Chemotherapy in Patients with Prostate Specific Antigen–Only Disease after Primary Therapy for Prostate Carcinoma

A Phase II Trial of Oral Estramustine and Oral Etoposide

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BACKGROUND. A Phase II study was initiated to evaluate the effectiveness of an oral regimen of etoposide and estramustine in patients with early recurrent prostate carcinoma.

METHODS. Patients with early recurrent prostate carcinoma as indicated by an increasing prostate specific antigen (PSA) level and without any evidence of metastatic disease were treated with oral etoposide 50 mg/m^2/day and estramustine 15 mg/kg/day in divided doses for 21 days, followed by a 7-day rest period. Patients received a maximum of four cycles.

RESULTS. Eighteen patients were entered in this study. The median serum PSA was 3.1 (range, 0.3–30.3) at the time of entry into the trial. Sixteen patients were assessable for response. Serum PSA declined to undetectable levels in 13 patients with 2 additional patients meeting the criteria for partial response; the median duration of response was 8.5 months (range, 1–18 months). Most patients developed gastrointestinal, cardiac, or hematologic complications. Grade 3 toxicities included neutropenia (one patient), deep venous thrombosis (three patients), and chest pain (one patient). One patient developed acute myelogenous leukemia (French–American–British, acute myelogenous leukemia M5) 23 months after initiating the chemotherapy.

CONCLUSIONS. The combination of oral etoposide and oral estramustine resulted in a high rate but only a short duration of response in patients with early recurrent prostate carcinoma. The regimen was poorly tolerated, and the toxicity was significant. This regimen should not be considered standard therapy for the treatment of early recurrent prostate carcinoma, but further exploration of treatment in this setting is warranted. ***Cancer* 2001;91:2175–80.** *© 2001 American Cancer Society.*

KEYWORDS: prostate carcinoma, early recurrent, etoposide, estramustine, chemotherapy, leukemia, thrombosis.

Prostate carcinoma is one of the most commonly diagnosed cancers in American men. In 1999, 179,300 men were expected to receive a diagnosis of prostate carcinoma in the United States, and 37,000 men were predicted to die of the disease.[1] The widespread use of prostate specific antigen (PSA)–based testing has resulted in a dramatic increase in the number of men diagnosed with localized disease.[2] Many of these men will undergo either radical prostatectomy or radiotherapy. Unfortunately, approximately 50% of the patients undergoing prostatectomy[3] and approximately 60% of men treated with radiotherapy will have biochemical recurrence within 10 years.[4] Recurrent prostate carcinoma is a significant problem. Some

of these patients may be offered additional local therapy, and many will be treated with hormonal therapy.[5] A significant proportion of these patients will develop metastatic disease. Unfortunately, the duration of remission with hormonal therapy is limited in patients with metastatic disease, with androgen failure often occurring within 18–24 months of starting therapy.[6] Consequently, the survival rates of patients with recurrent disease have not increased over the past 5 decades.[7]

Prostate carcinoma consists of both androgen-dependent and androgen-independent clones. Tumor progression after androgen ablation is due to proliferation of androgen-independent cells.[8] Chemotherapy has been used to treat patients whose cancers have become refractory to androgen therapy. Treatment with an oral regimen of etoposide and estramustine can achieve a significant response in these patients.[9,10] Several additional regimens also have been demonstrated to have activity in patients with advanced prostate carcinoma.[11] Unfortunately, the median survival in these Phase III trials of these regimens is only 11–12 months despite the use of chemotherapy.[12,13] Patients with advanced prostate carcinoma have a significant tumor burden, which may limit the effectiveness of the chemotherapy in these trials. There have been, to our knowledge, no trials reporting treatment of patients with early recurrent prostate carcinoma with chemotherapy. Here, we report the results of a trial in patients with minimal disease, as demonstrated by increasing PSA and without any evidence of metastatic disease, who were treated with an oral regimen of etoposide and estramustine. The objective of this Phase II study was to assess the toxicity of this regimen in this population and the response of minimal disease to therapy as measured by the serum PSA level.

