Dose Escalation of Oral Vinorelbine in Combination with Estramustine in Hormone-Refractory Adenocarcinoma of the Prostate

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BACKGROUND. The primary objective of the current study was to identify the tolerable dose level of oral vinorelbine when given in combination with estramustine to men with hormone-refractory prostate cancer (HRPC). The secondary objectives were to describe the toxicities of the combined regimen in patients with HRPC and to estimate the efficacy of oral vinorelbine in combination with estramustine based on the prostate-specific antigen (PSA) response.

METHODS. Thirty-three patients with HRPC were treated on a 28-day cycle with estramustine at a dose of 140 mg orally 3 times a day on Days 1-3 and 8-10. Vinorelbine was given orally on Days 2 and 9. The initial dose of vinorelbine was 50 mg/m^2 and was escalated to 70 mg/m^2 using the time-to-event continual reassessment method.

RESULTS. Three of 17 patients experienced dose-limiting toxicity at the 70 mg/m^2 dose level of oral vinorelbine. One patient experienced dose-limiting toxicity at a dose of 60 mg/m^2 and no dose-limitig toxicities were reported at the 50 mg/m^2 dose. The overall response rate by $\geq$50% reduction in PSA was 17.2%, (95% confidence interval, 5.9-35.8%).

CONCLUSIONS. Oral vinorelbine at doses of 70 mg/m^2 may be safely combined with estramustine. The combination appears to have modest activity in men with advanced prostate cancer. The trial design employed the time-to-event continual reassessment method, which potentially allows for rapid accrual, a more complete assessment of toxicities, and a larger fraction of patients to be treated at an effective dose. More active regimens are needed to further evaluate the utility of this clinical trial design in patients with prostate cancer. ***Cancer*** **2006;106:2617–23.**

KEYWORDS: prostate cancer, Phase I trials, biochemical resistant, clinical trials, adult medical oncology.

Adenocarcinoma of the prostate is the second leading cause of death from neoplasia in men.[1] Roughly 50% of men will recur with advanced disease after definitive local therapy and most are effectively treated with androgen ablation. The duration of response to androgen ablation is limited, however, with most patients developing disease recurrence with hormone-refractory prostate cancer (HRPC). Responses to secondary hormonal therapies are typically short-lived and remain only a temporary option. In general, chemotherapy for HRPC has been considered to be palliative, although recent studies have shown improvements in survival and quality of life.[2–5]

A number of chemotherapy agents that block the microtubule apparatus have been evaluated in combination or as single agents in HRPC. Estramustine (Emcyt; Pfizer, Groton, CT), a nor-nitrogen mus-

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tard linked to an estrogen, has been used in combinations with taxanes and vinca alkaloids to create complementary inhibition of microtubule assembly and function.[6–8] Estramustine binds to microtubule-associated proteins, inhibiting microtubule assembly. Vinorelbine (Navelbine; GlaxoSmithKline, Philadelphia, PA), a vinca alkaloid, inhibits mitosis at metaphase through interaction with tubulin. In contrast to other vinca alkaloids, vinorelbine appears to bind preferentially to the mitotic spindle, with lesser effects on the microtubules in neural structures.[9]

In a Phase II trial of 25 patients with metastatic prostate cancer using the combination of intravenous vinorelbine and estramustine, 9 patients had a >65% decline in prostate-specific antigen (PSA), whereas 10 patients had stable disease. Toxicities were minimal and included alopecia, nausea/vomiting, and anorexia.[10] A second Phase II trial of this combination demonstrated a ≥50% decline in PSA in 15 of 21 patients with HRPC. The most frequent adverse events were edema and thromboembolic complications.[11] Oral vinorelbine is a newer formulation. A Phase II evaluation of oral vinorelbine in locally advanced or metastatic breast cancer demonstrated response rates of 30%. The main adverse events were neutropenia and gastrointestinal disorders. The efficacy and toxicity profiles of the oral formulation appeared to compare favorably with those of intravenous vinorelbine.[12]

We conducted a Phase I trial to determine the tolerable dose of oral vinorelbine in combination with oral estramustine on an intermittent schedule in patients with HRPC. The secondary objective of the study was an initial assessment of the efficacy of this combination.

MATERIALS AND METHODS

Patient Eligibility

Eligible patients had a histologic diagnosis of adenocarcinoma of the prostate with measurable (bidimensional) or evaluable (bone scan or rising PSA) disease. All patients underwent nonsteroidal antiandrogen withdrawal with a demonstrated rise in PSA after withdrawal. Those with PSA as their only evidence of progressive disease had to have a value ≥4 ng/mL. Eligibility criteria included a granulocyte count ≥1500 cells/mm^3, a platelet count ≥100,000 cells/mm^3, bilirubin ≤1.5 times the institutional upper limit of normal, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≤2.5 times the institutional upper limit of normal, creatinine ≤1.2 times the institutional upper limit of normal, an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, age ≥18 years, and an estimated life expectancy ≥12 weeks. Patients were excluded if they had received prior vinca alkaloid-based cytotoxic chemotherapy or radiation to ≥50% of the total bone marrow or if they had evidence of brain metastasis or untreated spinal cord compression. No prior malignancy except for in situ carcinoma, nonmelanoma skin cancer, or adequately treated malignancy that had been inactive for <3 years was allowed. Patients with preexisting neuropathy ≥Grade 2, active gastrointestinal disease, or a disorder that altered gastrointestinal motility or absorption were also excluded. The Institutional Review Board of the University of Michigan Medical School (Ann Arbor, MI) reviewed and approved the trial and the informed consent document. Written informed consent was obtained from all patients before enrollment in the study. Data and safety monitoring were conducted under the criteria of the National Cancer Institute (NCI)-approved plan for the University of Michigan Comprehensive Cancer Center.

