The Prostate 46:257–261 (2001)

A Phase II Trial of Estramustine and Etoposide in Hormone Refractory Prostate Cancer: A Southwest Oncology Group Trial (SWOG 9407)

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BACKGROUND. The combination of oral estramustine and oral etoposide has generated response rates of 40–50% in patients with hormone refractory prostate cancer in single institution trials. This study tested this regimen in a multi-institutional setting.
METHODS. Fifty-five patients were accrued over a period of 4 months between 1 March 1996 and 1 July 1996. Two patients were not analyzable and two patients were ineligible. They were given an oral regimen consisting of estramustine 15 mg/kg/day (capped at 1120 mg per day) and etoposide 50 mg/M^2/day, days 1–21 every 28 days. Patients received a median of two cycles of therapy.
RESULTS. Toxicities included 11 patients (20%) with grades 3 or 4 granulocytopenia, 5 patients (10%) with grades 3 or 4 edema, and 3 patients (6%) with a thrombotic event. There were two treatment-related deaths, one as a result of anemia and the other as a result of a myocardial infarction. Of the 32 men who received at least 2 cycles of therapy, 7 men (22%) demonstrated a partial response to this regimen as measured by prostate-specific antigen (PSA) criteria of a 50% decline from pretreatment values.
CONCLUSIONS. This trial demonstrates the toxicity of estramustine delivered in high dose. It also illustrates the difficulty of conducting phase II trials in prostate cancer in the cooperative group setting where the experience and comfort level of oncologists with new agents is less

Grant sponsor: PHS Cooperative Agreement grant numbers awarded by the National Cancer Institute, DHHS: CA38926; CA32102; CA27057; CA45560; CA35431; CA42777; CA14028; CA76447; CA96429; CA04920; CA58882; CA35090; CA58348; CA58686; CA45450; CA04919; CA35178; CA58416; CA12644; CA46282; CA46113; CA22433; CA63845; and CA20319. Grant sponsor: Bristol-Myers Squibb; Grant sponsor: Pharmacia.

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Received 14 June 2000; Accepted 9 October 2000

than that of the physicians at the institution where the therapy was developed. As the activity of this regimen with low-dose estramustine is defined, further multi-institutional studies may be warranted. *Prostate 46:257–261, 2001.* © 2001 Wiley-Liss, Inc.

KEY WORDS: **PSA; androgen-independent; nuclear matrix**

INTRODUCTION

Prostate cancer is the most frequently diagnosed cancer and the second leading cause of cancer death among men in the United States. In 1999, it is estimated that more than 39,000 men died of this disease [1]. Treatment of metastatic disease remains palliative with androgen deprivation as the first line of treatment. Men who have progression of prostate cancer in the presence of total androgen blockade are defined as having androgen-independent prostate cancer or hormone refractory prostate cancer (HRPCa). No effective ''standard'' chemotherapy which has been demonstrated to prolong life exists for this patient population which has a median survival of 12 months [2].

The nuclear matrix, the dynamic skeleton of the nucleus which organizes DNA structure and function, has been a target for prostate cancer chemotherapy for the last several years [3]. Estramustine, an estradiol with a nitrogen mustard attached, has been demonstrated to be preferentially taken up by prostate cancer cells and bind to the nuclear matrix. Preclinical studies demonstrated that estramustine interacted with the chemotherapeutic agent etoposide, a topoisomerase II inhibitor which also acts at the level of the nuclear matrix and DNA transcription [3,4].

Based on these preclinical studies, a single institution phase II clinical trial was performed [5]. Both agents were given orally (estramustine 15 mg/kg/day in four divided doses and etoposide 50 mg/M^2/day in two divided doses) for 3 weeks with a 1-week rest period. Estramustine caused grade 3 or 4 nausea in 29% of the patients and two patients withdrew secondary to this toxicity. Deep venous thrombosis was noted in 10% of the patients. Of 18 patients with measurable disease, three had a complete response and six had a partial response (50% response rate). A PSA decline of $> 50\%$ from baseline was demonstrated in 55% of the patients [5]. Because of these early promising results it was elected to test this regimen in a multi-institutional setting.