MATERIALS AND METHODS

Patients were eligible if they had histologically confirmed adenocarcinoma of the prostate associated with elevated PSA that had returned to normal after primary therapy ($<$ 1.0 ng/mL for prostatectomy patients or $<$ 4.0 ng/mL for radiation therapy patients) and had an increasing PSA level that had at least doubled from their lowest PSA level after the primary therapy. Patients were required to have a performance status of 3 or better, with a life expectancy of 12 weeks or greater, and an adequate bone marrow reserve with an absolute neutrophil count (ANC) greater than 1500/mm^3 and a platelet count greater than 100,000/mm^3. Patients were excluded if computed tomography (CT) scan or bone scan demonstrated metastatic disease, or if they had received hormonal therapy for the treatment of metastatic disease before enrolling in this trial. All patients gave written informed consent in accordance with federal, state, and institutional guidelines.

Pretreatment evaluations consisted of a history and physical examination with assessment of performance status, and laboratory studies including complete blood count, serum chemistry profile, prothrombin time, PSA level, radionuclide bone scan, CT scan of the abdomen and pelvis, and chest X-ray. Complete blood counts were monitored weekly, and the serum PSA was monitored before each cycle. After 4 cycles of therapy, serum PSA was measured every 12 weeks.

Patients in this study were treated and followed in the outpatient clinic. Estramustine was provided by Pharmacia & Upjohn (Kalamazoo, MI) and etoposide was supplied by Bristol-Myers Squibb (Nutley, NJ). Oral estramustine was given at a dose of 10 mg/kg/day rounded to the nearest multiple of 140 (maximum 2 pills 3 times a day) and oral etoposide 50 mg/m^2/day rounded to the nearest multiple of 50 (maximum 2 pills per day) for 21 days, repeated every 28 days. The dose of etoposide was decreased to 1 tablet a day alternating with 1 tablet twice a day for patients with a body surface area of less than 1.75 m^2.

Patients were treated with a maximum of four cycles of therapy. Retreatment required that the ANC was greater than 1500/mm^3, and the platelet count was greater than 75,000/mm^3 on Day 1 of each cycle. Dose modification of etoposide was based on Day 21 ANC and platelet count of the preceding cycle for the next and additional cycles. Etoposide was decreased to 1 tablet per day alternating with 1 tablet twice a day for ANC between 1000/mm^3 and 1499/mm^3 and/or for platelets between 50,000/mm^3 and 74,999/mm^3. Etoposide was further decreased to 1 tablet per day for ANC less than 1000/mm^3 and/or for platelets less than 50,000/mm^3. Etoposide was held for the remainder of the cycle if patient had an ANC less than 1500/mm^3 or platelet count less than 75,000/mm^3 on Days 7 or 14. Patients were transfused for hemoglobin less than 8.0 g/dL or for symptomatic anemia as evidenced by shortness of breath or severe fatigue. Patients with Grades 1 and 2 nausea were treated with antiemetics. Patients with Grade 3 nausea had their drugs discontinued and were taken off study secondary to toxicity. After the tenth patient had been enrolled, the subsequent patients on this protocol were maintained on 1 mg/day of warfarin for prophylaxis against deep venous thrombosis.

The study initially was designed to assess response as measured by PSA criteria. Complete response was defined as a decrease in PSA to undetectable levels for at least 4 weeks with maintenance of

performance status and without the appearance of new lesions. Partial response was defined as a decrease in PSA of greater than or equal to 50% lasting at least 4 weeks, again with maintenance of performance status and without the appearance of new lesions. Disease progression was defined as increase in the serum PSA level of 100% over baseline or the appearance of new lesions. The protocol used a standard two-stage Phase II design to limit accrual if extreme results were demonstrated. Twenty evaluable subjects were to be enrolled in the first phase, followed by enrollment of an additional 20 subjects if more than one but less than six subjects had response. Criteria for halting enrollment after the first phase also included excess toxicity or short duration of response. This design has a power of 82% to detect a true response rate greater than or equal to 25% with a significance of 0.0449. Toxicity was graded according to the revised National Cancer Institute Common Toxicity Criteria.

