Phase II Study of Estramustine and Vinorelbine in Hormone-Refractory Prostate Carcinoma Patients

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The purpose of this study was to evaluate the antitumor activity of vinorelbine and oral estramustine phosphate in patients with metastatic, hormone-refractory prostate cancer. We evaluated the activity of this association using the following schedule: estramustine phosphate 600 mg/m^2/day orally days 1–42 and vinorelbine 25 mg/m^2 days 1, 8, 22, 29 cycles repeated every 56 days. Twenty-five patients were included in the study, 24 being evaluable for response and 25 for toxicity. Out of 5 patients with measurable disease, none had an objective response. Of the 24 assessable patients with bone metastases, 9 patients had a $>$ or $=$ 65% decline in pretreatment prostate-specific antigen (PSA) level, stable disease was observed in 10 and 5 patients progressed. Toxicities were minimal. Anemia was observed in 5 patients, alopecia in 4 and nausea and vomiting was observed in 6 patients. Anorexia and weight loss of more than 10% were observed in 2 patients. This combination is active and well tolerated in hormone-resistant prostate cancer. These results support the therapeutic strategy of combining agents that impair microtubule function.

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Prostatic carcinoma is the most common malignancy diagnosed in men and the second leading cause of death from cancer in American males (1). Treatment of the metastatic cancer with hormone therapy temporarily controls symptoms in 70–80% of patients (2). However, for the majority of patients the median duration of response is only 12 months. Once hormone-refractory disease is documented, treatment options are limited and prognosis is dismal. Most patients will die within 9 months (3). Antitumor response induced by chemotherapy is generally limited and of short duration. Moreover, chemotherapy is not well tolerated and is not always feasible in this subset of patients. For all these reasons new agents and strategies are needed.

Estramustine phophate, a non-nitrogen mustard carbamate derivative of estradiol 18-beta-phosphate, binds to microtubule-associated proteins, inhibits assembly and disrupts microtubule organization in vitro (4). This cellullar mechanism, rather than the hormonal effect attributable to the estrogen moiety or alkylating activity due to nitrogen mustard, is believed to be responsible for the cytotoxic effects of the compound.

Vinorelbine is a new vinca alkaloid that has demostrated high activity in different solid tumors. Encouraging results have been observed in breast cancer (5) and lung cancer (6). The main toxicities resulting from this drug are myelosupression and phlebitis. Neurotoxicity is rare and vinorelbine is probably the vinca alkaloid with the least neurotoxicity (7).

Recent phase II studies have shown promising results in metastatic hormone-resistant prostate cancer using combinations of estramustine and vinblastine (8), taxol (9, 10), or etoposide (11). Taking all these factors into account, we researched the hypothesis that vinorelbine used in combination with estramustine would be a logical approach to enhance cytotoxicity through combined though distinct antimicrotubule activity.

In this paper we report the results of a phase II study carried out between 1994 and 1996 to assess the efficiency of estramustine and vinorelbine on progressive metastatic hormone-refractory prostate cancer.

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MATERIAL AND METHODS

Patient selection

From April 1994 to February 1996, 25 eligible patients were included from the five centers that participated in this phase II study. Patients were required to have a histologic diagnosis of adenocarcinoma of the prostate with progressive metastatic disease after medical or surgical castration. For patients who had received an antiandrogen as part of the initial hormonal therapy, discontinuation of the antiandrogen for a minimum of 8 weeks was required with continued evidence of progressive disease before enrolment. Also required were a minimum life expectancy of >3 months and a Karnofsky performance status equal to or greater than 60%; no prior chemotherapy; age less than 80 years, white blood cell, hemoglobin and platelet counts above 3500 cells $\times$ mm^3, 12 g/dL and 150000 cells $\times$ mm^3 respectively; adequate renal and hepatic functions, defined as a creatinine concentration of less than or equal to 2.0 mg/dL, bilirrubin of less than 1.5 mg/dL; and measurable disease, defined as non-osseous tumor measurable in at least two dimensions, or for patients with bone metastases only, a serum prostate-specific antigen (PSA) level >10 ng/mL. Patients with a history of myocardial infarction or active angina pectoris within the 12 months preceding registration were excluded, and those with a history of deep venous thrombosis were ineligible. Patients who had received radiotherapy within 4 weeks of study entry were also excluded. All patients gave written informed consent.

