Vinorelbine and Estramustine in Androgen-Independent Metastatic Prostate Cancer

A Phase II Study

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BACKGROUND. The aim of this study was to determine the safety and activity of vinorelbine in combination with estramustine in men with androgen-independent metastatic prostate cancer.

METHODS. Twenty-five men with androgen-independent metastatic prostate cancer were treated with the combination of vinorelbine and estramustine. Vinorelbine 25 mg/m^2 was administered by intravenous bolus on Days 1 and 8. Estramustine 140 mg was administered three times a day by mouth on Days 1 through 14. Treatment was repeated every 21 days.

RESULTS. A total of 132 cycles of treatment were administered. The median number of cycles per patient was 5 (range: 1–16). Mild Grade 1 or 2 gastrointestinal toxicity and fatigue were the most common adverse effects. Hematologic toxicity was minimal. Treatment resulted in a sustained $>$ 50% decrease in serum prostate-specific antigen (PSA) in 6 of 25 patients (24% of patients; 95% confidence interval (CI) 9–45%). The median duration of PSA response was 10 weeks (range: 3–39 weeks). Of the five men with bidimensionally measurable disease, none achieved a complete or partial response. There were no documented improvements in post-treatment bone scans. Median overall survival time was 14.1 months.

CONCLUSIONS. The combination of vinorelbine and estramustine is a well-tolerated and modestly active regimen in men with androgen-independent metastatic prostate cancer. ***Cancer*** **2000;89:1824–8.** © *2000 American Cancer Society.*

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Estramustine phosphate, a nornitrogen mustard carbamate derivative of estradiol, is rapidly dephosphorylated to estramustine in vivo.[1] Preclinical studies have indicated that estramustine acts by binding to microtubule-associated proteins, depolymerizing cytoplasmic microtubules, inhibiting P-glycoprotein function, and by disrupting the nuclear matrix.[2] In Phase II clinical studies of single agent estramustine phosphate for men with androgen-independent prostate cancer, objective response rates between 19% and 69% have been reported.[3] In a contemporary, multicenter, Phase II study of 42 men with androgen-independent prostate cancer, treatment with single agent estramustine produced a $>$ 50% posttreatment decrease in serum prostate-specific antigen (PSA) levels in 21% of men and subjective pain relief in 31% of men.[4]

Preclinical and clinical studies have suggested that an additive or synergistic activity occurs when a combination of estramustine and other antimitotic agents (including vinblastine, etoposide, paclitaxel, or docetaxel) is used.[5] Vinorelbine, a semisynthetic vinca alkaloid, inhibits microtubule assembly and acts as a single agent in a variety

of solid malignancies.[6] In a Phase II study of androgen-independent prostate cancer, 14 of 37 men (38%)treated with single-agent vinorelbine received a clinical benefit.[7] Among the 14 patients who experienced clinical benefit from this therapy, 4 (29%) had a $>$ 50% decrease in their posttreatment PSA levels.

The current study is also a Phase II clinical study of vinorelbine and estramustine for men with androgen-independent prostate cancer. Our study endpoints included posttreatment PSA level decrease, measurable disease response, pain intensity, narcotic analgesic use, and survival time for each patient in the study.

PATIENTS AND METHODS

Patient Eligibility

Between January 1998 and April 1999, 25 men entered the study. All of these patients had adenocarcinoma of the prostate confirmed by histology, metastatic disease confirmed by computed tomography or bone scan, and all had exhibited disease progression after androgen deprivation and antiandrogen withdrawal. Disease progression was defined as either (1) increase in the product of bidimensional diameters of one or more sites of measurable disease or (2) increase in serum PSA on two consecutive determinations with an entry PSA value of $>$ 2 ng/mL and $>$ 150% nadir value.

Exclusion criteria were prior chemotherapy for prostate cancer, prior treatment with suramin, radiation therapy within four weeks of the start of the study, radiopharmaceutical treatment within eight weeks of the study, treatment with an antiandrogen or steroids within four weeks of the study, significant peripheral neuropathy, myocardial infarction or deep venous thrombosis during the year before the study, and New York Heart Association Class III or IV heart disease. Upon entering the study, all patients had a Karnofsky performance status (KPS) score of $>$ 50, a white blood cell (WBC) count of $>$ 3000 cells/mm^3, an absolute neutrophil count (ANC) of $>$ 1000 cells/mm^3, a platelet count of $>$ 100,000 cells/mm^3,a serum creatinine level of $<$ 2.0 mg/dL, a total bilirubin concentration of $<$ 1.5 times the upper limit of institutional normal, and a serum alanine aminotransferase (ALT) level of $<$ 3 times the upper limit of institutional normal. The Institutional Review Board approved this study. All patients provided written informed consent before they entered the study.