RESULTS

Between April 1996 and April 1998, 18 patients with increasing PSA after primary therapy for prostate carcinoma were entered onto this trial. The trial was halted early due to the toxicity of the regimen. Initial patient characteristics are summarized in Table 1. Most (nine patients) of the patients had been treated with both radiation and surgery. Six patients had received only radiation treatment, and two patients had been treated with prostatectomy only. One patient had been treated with cryosurgery and therefore was ineligible to participate in the study. Six patients had received neoadjuvant hormonal therapy with a duration ranging from 1 to 6 months. All six had received luteinizing hormone-releasing hormone (LHRH) agonist therapy, with at least four receiving combined androgen blockade (data not available on one subject). These patients had a median time to progression from initiation of hormonal therapy of 12.5 months (range, 8–21 months). Overall, the patients enrolled had a median of 22 months from completion of primary and/or secondary therapies to biochemical recurrence of their prostate carcinoma. The median PSA at the time of entry into the trial was 3.1.

Estramustine and etoposide were administered orally. Thirteen patients completed all 4 cycles. One patient completed only three cycles because of severe agitation. One patient completed two cycles of chemotherapy and then was removed from the study due to rapidly progressing disease; he also had a popliteal deep venous thrombosis. Two additional patients stopped after two cycles of therapy: one patient developed deep venous thrombosis, and the other patient because of tachycardia. One patient had chest pain while receiving his first cycle of therapy and was taken off the study.

TABLE 1
Patient Characteristics

Characteristic	*n*
No. enrolled	18
Age (yrs)	
Median	62
Range	48–75
Initial Gleason score	
Median	7
Range	5–9
PSA at time of diagnosis	
Median	18
Range	3.5–79
Initial therapy	
Radiation	6
Prostatectomy	2
Both	9
Cryosurgery	1
Neoadjuvant hormonal therapy	6
Interval (mos) between completion of primary therapy and increase in the serum PSA	
Median	22
Range	3–57
PSA at the time of chemotherapy	
Median	3.1
Range	0.3–30.3

PSA: prostate specific antigen.

Most patients developed gastrointestinal symptoms (Table 2). Of the 18 patients, 14 patients developed either Grade 1 or 2 nausea, 4 patients developed Grade 1 vomiting, and 4 patients had either Grade 1 or 2 diarrhea. Seven patients complained of fatigue, and four patients had anorexia. Five patients developed Grade 1 alopecia. Four patients developed deep venous thrombosis, of which three patients had Grade 3 deep venous thrombosis. The incidence of deep venous thrombosis was 3 of 10 patients in the group that was not receiving prophylactic doses of warfarin and 1 of 8 patients in the group that was receiving warfarin. One patient developed superficial thrombophlebitis; he was not receiving warfarin. Two patients had major cardiac toxicity with one patient developing chest pain and the other patient developing arrhythmia. Four patients had neutropenia, including one patient who developed Grade 3 toxicity. Two patients had Grade 2 anemia. Other toxicities included bronchitis (three patients), edema (two patients), gynecomastia (two patients), depression (two patients), anxiety (two patients), and rash (one patient).

One patient, who had received a total oral etoposide dose of 4200 mg/m^2, developed acute myeloge-

TABLE 2
Toxicity

	Grade (no. of patients)				
Toxicity	**1**	**2**	**3**	**4**	**Percentage**
Nausea	12	2			78
Fatigue	7				39
Alopecia	5				28
Anorexia	4				22
Neutropenia	2	1	1		22
Venous thrombosis		1	3		22
Vomiting	4				22
Diarrhea	2	2			22
Bronchitis	1	2			17
Anemia		2			11
Cardiac		1	1		11
Edema		2			11
Depression		2			11
Anxiety		2			11
Gynecomastia	2				11
Rash		1			6
Thrombophlebitis		1			6

TABLE 3
Results

Result	***n* (range)**
No. of cycles	62 (1–4)
Response	
Undetectable PSA (CR)	13
PR	3
Total (CR/PR)	16/17
Median duration of CR	6 (1–18)
Median duration of response	8.5 (1–18)
No. receiving hormonal therapy after treatment failure	15

PSA: prostate specific antigen; CR: complete response; PR: partial response.

nous leukemia, French–American–British (FAB) classification system M5, 23 months after initiation of treatment with etoposide and estramustine. He was noted to have a mildly elevated leukocyte count with circulating early leukocyte precursors. Bone marrow aspirate showed acute myelogenous leukemia, monocytoid form. Bone marrow cytogenetics showed that 22 of 26 cells had translocation between the long arm of chromosome 11 and a short arm of chromosome 19 (46, XY, t[11;19][q23;p13]). Two of 26 cells had, in addition to the t(11;19) translocation, a trisomy 8 and an abnormal chromosome consisting of the long arms of chromosome 10 and 15. He underwent induction with cytosine arabinoside and idarubicin. Repeat bone marrow cytogenetics showed that the patient had persistent t(11;19) translocation, indicating the presence of residual leukemia. He subsequently received consolidation therapy with two cycles of high dose cytarabine and underwent a matched-unrelated donor allogeneic bone marrow transplant. At more than 450 days after transplant, he was without evidence of recurrence of his acute myelogenous leukemia (AML).