MATERIALS AND METHODS

Patients

Eligible patients were required to have a histologic diagnosis of adenocarcinoma of the prostate, Stage D2, that was unresponsive or refractory to hormone therapy, i.e., must have a rising PSA 1 month following cessation of all antiandrogen therapy. Patients had to have bidimensionally measurable disease documented within 28 days prior to registration or evaluable disease as measured by serum PSA within 28 days prior to registration. Minimum serum PSA to be entered on the study was 20 ng/ml. X-rays and scans of all nonmeasurable disease were completed within 42 days prior to registration and all sites of disease were to be assessed. No other chemotherapeutic, biological response modifiers, radiation therapy or hormonal concomitant therapy could be planned to be given during protocol treatment. Patients were required to have AGC $\geq$ 1,500 cells/mm^3 and platelet count $\geq$ institutional lower limit of normal, obtained within 28 days prior to registration. Patients were required to have baseline liver function tests including SGOT $\leq 2.5 \times$ institutional upper limits of normal and serum bilirubin $\leq 1.5 \times$ institutional upper limit of normal, unless this was due to metastatic liver disease (which should be confirmed by immunoperoxidase staining for acid phosphatase and PSA). Patients had to have a performance status of 0–3 by Southwest Oncology Group Criteria. For those patients with a PS of 3, the cause must be due to pain secondary to bone metastases in order to be eligible. Prior radiation therapy (to less than 25% of the bone marrow only) and surgery are allowed. At least four weeks must have elapsed since the completion of radiation therapy and patients must have recovered from side effects. At least three weeks must have elapsed since completion of surgery. Patients with a history of brain metastases or who currently had treated or untreated brain metastases were not eligible. Patients must have recovered from major infections and/or surgical procedures and, in the opinion of the investigator, not have significant active concurrent medical illness precluding protocol treatment or survival. No other prior malignancy was allowed except for the following: adequately treated basal cell or squamous cell skin cancer; adequately treated Stage I or II cancer from which the patient is currently in complete remission; or any other cancer from which the patient has been disease-free for five years. All patients were informed of the investigational nature of this study and had to sign and give written informed consent in accordance with institutional and federal guidelines.

Evaluation of Response

Standard solid tumor response criteria were used; however, the definitions of response were modified from those previously described for Southwest Oncology Group studies to add PSA criteria [6]. PSA complete response was considered to be normalization (PSA$<$ 4 ng/ml). PSA partial response was a greater than or equal to 50% decrease of PSA levels from baseline, over a time period of at least 4 weeks. PSA was to be drawn at the end of each cycle. Progression by PSA was defined as a 50% increase over the minimum PSA obtained.

Treatment

All therapy was administered in the outpatient setting. Estramustine was provided by Pharmacia and Upjohn (Kalamazoo, MI). Etoposide was supplied by Bristol-Myers Squibb (Nutley, NJ). Patients were given an oral regimen consisting of estramustine 15 mg/kg/day (to be capped at 1,120 mg per day) and etoposide 50 mg/M^2/day days 1–21 every 28 days. Estramustine is supplied in 140 mg tablets and the dose was rounded to the nearest number of tablets to be given in a regimen four times per day. Etoposide is supplied as 50 mg tablets and for the majority of men on this study, this resulted in a dose of one tablet given two times per day.

