations
Pretreatment evaluations consisted of a history and physical examination with assessment of performance status and laboratory studies, including complete blood count, serum chemistry profile, PSA level, radionuclide bone scan, computed tomography (CT) scans of the abdomen and pelvis, and chest X-ray. Complete blood counts, including differential and platelet counts, were monitored weekly, and chemistry profiles and PSA assessments were repeated every 3 weeks. Bone scans and CT scans were repeated every 9 weeks (3 treatment cycles) if they were positive at baseline.

Treatment Regimen
All therapy in this study was administered in the outpatient clinic. Estramustine was provided by Pharmacia and Upjohn (Kalamazoo, MI). Etoposide, paclitaxel, and carboplatin were supplied by Bristol-Myers Squibb (Nutley, NJ). Treatment was comprised of oral estramustine, 280 mg three times daily, and oral etoposide, 50 mg/m^2 daily, on Days 1–7, and paclitaxel, 135 mg/m^2 i.v., over 1 hour followed by carboplatin

(area under the curve, 5) on Day 2 of each 21-day treatment cycle. Patients initially received three cycles, and three additional cycles were given to patients who achieved a complete or a partial response or who had stable disease. Before the administration of paclitaxel, patients were premedicated with dexamethasone at a dose of 20 mg orally 12 hours and 6 hours pretreatment and immediately preinfusion with diphenhydramine, 50 mg i.v., and famotidine, 20 mg i.v.. Granisetron at a dose of 2 mg orally was given as a standard antiemetic regimen for paclitaxel. Oral prochlorperazine was used as a standard antiemetic regimen during therapy with oral estramustine and etoposide.

All subsequent cycles of therapy required that toxicity resulting from the prior cycle had resolved and that hematologic parameters had recovered to at least meet the entry criteria (i.e., ANC $\geq 1500/m^3$ and platelet count $\geq 100,000/m^3$). Dose modifications for etoposide and paclitaxel were based on counts obtained on Day 21 of each treatment cycle or the occurrence of febrile neutropenia. If bone marrow suppression was present on Day 21, then treatment was delayed until the resolution of toxicity and was resumed with the etoposide decreased to 50 mg per day alternating with 100 mg per day and paclitaxel reduced by 25% (for patients with Grade 2 toxicity on Day 21) or etoposide 50 mg per day and a 50% dose reduction of paclitaxel (for patients with bone marrow suppression $\geq$ Grade 3 on Day 21). Febrile neutropenia resulted in the same dose modification that was used for patients with Grade 2 bone marrow suppression at Day 21. Estramustine doses were not reduced for hematologic toxicity, and doses were held only in the event of nausea and emesis that were not controlled by antiemetics.

Patients who were responding to therapy were eligible for at least six cycles on this study. Patients with evidence of response were monitored after completion of every third cycle and were eligible for retreatment until the point of disease progression. Patients who had not undergone an orchiectomy were not maintained on a luteinizing hormone-releasing hormone analog, because estramustine reliably results in castrate levels of testosterone when given in this fashion. At the end of treatment, patients who had not undergone an orchiectomy were restarted on a luteinizing hormone-releasing hormone analog during the monitoring period.

Toxicity and Response Criteria
Toxicity was graded according to the revised National Cancer Institute Common Toxicity Criteria, version 2.0. Response was assessed using standard criteria for measurable disease, if present. In the patients who had elevations in serum PSA levels or bone-only disease, a complete response required the disappearance of all measurable and nonmeasurable but assessable lesions with a decrease in serum PSA levels to < 1.0 ng/mL for at least 6 weeks' duration. A partial response was defined as a decrease $\geq$ 50% in any measurable lesions and/or a decrease $\geq$ 50% in serum PSA level without worsening of disease-related symptoms for at least 6 weeks' duration. Disease progression was defined as the appearance of new signs and symptoms of metastatic disease, new lesions, an increase in PSA of 50% over baseline or nadir value, or an increase = 25% or $\geq$ 10 cm^2 in the size of any measurable lesion. All patients who did not meet these definitions were considered to have stable disease.