Sixteen of the 18 patients were assessable for response (Table 3). One patient was excluded even though he had completed all four cycles because he previously had been treated with cryosurgery and was ineligible to participate per protocol. A second patient was not evaluable because he was placed on total androgen blockade after developing a deep vein thrombosis during his second cycle of therapy. Both of these patients are included in assessing the toxicity of this regimen. Thirteen patients had a decline in their serum PSA to undetectable levels. The duration of the serum PSA nadir was a median of 6 months, ranging from 1 to 18 months. Two of the remaining three evaluable patients met the criteria for partial response, for an overall response rate of 94% (15 of 16). Median duration of response was 8.5 months with a range of 1 to 18 months. Patients were treated with hormonal therapy within a median of 3 months after failing chemotherapy. One patient, who completed only two-thirds of a cycle of protocol therapy, was not treated with hormonal therapy for almost 2 years. His serum PSA decreased to a nadir of 0.3 2 months after withdrawing from the trial, with subsequent slow increase over the following 21 months to reach a high of 6.6 at the time of initiation of hormonal therapy. These subsequent therapies consisted of bicalutamide and finasteride (9 patients), total androgen blockade (4 patients), and LHRH agonist monotherapy (3 patients). One patient took finasteride for 2 months and then was placed on total androgen blockade. All but one of the patients responded to initiation of hormonal therapy with a prompt decrease in PSA. The nonresponding patient was the one who developed rapidly progressive disease while on protocol therapy. He had no response to total androgen blockade and died of progressive disease 7 months after entry onto the protocol.

DISCUSSION

There are increasing numbers of patients with prostate carcinoma who at the time of recurrence have only minimal disease. The optimal treatment strategy for these patients is not known. In this trial, we treated this select group of patients with an oral regimen of etoposide and estramustine.

Sixteen patients were assessable for response. Because the patients did not have detectable disease by bone scan or computed tomography, the response to therapy was assessed with serum PSA level. Fifteen of the 16 patients met the criteria for response, with

complete response in 13 patients. The median duration of response was 8.5 months, with a maximum duration of response of 18 months. This response is possibly due to the hormonal effect of estramustine, which has been reported to induce castrate levels of serum testosterone.[14] Serum testosterone levels were not measured as part of this study. The relative contributions of this hormonal effect to the overall efficacy of the therapy therefore is not clear. In an earlier trial in patients with hormone refractory prostate carcinoma using the same dose of etoposide and estramustine as in this study, the serum PSA declined by at least 50% from baseline in 39% of the patients.[15] Thus, by treating patients with minimal disease, we were able to achieve a higher response rate, as would be expected in patients with androgen-dependent disease. Unfortunately, all patients eventually recurred, and nearly all were treated subsequently with hormonal therapy.

The toxicity of this regimen was substantial and resulted in early termination of the study. Grade 3 toxicities included neutropenia, venous thrombosis, angina, and dysrhythmia. Five of 18 patients failed to complete all 4 cycles. Chest pain, dysrhythmia, and venous thromboses were the main reasons for discontinuation of the therapy. Most of these symptoms were in patients who were not receiving prophylactic doses of warfarin. Four patients developed deep venous thrombosis, only one of whom was receiving 1 mg/day of warfarin. The two patients who withdrew from the study because of deep venous thrombosis were not receiving warfarin. In the prior report with 62 hormone refractory disease patients using the same chemotherapy dosages, only Grade 1 venous thrombosis was observed, with no patient stopping therapy as a result, despite no prophylaxis for thrombosis.[10] Furthermore, the patients in that report were not maintained on prophylactic doses of coumadin. Fourteen of the 18 patients on this study reported nausea, most being Grade 1 nausea. No patients withdrew from the study secondary to nausea. In the previous study involving patients with more advanced disease, three (5%) patients quit secondary to Grade 3 nausea.[10] The discrepancy in toxicity between this study and the earlier study may be an artifact of the low number of patients enrolled or may be due to factors associated with the stage of disease.