Patients who experienced stabilization, partial, or complete remission while being treated continued to receive drug as outlined above. All subsequent cycles of therapy required that toxicity resulting from the prior cycle had resolved. Dosage modification was based on day 21 granulocyte and platelet count of the preceding cycle for the next and additional courses. Etoposide was not be administered until granulocyte count is $\geq$ 1,500 cell/mm^3 and platelet count $\geq$ 100,000. Once hematologic parameters were recovered, subsequent dosage was based on granulocyte and platelet counts. If the granulocytes were $>$1,500, but platelets were 75,000–99,999, etoposide dose was reduced by 20%. If the granulocytes were $<$ 1,500 or platelets were $<$ 75,000, etoposide dose was reduced by 50%. If patients experienced nausea due to estramustine treatment, 10 mg compazine was to be given orally, 1 hr prior to dose. If patients continued to experience nausea, the fourth dose of estramustine was to be eliminated. It was recommended that patients take estramustine with meals, and to avoid milk products with those meals.

Statistical Considerations

The study was designed to assess the efficacy of this combination with a primary endpoint of tumor response. A response probability of 20% or greater would be of interest, while further testing would not be pursued if the response probability is 5% or lower. Initially 20 patients were to be accrued. If none of the first 20 patients responded to treatment, then the study was to be closed and the regimen concluded to be inactive. If at least one of the first 20 patients responded, then an additional 20 patients would be accrued. Five or more responses out of 40 patients would be considered evidence warranting further study of the regimen provided other factors, such as toxicity and survival, also appear favorable. This design has a significance level (probability of falsely declaring an agent with 5% response probability to warrant further study) of 5%, and a power (probability of correctly declaring an agent with 20% response probability to warrant further study) of 92%. Forty patients were sufficient to estimate the probability of response or a particular toxicity to within 16%. Any toxicity occurring with at least a 10% probability is likely to be seen at least once (99% chance). The accrual rate was expected to be seven patients per month based on SWOG-9235. Due to the rapid accrual rate of this study, 55 patients were accrued before the trial was closed.

RESULTS

Between 1 March 1996 and 1 July 1996, 55 patients from 24 institutions were accrued to this phase II study, SWOG 9407. Two patients were ineligible due to insufficient information. Two other patients never started drug therapy and are not included in the analysis. The characteristics of the remaining 51 patients are listed in Table I. Median age of the pat-

TABLE I. Patient Characteristics

Total number of eligible and analyzable Patients	51
Age (years)	
Median	72
Range	48–85
Race	
Caucasian	42 (81%)
African American	9 (18%)
Prior Therapy	
Hormonal regimens	
1	37 (70%)
2	15 (28%)
$\geq$3	1 (2%)
Chemotherapy	13 (24%)
PSA	
Median	178 ng/ml
Range	9–5,027 ng/ml

TABLE II. Major Toxicities

Toxicity	Grade 3	Grade 4	Grade 5
Granulocytopenia	6	5	
Edema	4	1	
Malaise/fatigue	10		
Anemia	7	1	1
Vomiting	1	3	
Nausea	8		
DVT[a]	3		
Stomatitis	3	2	
Myocardial infarction			1

[a]DVT, deep venous thrombosis.

ients was 72 with a range of 48–85. Forty-two patients (82%) were white and 9 (18%) were African American. All patients had a performance status of 0–2. Fifteen patients (29%) had measurable disease and 36 (71%) had evaluable disease only. Thirty-seven patients (70%) had experienced disease progression on one prior hormonal regimen, 15 (28%) on two, and one (2%) on three hormonal regimens. Thirteen patients (24%) had received prior chemotherapy. The median PSA was 178 ng/ml with a range of 9–5027 ng/ml.

A total of 124 cycles of therapy were delivered, with a range of 1–10 cycles and a median of two cycles. Eleven patients received one cycle, 17 patients received two cycles, four patients received three cycles, five patients received four cycles, and six patients received five or more cycles. Insufficient follow-up data was available on nine patients. Nineteen patients (51%) received one cycle of therapy or less. In general, this appeared to be secondary to toxicities associated with estramustine (nausea, edema, deep venous thrombosis). Overall, granulocytopenia was the most common toxicity with 11 patients demonstrating grade ≥ 3 toxicity (21%). Ten patients developed grade ≥ 3 malaise. Nine patients developed grade $3 \geq$ nausea and/or vomiting (5 had only nausea, 1 had only Grade 3 vomiting, and 3 had nausea and vomiting). Nine patients developed grade ≥ 3 anemia (one death). Five patients developed grade ≥ 3 edema (Table II). Three patients suffered deep venous thrombosis (DVT). One died of a myocardial infarction while on treatment. Seventeen patients received excessive estramustine doses because their regimens were not capped at 15 mg/kg/day. These patients accounted for many of the patients who received less than one cycle of therapy.