Statistical Considerations
Statistical significance for the preclinical studies was determined with the Student t tests and analyses of variance using SigmaStat software (Jandel Scientific, San Rafael, CA). The clinical trial was designed to assess the efficacy of this combination with a primary endpoint of tumor response. Response was assessed using serum PSA levels and measurable disease, if present. A 2-stage design was planned, with 22 response-assessable patients accrued in the first stage. The initial design required that at least 12 patients had evidence of response for further enrollment. However, as the trial progressed, 11 of the initial 20 patients had evidence of response, and enrollment was closed due to poor accrual. With 19 response-assessable patients, a response rate of 70% could be distinguished from 50% with a power of 69% at the 10% significance level. Response rates were assessed using PSA criteria for all patients and classic criteria for patients with measurable disease. Patients who were not assessable for response were included in the denominator unless stated otherwise, providing a conservative estimate. Estimates of response duration and overall survival were obtained using the Kaplan–Meier method. Time to disease progression was measured from the initiation of therapy to the date of treatment failure. Treatment failure included an increase in PSA of at least 50% more than the nadir value, progression of disease by standard clinical criteria, or the institution of additional therapy for prostate carcinoma. The date of treatment failure was defined as the date of first occurrence of any of these events; otherwise, the patient was censored at the time of the last PSA measurement. Survival was measured from initiation of therapy to death, or the patient was censored at the date of last follow-up.

TABLE 1
Patient Characteristics

Characteristic	No. of patients (%)
Total patients	20
No. evaluable for response	19 (95)
No evaluable for toxicity	20 (100)
Race	
White	19 (95)
Asian	1 (5)
Age (yrs)	
Median	64
Range	41–76
Measurable disease	12 (60)
Gleason score	
9–10	8 (40)
8	5 (25)
7	4 (20)
6	3 (15)
PSA (ng/mL)	
Median	94.0
Range	0.6–784.0
Prior hormone therapy	
One regimen	12 (60)
Two or more regimens	8 (40)
Prior chemotherapy	
No regimens	8 (40)
One or two regimens	12 (60)
Prior radiation therapy	16 (80)

PSA: prostate specific antigen.

TABLE 2
Toxicity

Toxicity	No. of patients	
	Grade 3	Grade 4
Neutropenia	5	4
Anemia	3	1
Thrombocytopenia	2	4
Deep vein thrombosis	1	0
Diarrhea	0	1

TABLE 3
Response by Measurable Disease and Prostate Specific Antigen Criterion

Response	No. of patients (%)			
		Measurable		
	PSA	PE	CT	Total
No. of patients	19	4	10	12
CR	0 (0)	3 (75)	1 (10)	3 (25)
PR	11 (58)	0 (0)	4 (40)	4 (33)
SD	8 (42)	1 (25)	5 (50)	5 (42)

PSA: prostate specific antigen; PE: physical examination; CT: computed tomography; CR: complete response; PR: partial response; SD: stable disease.

RESULTS

Between September 1997 and April 2000, 20 patients were enrolled onto this Phase II study. All patients developed disease progression on at least one hormone therapy regimen in addition to antiandrogen withdrawal (Table 1). Twelve patients had 1 form of hormone therapy, with 8 patients receiving 2 or 3 + hormone therapies each. A total of 12 patients had received chemotherapy prior to enrolling on this study (8 patients had received 1 prior chemotherapy regimen, and 4 patients had received 2 prior chemotherapy regimens). Two patients had received estramustine and etoposide when they developed a rising PSA level without evidence of metastases, and one patient had received weekly paclitaxel with estramustine for hormone-refractory disease. The other patients were treated with cyclophosphamide and prednisone (six patients), mitoxantrone and prednisone (three patients) and the oral 5-flourouracil analog UFT (two patients), which was available previously as a study regimen at our institution. Sixteen patients received radiation therapy. Twelve patients (60%) had evidence of measurable soft tissue disease, and 8 of those 12 patients also had evidence of bone involvement. The remaining eight patients had bone-only disease.

A total of 86 cycles of therapy were delivered, with a range of 1–6 cycles per patient. Nine patients completed the six cycles of therapy initially planned. Only five patients required a dose reduction, but two patients were able to continue for the full six cycles. Neutropenia was the most common hematologic toxicity, with nine patients experiencing toxicity ≥ Grade 3 (Table 2). Six patients had thrombocytopenia ≥ Grade 3. Four patients developed both neutropenia and thrombocytopenia ≥ Grade 3. Four patients had anemia ≥ Grade 3. One patient developed a deep venous thrombosis that was treated successfully with anticoagulation, and another patient experienced Grade 4 diarrhea. Only three patients developed Grade 3 nausea, and only one patient had Grade 3 emesis. Myalgias and arthralgias were common and occurred 48–72 hours after the administration of paclitaxel. In addition, mild peripheral neuropathy was common. The pattern of neuropathy and its transient nature were typical for paclitaxel.