One of the patients developed AML, FAB M5 subtype, 23 months after initiation of treatment with oral etoposide and estramustine. Etoposide is well known to increase the risk of leukemia, particularly acute myelomonocytic (FAB M4) and acute monocytic (FAB M5) leukemias.[16] The median latency period between treatment with etoposide and the development of leukemia is 28 months (range, 11–84 months). The risk of developing secondary leukemia is 2–4%, with risk increased in those patients who have received higher cumulative dose (>2000 mg/m^2 parenterally) and in those patients receiving the etoposide on a weekly or biweekly schedule. The cumulative dose of oral etoposide received by patients in this trial who complete all 4 cycles is 4200 mg/m^2. The bioavailability of oral etoposide is approximately 50%, although the range varies widely from 25% to 75%.[16,17] Thus, the equivalent parenteral dose received by patients in our trial ranged from 1050 to 3150 mg/m^2. Approximately 1% (2 patients) of the patients with recurrent prostate carcinoma who have been enrolled in trials involving treatment with etoposide have developed AML at our institution. Patients with secondary leukemia from etoposide characteristically have translocations involving the short arm of chromosome 9 or the long arm of chromosome 11. Our patient had t(11;19)(q23;p13) translocation, and because durable remission with standard therapy was unlikely, he underwent allogeneic bone marrow transplantation.

We treated a small, but heterogeneous group of patients with chemotherapy. The initial Gleason scores ranged from 5 to 9, and the interval between primary therapy and an increase in the serum PSA level ranged from 3 to 51 months. Recently, the natural history of prostate carcinoma in patients who have elevated PSA levels as the only manifestation of recurrence, similar to patients in this trial, has been described.[18] The median time to metastasis was 5 years from the time of PSA elevation, and only 34% of the patients developed metastasis at 5 years. The risk of developing metastatic disease after biochemical recurrence correlated with the time to biochemical progression, the Gleason score, and the PSA doubling time. Using this information, it is possible to predict which patients are likely to progress to have metastatic disease and which patients will have indolent disease. The patients in our trial would have been predicted to have a high likelihood of developing metastatic disease over the next 5 years. Even though watchful waiting may be a reasonable option for those patients predicted to have indolent disease, it would not have been the best course of action for most of the patients enrolled in our trial.

Besides watchful waiting, patients with biochemical recurrence have been treated with hormonal therapy. There has been significant controversy surrounding the optimal time to initiate hormonal treatment. A large randomized study conducted by the Veteran's Administration Co-operative Urological Research Group found no survival advantage with early treatment.[19] A more recent study reported a trend toward increased survival with early therapy.[20] There were

significantly fewer spinal cord compressions and pathologic fractures in the group treated with early hormonal therapy on this study. A recently reported prospective Phase III trial showed that there was improved survival for patients with lymph node positive disease treated with early hormonal therapy compared with delayed hormonal therapy.[21]

In summary, treatment with an oral regimen of etoposide and estramustine resulted in a high response rate but was poorly tolerated in this group of men with biochemical recurrence of their prostate carcinoma. Toxicity with this regimen was substantial, and the duration of response was short. We therefore would not recommend that this regimen be incorporated into the standard treatment of biochemically recurrent hormone-responsive prostate carcinoma. Despite this somewhat discouraging result, further exploration of therapy in this setting is clearly warranted. The median survival for patients with hormone refractory prostate carcinoma remains approximately 1 year, pointing to the urgent need to find treatments for patients with recurring prostate carcinoma before their progression to androgen-independent disease. The development of new regimens and novel approaches and a better understanding of the biology of prostate carcinoma and the further development of prognostic indicators that will allow the identification of those patients at risk for death due to prostate carcinoma will allow us to further evaluate the concept of treatment in the setting of minimal disease. Treatment in this clinical setting will require a careful assessment of the potential benefits and toxicities of therapy, particularly in light of the asymptomatic status of most of this population. The need to minimize toxicity must be balanced by the risk that several of these patients will go on to develop symptomatic metastatic disease that may prove lethal. Regimens currently under development hopefully will have fewer toxicities and greater efficacy allowing the promise of early therapy for metastatic disease to be realized.

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