Treatment Regimen

Pretreatment evaluation included physical examination, determination of KPS score, electrocardiogram, a complete blood count, serum chemistries, serum PSA, a bone scan, a chest radiograph, and an abdominal-pelvic computed tomography (CT) scan.

For one week before the start of treatment, all patients completed a daily pain diary and a diary of analgesic use. Pain was assessed using the visual analog scale (VAS).[8] Analgesics were converted to their morphine equivalents to derive a daily score of analgesic use.[9]

Each 21-day treatment cycle consisted of vinorelbine 25 mg/m^2 intravenously on Days 1 and 8 and estramustine 140 milligrams orally three times per day on Days 1 through 14. Vinorelbine was administered by intravenous bolus over 6–10 minutes. Estramustine was administered one hour before or two hours after meals.

Treatment was continued until progressive disease occurred or intolerable adverse effects developed. Men who were not castrated surgically continued treatment with a gonadotropin-releasing hormone (GnRH) agonist throughout the study. Radiation therapy or additional chemotherapy was not permitted.

Response and Toxicity Criteria

Physical examination, symptom assessment, KPS determination, and CBC, serum creatinine, serum ALT, total bilirubin, and serum PSA tests were repeated before each three week treatment cycle. Bone scans were repeated every three cycles (i.e. every nine weeks). For patients with bidimensionally measurable disease, abdominal-pelvic CT scans also were repeated every three cycles. Toxicity was assessed at least every three weeks using National Cancer Institute (NCI) common toxicity criteria. Men who were able to evaluate their pain and baseline narcotic analgesic use completed daily pain and analgesic use diaries for the duration of the study.

All patients who started treatment were evaluated for toxicity, PSA response, and measurable disease response. PSA response was defined as a $>$ 50% posttreatment decrease in serum PSA that was maintained on two determinations at least three weeks apart. Measurable disease response was defined as $>$ 50% posttreatment decrease in the product of the bidimensional diameters of one or more sites of measurable disease. For responding patients, response duration was defined as the interval between response to the drug therapy and onset of progressive disease (defined below).

Evaluable pain was defined as a baseline pain intensity of greater than or equal to 20 millimeters on the VAS. Positive response in pain intensity was defined as a decrease in patient-reported pain to $<$ 50% baseline pain intensity lasting for at least four consecutive weeks. Evaluable narcotic use was defined as analgesic baseline daily analgesic scores of greater than or equal to 10 morphine milligram equivalents. Positive response to

TABLE 1
Patient Characteristics

No. of patients	25
Age (yrs)	
Median	71
Range	49–88
Karnofsky Performance Status	
Median	90
Range	70–100
PSA (ng/mL)	
Median	230
Range	41–1663
Hemoglobin (g/dL)	
Median	12.3
Range	8.6–14.9
Metastases, no. of patients (%)	
Bone	23/25 (92)
Soft tissue	5/25 (20)
PSA-only	0/25 (0)
Measurable disease	5/25 (20)
Evaluable pain intensity	7/25 (28)
Evaluable narcotic use	4/25 (16)

narcotic analgesic use was defined as a decrease in narcotic analgesic use to $<$ 50% baseline use lasting for at least four consecutive weeks.

Progressive disease was defined as an occurrence of any of the following: the appearance of new sites of metastatic disease, the need for radiation therapy, a duration of $>$ four weeks of patient-reported pain increase from baseline by $>$ 20 millimeters on the VAS, a $>$ 25% increase in the product of the bidimensional diameters of one or more sites of measurable disease, a posttreatment PSA level increase to $>$ 150% of the study nadir that was maintained on two determinations at least three weeks apart.

Statistical Analysis

The primary objective of this study was to define the activity of vinorelbine and estramustine in men with metastatic androgen-independent prostate cancer. Survival was defined as the time between initiation of treatment and death. If death had not occurred, survival time was considered statistically censored at the last follow-up. Overall survival was analyzed by the Kaplan–Meier method.