Evaluations

Initial staging consisted of a complete physical examination, weight, evaluation of performance status (Karnofsky scales), chest x-ray, computed tomography of the abdomen and pelvis, bone scan, complete blood cell count, serum chemistry profiles including PSA and ECG. The evaluation during therapy consisted of a complete blood count and a PSA determination on the administration day of vinorelbine. A monthly biochemical profile and bimonthly bone scans, computed tomography of the abdomen and pelvis or chest x-ray were taken as indicated.

Treatment program

All treatment programs were administered on an outpatient basis. For 6 weeks 600 mg/m^2 estramustine was administered orally in three divided doses daily with a 2-week rest period between cycles. The estramustine dosage was determined by rounding to the nearest 140 mg (Table 1). Vinorelbine at 25 mg/m^2 days 1, 8, 22 and 29 was administered intravenously followed by a 3-week rest period. The patients were instructed not to take estramustine with food or milk products in order to avoid impaired absorption. Vinorelbine was withheld for a granulocyte count below 1500 cells per mm^3 or a platelet count of less than 75000 cells per mm^3. Estramustine was withheld for any grade 4 non-hematologic toxicity (predominantly nausea and vomiting) believed to be due to its effects. In grade 3 toxicity, the estramustine dose was reduced to one tablet every 8 h.

Treatment was discontinued in cases of patient refusal, acute life-threatening grade 3 or 4 toxicities according to CALBG Expanded Common Criteria, or progression of disease. Medical castration with a luteinizing hormone agonist was discontinued before entry. No other hormonal or corticoid therapy was allowed during treatment.

Toxicity and response criteria

Toxicity was graded according to the revised common toxicity criteria (CALBG Expanded Common Toxicity Criteria). Therapeutic effect was assessed using criteria for measurable disease, if present, and for change in serum PSA. Complete response required disappearance of all indicator lessions and normalization of biochemical parameters and PSA on two successive determinations. For patients with bidimensionally measurable soft tissue metastases, a partial response required a $\geq 50\%$ reduction in the sum of the products of the longest perpendicular diameters of all indicator lesions and a decrease from the baseline PSA value by 65% or greater (without normalization) on three successive evaluations. Progressive disease was defined as a $>25\%$ increase in any indicator lesion, the appearance of new lesions or a $>50\%$ increase in PSA level from baseline or lowest value achieved for three successive measurements at 3-week intervals. Patients who did not meet the criteria for a complete or partial response or progression were listed in a stable disease category.

If a patient presented a continued improvement in one category from the baseline Karnofsky performance status for a period of 9 weeks, he was considered a responder in clinical benefit.

Statistical analysis

The primary endpoint of this trial was antitumor response as determined by the effect of treatment on PSA and measurable disease, if present. Survival times were established from the date the patient entered into the study until time of death or the last follow-up. Survival curves were calculated by the Kaplan-Meier method (12).

Table 1

Estramustine phosphate dose according to body surface area

Body surface area	No. of pills
<1.52	2–2–2
1.52–1.74	3–2–2
1.75–1.98	3–2–3
>1.98	3–3–3

Table 2

Patient characteristics

Characteristics	No.	%
No. eligible	25	
No. assessable	24	
Age years		
Median	66	
Range	53–79	
Karnofsky PS		
Median	70%	
Range	60–90%	
Osseous disease	24	96
Measurable extraosseous disease		20
Lymph nodes	5	
Prior hormonal therapy		
Orchiectomy ± antiandrogen	5	20
LHRH agonist + antiandrogen	20	80
Gleason score		
Median	6	
Range	3–9	
PSA (ng/ml)		
Median	384	
Range	2–2693	
Pain		
Requiring narcotic	15	60
Requiring non-narcotic medication	10	40

Abbreviations: LHRH = luteinizing hormone-releasing hormone; PS = performance status.