Nineteen patients were assessable for response (Table 3). Seven of 12 patients with measurable disease had at least a partial response, for an overall response rate of 58% (95% confidence interval [95% CI],[23] 28–85%). Four of 12 patients with bidimensionally measurable disease were evaluable by physical

examination. Three of those four patients achieved a complete response in their palpable lesions alone, including a rectal mass, a sternal mass, and a supraclavicular lymph node. Of eight patients with measurable disease only on CT scans, one patient had a complete response, and three patients had partial responses by that criterion alone.

All patients enrolled had measurable PSA levels at baseline, with values ranging from 0.6 ng/mL to 783.8 ng/mL. One patient withdrew early and did not have a PSA evaluation after his only cycle of therapy; thus, response was assessed by PSA criteria in the remaining 19 patients. Eleven patients (58%; 95% CI, 34–80%) had decreases > 50% in PSA levels during therapy for at least 6 weeks; 9 of those 11 patients had a decreases > 75%. All but two of those responding patients completed six cycles of therapy.

The median time to disease progression for all patients was 5.6 months (95% CI, 4.4–6.2 months), and the longest was 18.4 months. The median survival was 14.4 months (95% CI, 11.6–28.0 months). At the time of this analysis, 17 patients had died. Of those who remain alive, one patient has been followed for 43.5 months.

Associations between measurable disease and PSA response were evaluated. Seven patients had a response in their bidimensionally measurable disease, as noted above. Four of those seven patients had reductions ≥ 50% in PSA levels from baseline. Of the three patients who did not qualify for a PSA response, one patient had a baseline PSA level of 1.3 ng/mL that decreased to a nadir of 1.1 ng/mL, another patient had a decline in PSA level of 42%, and the third patient had a decline in PSA level of 60% but developed disease progression within 6 weeks. Five patients had stable, bidimensionally measurable disease. Four of those 5 patients also had reductions ≥ 50% in PSA levels from baseline. None of the patients who had achieved a response according to PSA criterion and measurable disease had evidence of progression of the measurable disease while their PSA was decreasing.

In patients who had only bone scan evidence of disease, 3 of 3 patients (100%) who had not received prior chemotherapy had reductions ≥ 50% in their PSA levels. In contrast, only 1 of 4 patients (25%) with bone-only disease who had received prior chemotherapy had reductions ≥ 50% in their PSA levels. Four of 5 patients (80%) with bidimensionally measurable disease who had not received prior chemotherapy had a soft tissue response, compared with only 3 of 7 patients (43%) who had received prior chemotherapy.

Overall, prior chemotherapy did not seem to influence the response to this regimen as measured by PSA. Five of 8 patients (62%) who had no prior therapy had reductions ≥ 50% in PSA levels compared with 6 of 11 patients (54%) who had received prior chemotherapy. When analyzed by evaluable disease, 2 of 5 patients (40%) with bidimensionally measurable disease who had no prior therapy had reductions ≥ 50% PSA levels compared with 5 of 7 patients (71%) who had received prior chemotherapy.

Prior chemotherapy also appeared to have no significant effect on the amount of toxicity experienced with this regimen, presumably due to cumulative bone marrow toxicity. The rate of significant bone marrow suppression (≥ Grade 3 neutropenia, thrombocytopenia, and anemia) was comparable between patients who had no prior chemotherapy and patients who had at least one prior course. Overall, 8 of 12 patients who had received prior chemotherapy and 7 of 8 patients who had not received prior chemotherapy had bone marrow suppression ≥ Grade 3. Grade 4 neutropenia and thrombocytopenia occurred in two patients in each group.

DISCUSSION

Recent clinical trials of combination chemotherapy in patients with HRPC have demonstrated that responses can be obtained. Unfortunately, these responses typically have been of short duration, and no survival benefit has been demonstrated with any of the combinations studied to date. Clearly, there is a need for more effective therapies for patients with HRPC. We previously demonstrated that the combination of TEE had significant activity with a high response rate according to both measurable disease and PSA criteria.[2] With the success seen in other tumor models using the combination of platinum compounds and taxanes, and with preclinical data to support this combination in prostate carcinoma cell lines, the current Phase II clinical trial investigated the potential benefit of adding carboplatin to TEE.