RESULTS

Patient Characteristics

Table 1 summarizes the clinical characteristics of the 25 men who entered into the study. Their median age was 71 years. Their median KPS score was 90. Twenty-three (92%) patients had bone metastases, and 5 (20%) patients had measurable visceral metastases. No patient had PSA-only disease. Their median serum PSA level at study entry was 230 ng/mL (range: 41–1662 ng/mL).

TABLE 2
Clinical Outcomes

Outcome	No. of Patients	Percent of Patients	95% CI
PSA (n = 25)			
$>$ 50% PSA decrease	6/25	24	9–45%
$>$ 80% PSA decrease	1/25	4	0–20%
Measurable disease (n = 5)	0/5	0	—
Pain intensity (n = 7)	1/7	14	—
Analgesic use (n = 4)	1/4	25	—

Toxicity

A total of 132 treatment cycles were administered to 25 patients. The median number of cycles per patient was 5 (range: 1–16 cycles). Twenty-three (92%) patients completed 2 or more cycles of treatment. Seventeen (68%) patients discontinued treatment because of progressive disease. Six (24%) patients discontinued treatment due to toxicity. One (4%) patient whose disease had stablized after four cycles of treatment withdrew consent for additional treatment. One (4%) patient who responded to treatment elected to discontinue therapy after 11 cycles.

One patient died from an unwitnessed cardiac arrest two weeks after starting therapy. No postmortem examination was performed. This event possibly was related to study treatment. There were no other treatment-related deaths.

Hematologic toxicity was minimal; one patient experienced Grade 3 leukopenia. There were no other Grade 3 or greater hematologic toxicities. Seven patients experienced Grade 3 nonhematologic toxicities including deep venous thrombosis (one patient), myocardial ischemia (one patient), fatigue (one patient), hearing loss (one patient), exacerbated macular degeneration (one patient), dyspnea (one patient), and infection (one patient).

The most common adverse events were mild fatigue and gastrointestinal toxicity. Seven patients (29%) experienced Grade 1 or Grade 2 fatigue. Five patients (20%) experienced Grade 1 or Grade 2 anorexia, nausea, or vomiting. One patient discontinued treatment because of Grade 2 gastrointestinal toxicity.

Response and Survival

Table 2 summarizes the clinical outcomes. All patients had elevated baseline PSA levels that could be evaluated for PSA response to treatment. Treatment resulted in a sustained $>$ 50% decrease in serum PSA in 6 of 25 patients (24%; 95% CI 9–45%). Treatment resulted in a sustained $>$ 80% decrease in serum PSA

TABLE 3
Clinical Trials of Vinorelbine for Androgen-Independent Prostate Cancer

Regimen	Author (reference)	n	> 50% PSA response rate (95% CI)	> 80% PSA response rate (95% CI)	Measurable disease response (%)	Survival time
Vinorelbine 22 mg/m^2/week	Fields-Jones (7)	49	Not reported	Not reported	0/5 (0)	10.6 mos
Vinorelbine 20 mg/m^2 Day 1–8, 28, 35 Estramustine 400 mg/m^2 Day 1–42 Etoposide 50 mg/m^2 Day 1–14, 28–42	Colleoni (12)	25	56% (37–75%)	24% (7–41%)	2/3 (66)	11.7 mos
Vinorelbine 25 mg/m^2 Day 1–8, 22, 29 Estramustine 600 mg/m^2 Day 1–42	Carles (11)	25	38% (18–57%)	Not reported	0/5 (0)	10.5 mos
Vinorelbine 25 mg/m^2 Day 1–8 Estramustine 420 mg Day 1–14	Smith[a]	25	25% (9–45%)	4% (0–20%)	0/5 (0)	13.8 mos

Response duration and survival are median values. Clinical benefit response is abbreviated CBR.
[a] Present study.

in 1 patient (4%; 95% CI 0–20%). For the 6 patients with PSA responses to therapy, the median duration of response was 10 weeks (range: 3–39 weeks).

Among five patients with bidimensionally measurable disease, none (0%) experienced a complete or partial measurable disease response. Two patients with measurable disease had a > 50% posttreatment decrease in their serum PSA levels; their maximum posttreatment PSA decreases were 98% and 66%, respectively. Twenty-three out of 25 (92%) patients had bone scans positive for metastases at study entry. There were no objective improvements in their posttreatment bone scans.