Although 16 patients had measurable disease, follow-up data to measure response rate is not available as none of these patients stayed on therapy for at least two cycles. Four patients received greater than eight cycles of therapy. Thirty-two patients received at least two cycles of therapy and were assessable for response by PSA. Utilizing standard criteria of a decrease in PSA of 50% from baseline that was held for at least 4 weeks, 7 out of 51 patients demonstrated a partial response to this regimen (14%). Utilizing the 32 patients who received at least two cycles of therapy, the response rate was (22%) as measured by PSA decline. Median survival for all patients was 13 months.

DISCUSSION

Since the early 1990s efforts at novel drug development targeting prostate cancer has intensified. Many of these regimens incorporated estramustine, capitalizing on its observed preclinical synergy with a variety of anti-microtubule or topoisomerase II inhibitory agents. Estramustine plus etoposide represented one of the earliest promising combinations. However, as is the case with any new regimen, validation beyond single institution experience is necessary for the introduction of these treatments into the clinic.

This study represents the first cooperative group testing of a promising contemporary chemotherapy in hormone refractory prostate cancer. This combination was chosen for testing because of the high percentage of response rates in measurable disease sites including liver, lymph nodes, and lung as well as a high percentage of responders as measured by decrease in PSA from baseline. The original trial reported a response rate of 50% in measurable disease and 55% by PSA criteria. A second reason for choosing this regimen was the relatively shorter duration of estramustine administration as compared to the estramustine/vinblastine regimen, thus hoping to minimize side effects.

This study, unlike most prior trials in HRPCa, allowed for evaluable and measurable disease and introduced PSA as a response surrogate, thus allowing for extremely rapid accrual. This gave physicians very little time to become comfortable with the administration of this regimen. This trial was characterized by a greater than anticipated nonhematologic toxicity, most of which appears to be estramustine-related. The optimal estramustine dose to be used in combination has yet to be determined, however, it would appear that lower doses than that used within this trial have comparable response rates. In one trial, estramustine was given as 10/mg/kg/day [7]. Twenty-four of 62 patients (39%) demonstrated a decrease in pretreatment PSA levels of at least 50% from baseline. In the second trial, 30 out of 56 patients (58%) demonstrated more than a 50% decline in PSA values [8]. Both of these latter trial were single or dual institution trials. A review of patient characteristics between this trial and the three single institution trials does not reveal major

differences between the patient characteristics, although in this SWOG trial the median age of the patients was 72 as compared to 64, 65, and 67. Other potential prognostic factors such as performance status and prior systemic therapy were not appreciable [5,7,8].

A high percent of patients were removed from the study without an attempt at dose reduction of estramustine and this reflects the importance of the learning curve which comes from experience with a particular regimen. As the most, institutions only contributed one patient to the study; there was little opportunity to generate experience with the agents. While in general it is expected that a cooperative group trial have response rates lower than institutional experiences, the discrepancy in this setting is more than expected. This can be explained by the amount of early toxicity experienced by the patients and the high number that were not evaluable for response since they did not receive two cycles of therapy. Much of this toxicity was due to patients receiving an overdosage of estramustine. Forty-seven percent of patients were not evaluable for response.

CONCLUSIONS

The regimen of oral estramustine and oral etoposide as tested had greater than expected non-hematologic side effects which were related to increased doses of estramustine. It has a modest response rate as measured by PSA declines. Trials of this combination with lower doses of estramustine appear to warrant additional evaluation.

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