RESULTS

The pretreatment characteristics of the 25 patients enrolled in the study are listed in Table 2. All the patients were assessable for survival and toxicity and 24 were assessable for response. One patient died a few days after the first cycle and was therefore lost to the study.

All of the patients discontinued antiandrogen therapy at least 8 weeks before protocol treatment and had continued evidence of progressive disease with increasing PSA levels. All 25 patients received one prior hormonal treatment. Five of 24 patients (20.8%) had bidimensionally measureable soft tissue metastases, and all patients had bone metastases.

As of 31 October 1997, all 24 patients had progressed, 21 have since died and none was disease free. The median survival time was 10.5 months (see Fig. 1). Two patients who experienced a partial response were retreated after progression: One experienced a new partial response and the other a stabilization of the disease. None of the others received subsequent hormonotherapy or chemotherapy, with the exception of treatment with corticoids after progression.

A total of 65 cycles of treatment was administered. A median of 3 cycles was received (range 1–7); 264 vinorelbine administrations were performed, with median administrations of 10 per patient (range 2–28).

Therapeutic activity

Bidimensionally measurable soft tissue metastases were present in 5 out of 24 assessable patients. All had lymph nodes metastases. We observed 3 patients with stabilized disease and 2 with progressive disease, no objective responses were observed.

Improvement in one or more categories of the Karnofsky performance scale was observed in 12 (50%) out of 24 patients evaluable for response. Nine patients experienced a partial response measured by PSA level and the other three experienced disease stabalization.

All 24 patients had bone metastatic disease; PSA levels decreased by 65% in 9 (37.5% partial responses, 95% interval confidence limits 18–57%). Three patients (12.5%) experienced the disappearance of one or more metastatic foci on bone scan. One patient experienced a complete response by bone scan scintigraphy, and presented with a Karnofsky performance status of 90%, with bone pain requiring non-opioid drugs and a PSA level of 515 ng/mL. Complete remission was obtained after 3 cycles, but the PSA level was 17.1 ng/mL (normal < 4 ng/mL).

The mean duration of response was 11 months. Stabilization was obtained in 10 patients. Progressive disease was observed in 5 patients and was signaled by increasing metastatic disease and/or new disease-related symptoms and decline in performance status occurring before or together with PSA progression.

Toxicity

The toxicities of vinorelbine and estramustine phosphate are listed in Table 3. Hematologic toxicities were minimal.

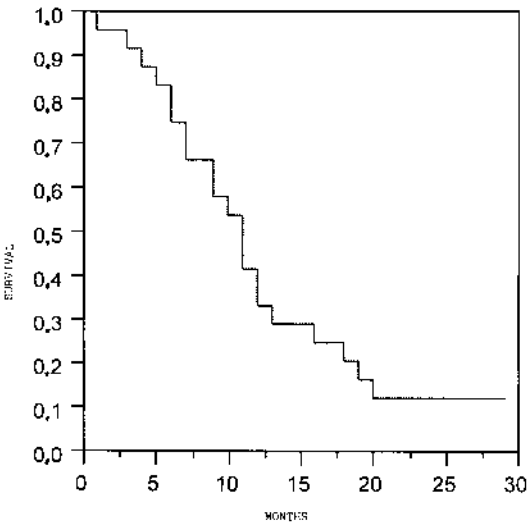

Fig. 1. Kaplan-Meier overall survival.