Eight men had evaluable baseline pain intensity and/or evaluable narcotic analgesic use (significant pain intensity only: four patients; evaluable narcotic use only: one patient; evaluable pain intensity and narcotic use: three patients). Among these eight patients, only one experienced a symptomatic response. This patient had both evaluable pain intensity and narcotic use. He experienced a positive pain response and discontinued narcotic analgesic use. This patient also experienced a PSA response; his duration of PSA response was the longest observed in this study (39 weeks). Among the other seven patients with evaluable pain intensity or narcotic use, there were no symptomatic responses. Among these 7 symptomatic nonresponders, 1 patient experienced a PSA response; his response duration was 17 weeks.

The median survival time was 14.1 months. The overall survival rate at one year for all patients in the study was 67%.

DISCUSSION

This study demonstrated that vinorelbine and estramustine was a well-tolerated and modestly active regimen in men with metastatic androgen-independent prostate cancer. Hematologic toxicity was minimal. The rate and severity of myelosuppression was less than that observed in a population of androgen-independent prostate cancer patients who were treated with vinorelbine (22 mg/m^2 weekly) alone.[7] In a prospective Hoosier Oncology and Fox Chase Network randomized study, the combination of vinblastine and estramustine was associated with less myelosuppression than treatment with vinblastine alone.[10] This observation suggests that estramustine may have a myeloprotective effect when administered in combination with vinblastine. The low rate of myelosuppression in the current study may reflect a similar myeloprotective effect in combination with vinorelbine. Alternatively, the low rate of myelosuppression in the current study might have occurred because of our vinorelbine dosing schedule and patient selection criteria.

Posttreatment decreases in serum PSA levels of > 50% and > 80% were observed in 24% and 4% of patients, respectively. Among five patients with bidimensionally measurable visceral metastases, there were no measurable disease responses. There were no objective improvements in posttreatment bone scans. Symptomatic responses were uncommon. The median overall survival time was 14.1 months.

The results from this study are comparable to other studies of vinorelbine for androgen-independent prostate cancer (Table 3). In a multicenter study, Fields-Jones et al.[7] reported that single agent vinorelbine resulted in a clinical benefit response rate of 39% and median response duration of 6 months. Among 14 patients with clinical benefit, 4 (29%) had > 50% PSA level decreases. There were no responses among five patients with measurable disease. The median survival time for these 5 patients was 10.6 months. Colleoni et al.[12] reported a > 50% posttreatment PSA level decrease in 14 of 25 (56%) patients treated with vinorelbine, estramustine, and oral etoposide. Treatment resulted in partial responses for two of three patients

with measurable visceral metastases. Their median survival time was 11.7 months. Carles et al.[11] reported a > 50% posttreatment PSA level decrease in 9 of 24 (38%) patients treated with vinorelbine and estramustine. There were no objective responses in five men with measurable visceral metastases. Their median survival time was 10.5 months.

The estramustine dose in the current study was lower than the dose used in other studies of combination therapy with estramustine plus vinblastine [10] or estramustine plus vinorelbine.[11] This lower estramustine dose was selected to minimize treatment-related gastrointestinal and thromboembolic toxicity. Gastrointestinal toxicity was mild, and only one patient discontinued treatment because of gastrointestinal side effects. The rate of thromboembolic events was similar to that observed in other combination studies.[10,11] Other investigators have evaluated shorter schedules of estramustine administration as a strategy to decrease treatment-related toxicity.[13–15] Intermittent administration of estramustine (Days 1–5) in combination with docetaxel was associated with similar rates of thromboembolic and gastrointestinal toxicity, although the gastrointestinal side effects were limited to the brief period of estramustine administration.[13] Additional studies are required to determine the optimal estramustine dose and schedule for combination therapy.

The modest activity of combination therapy with vinorelbine and estramustine suggests that other regimens are more appropriate for further clinical development. Recent studies of combination therapy with taxanes and estramustine have reported promising results with measurable disease response rates of 20–44% and PSA response rates of 53–82%.[13–18] Treatment was associated with activity by other outcome criteria including bone scan improvement, decreased pain intensity, and decreased narcotic analgesic use. In the current study, treatment was not associated with measurable disease responses or bone scan improvements. Symptomatic responses were uncommon. Based on its favorable safety profile, however, combination therapy with vinorelbine and estramustine may be an appropriate second-line treatment for patients who are not candidates for treatment with a taxane.

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