The TEEC combination showed significant activity in this largely pretreated patient population. The rate of response in terms of measurable disease and PSA criteria were not significantly different from the prior trial with TEE alone. Although responses were demonstrated in patients who had received multiple hormone and chemotherapy regimens, the duration of response was short, on the order of months. From this clinical trial, it does not appear that carboplatin adds significantly to the toxicity, response rate, or duration of response of TEE.

The TEEC regimen generally was tolerated well, with 45% of patients receiving all 6 cycles. Only 20% of patients failed to receive at least 3 cycles of therapy. The toxicity was primarily hematologic, with 20% of patients experiencing Grade 4 neutropenia, Grade 4

thrombocytopenia, or Grade 3 or 4 anemia. One patient developed a deep venous thrombosis. In general, the toxicity was expected and was not out of proportion to the addition of carboplatin. In addition, the severity of toxicity did not seem to correlate with the amount of prior chemotherapy.

The response rate by PSA criteria (58%) was comparable to that seen in other trials using combination chemotherapy with estramustine as well as TEE.[2,4,10,15,24] The measurable response rate was 58%: again, comparable to the response rate seen with TEE. In patients who had responses in bidimensionally measurable disease, only four of seven patients had a decline in PSA by at least 50%, although all had a decrease in PSA. No patients with measurable disease progressed while responding by PSA. A decline in PSA with therapy, therefore, does appear to be associated with response in measurable disease.

Overall, prior chemotherapy did not seem to affect the rate of PSA response. When patients were analyzed by response criteria, all patients with only bone scan evidence of disease who had no prior chemotherapy had a PSA response, compared with only 33% of patients who had received prior chemotherapy. This finding likely is due to the small sample size; because, when all patients with bone scan evidence of disease were compared for PSA response, there was no significant difference between those who had or had not received prior chemotherapy. It also is possible that the patients with bone-only disease may have had a different inherent biology, compared with patients who had additional soft tissue metastases, that made them more responsive to chemotherapy.

Investigators at MSKCC performed a dose-escalation trial in 56 patients with advanced prostate carcinoma using a similar combination.[22] Paclitaxel was given weekly as 1-hour infusions of 60–100 mg/m^2 with carboplatin (area under the curve, 6 mg/mL-minute every 4 weeks) and oral estramustine (10 mg/kg daily for 5 days), Those authors reported response rates of 45% in patients with measurable disease and 67% (95% CI, 55–79%) by PSA criteria. Similar to our trial, the duration of estramustine dosing was reduced to limit toxicities. Despite this, 25% of their patients developed thromboembolic disease. Additional Grade 3 or 4 adverse effects were limited to hyperglycemia (38%) and hypophosphatemia (42%). No significant bone marrow suppression or peripheral neuropathy was seen. The overall response rate and toxicities on the MSKCC trial were similar to those seen on the current trial.

This trial was able to show that, although the addition of carboplatin to TEE is tolerated, it does not seem to add significantly to the response rates dem-onstrated with TEE or other estramustine-based regimens. This trial was hindered by slow accrual and was halted prior to completing the planned enrollment. In addition, the length of treatment of estramustine and etoposide was shortened from 14 days in the original regimen to 7 days, which may have decreased the effectiveness of adding carboplatin to TEE.

Although the TEEC regimen had a reasonable response rate, the duration of response was relatively short. This is the typical pattern of response to chemotherapy in patients with this disease. Almost all of the responding patients progressed within weeks of completing their sixth and final planned cycle of chemotherapy. Subsequent therapy usually was unsuccessful in providing further control of the disease, and it is unknown whether continued therapy would have been effective in maintaining the response. Such therapy undoubtedly would have been of limited duration due to cumulative bone marrow toxicity. It is clear that few of the regimens currently in Phase II and III trials result in long-term control of androgen independent prostate carcinoma, suggesting that further exploration of new agents, schedules of existing regimens, and the timing of treatment is warranted. One potential approach is the use of regimens with documented activity in advanced prostate carcinoma earlier in the course of disease in patients who have a high likelihood of recurrence. Studies of the approach are being conducted now at several centers and are under consideration in the cooperative group setting. Hopefully, they will provide further insight that will improve the care of patients with advanced prostate carcinoma.

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