Table 3

Toxicities of vinorelbine/estramustine phosphate

Toxicity	Grade			
	1	2	3	4
Leukopenia	0	1	0	0
Plaquetopenia	0	0	0	0
Anemia	3	1	1	0
Anorexia	1	1	0	0
Fatigue	1	0	0	0
Nausea/vomiting	2	2	1	1
Mucositis	0	0	0	0
Diarrhea	0	1	0	0
Venous thrombosis	0	0	0	1
Weigh loss	1	2	0	0
Alopecia	3	1	0	0
Peripheral neuropathy	2	1	1	1

Leukopenia was mild, with only one patient experiencing grade 2 toxicity. We did not observe any evidence of thrombocytopenia. Anemia observed in 5 patients (3 grade I, 1 grade II and 1 grade III) was related to treatment.

Approximately 25% of patients experienced some degree of nausea and vomiting. Although usually mild to moderate and controlled with standard antiemetic medication, nausea and vomiting was severe enough to justify estramustine phophate reduction in one patient and withdrawal in another. The latter patient continued with vinorelbine treatment and a partial response was obtained. Mild asthenia was observed in 1 patient and weight loss ($>10\%$) in 2 patients. Gastric pain was observed in 5 patients, 2 with grade I, 1 with grade II, 1 with grade III and 1 with grade IV.

Thrombotic complications occurred in one patient, with the development of left femoral venous thrombosis associated with pulmonary embolism and death. This patient had stabilization of measurable disease (osseous and non-osseous) and a partial response in PSA level after two cycles with improvement in the Karnofsky performance status. There were no therapy-related deaths.

Survival

The estimated median survival time for all patients was 10.5 months (see Fig. 1). The median time of response was 11 months.

Six patients have survived for more than 18 months. Five patients were treated with LH-RH analogues and antiandrogens and one with orchiectomy and antiandrogen. All patients were treated with this regimen for at least 6 months. Four patients experienced a partial response and two a stabilization of disease.

DISCUSSION

The present study demonstrates the activity of the combination of estramustine and vinorelbine in hormone-refractory prostate cancer. Of the 24 patients included in the study, 9 had a decline greater than 65% in the measured PSA values and in 3 an amelioration was observed in the bone scan. However, we did not observe any objective response in patients with measurable disease. One patient experienced normalization of the bone scan, but PSA remained just above the normal values (PSA nadir 17.1 ng/mL). A combination of oral and endovenous administration of vinorelbine does not appear to be an uncomfortable route for patients of this type. Treatment was given on an outpatient basis and was well tolerated. No concurrent hospitalization was needed for febrile neutropenia or for other chemotherapy-related side effects.

In recent years, there has been increased interest in the treatment of hormone-resistant prostate cancer. Several studies employing different kinds of therapy have reported objective response rates of at least 50% in these patients. Although suramin is very active in the treatment of this tumor, toxicity, optimal schedule and widespread use warrant further study in cooperative group trials (13). Another interesting combination is high-dose ketoconazole with weekly doxorubicin by 24-h infusion reported by Sella et al. (14). Unfortunately this treatment can cause severe toxicity and complications requiring a high rate of hospitalization (45%).

Estramustine phosphate produces castrate testosterone levels and has been studied in several randomized trials by the National Prostate Cancer Project (NPCP) and by the European Organization for Research on the Treatment of Cancer (EORTC), both as single agents or in combination with other agents (15–17). Treatment of hormone-refractory patients with estramustine appears to give an objective response of 0%–37%. Other regimens consist of combinations of estramustine and vinblastine (8, 18), taxol (9, 10) or etoposide (11).

These results are remarkable in that estramustine alone produces only rare objective responses but produces a high response rate when in combination with others agents which interact with the nuclear matrix.

Our results are similar to those reported by other authors employing combinations of estramustine, but toxicity was mild and in most cases was associated with estramustine phosphate.

The results of this multi-institution phase II trial suggest that the combination of oral estramustine and endovenous vinorelbine is an active chemohormonal regimen in the treatment of hormonorefractory prostate cancer. Toxicity is mild and reversible and should be evaluated in a large series.

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