Trial Design

All patients were treated and followed as outpatients at the University of Michigan Comprehensive Cancer Center. The trial utilized a time-to-event continual reassessment method (TITE-CRM) design[13–15] for the dose escalation of vinorelbine. TITE-CRM was used to monitor the trial by estimating the rate of dose-limiting toxicity (DLT) while optimizing the number of patients treated at effective doses and maintaining open trial enrollment. The primary endpoint was to identify the oral vinorelbine level associated with toxicity in 30% of patients when given in combination with oral estramustine. Secondary endpoints included determining the toxicities, response rate, time to disease progression, number of cycles of response, and time to treatment failure.

Patients remained on primary androgen ablation during chemotherapy. Treatment consisted of 28-day cycles with estramustine at a dose of 140 mg orally 3 times a day on Days 1-3 and 8-10 and vinorelbine orally on Days 2 and 9. The estramustine dose was held constant, whereas the vinorelbine dose level was assigned using the TITE-CRM algorithm. The initial dose of vinorelbine was 50 mg/m^2 based on the toxicity estimates from prior studies. When a patient became eligible for enrollment, the DLT for each dose level was estimated based on our prior expectations of toxicity and on the trial experience up to that time, and the highest vinorelbine dose with an estimated DLT ≤30% was assigned to that patient. The experience of prior patients, who had not completed the 90-day acute toxicity observation window and who had not experienced a DLT, was weighted proportionally. The dose could not be escalated until at least 180 days of cumulative observation of acute toxicity in

patients enrolled at a particular dose level. Dose escalation was restricted to 1 level between patients but there was no restriction on the number of levels that the dose could be reduced. Doses could be decreased based on the accumulated toxicity data at any time when the algorithm indicated that the 30% threshold for toxicity rate had been exceeded.

After completion of 3 cycles, patients who achieved a ≥50% reduction in the PSA from baseline were observed until the PSA increased to ≥50% of the nadir value, at which point they were eligible for retreatment. Patients who had <50% decrease in PSA were continued on therapy until they had evidence of disease progression, toxicity, or patient/physician decision to discontinue therapy. Accrual for the study continued until 30 evaluable patients were entered, with evaluable defined as patients completing at least 1 cycle of chemotherapy or experiencing a DLT.

Dose Adjustments for Toxicity

No dose adjustments were made for an absolute neutrophil count (ANC) of ≥1500 cells/m^3 on the day of treatment. If the ANC was between 1500 and 1000 cells/m^3 the vinorelbine dose was reduced by 50%. If the ANC was <1000 cells/m^3, vinorelbine and estramustine were held. Patients were retreated after 1 week if the ANC reached the threshold values. Estramustine would then be given on Days 15-17 and vinorelbine given on Day 16. If retreatment criteria were not met, estramustine and vinorelbine were held until the next cycle. If chemotherapy could not be administered for 3 consecutive weeks then treatment was discontinued. Patients who had their dose reduced could have the dose escalated back to full dose if subsequent ANC nadirs were ≥1500 cells/m^3. Dose adjustments for vinorelbine were also made for hepatic toxicity. For a bilirubin level of 2.1 to 3.0 mg/dL, 50% of the prior dose was given, and >3.0 mg/dL 25% of prior dose was given. Dosing was also held for a Grade 2 or greater neurotoxicity. There was no dose modification for estramustine. If a patient was unable to tolerate estramustine they were to be withdrawn from the study.

Assessment of Toxicity and Response

DLT was defined using National Cancer Institute Common Toxicity Criteria (version 2.0), as Grade 4 hematologic toxicity lasting ≥7 days, any episode of febrile neutropenia, or ≥Grade 3 nonhematologic toxicity. At the completion of therapy, bone scan or computed tomography (CT) scans were obtained if positive on pretreatment evaluation and also at the time of progression by PSA criteria. A complete response (CR) was defined as a complete disappearance of all measurable and evaluable disease and/or a PSA <0.1 ng/mL for at least 6 weeks. A partial response (PR) was a ≥50% decrease from baseline in the sum of the products of perpendicular dimensions of all measurable lesions and/or a ≥50% decrease in PSA from baseline for at least 6 weeks. The response after each course was defined as a decrease of at least 50% from the maximum PSA value before that course of chemotherapy was started. Progression for the purposes of reinitiating therapy in patients who had responded was defined as a 50% increase in PSA from the lowest value measured during or after the prior course of treatment. At all other times, progression was defined as a 25% increase in PSA from baseline, measured at 2 successive levels at least 4 weeks apart (in those with a nadir PSA ≤0.1 ng/mL, the level had to be ≥0.5 ng/mL by the second measure) or a 25% increase in the sum of products of measurable lesions over the smallest sum observed, or appearance of any new lesion. For patients with bone-only disease, new lesions on bone scan were required to meet the definition of progression. Stable disease was defined as not meeting criteria for CR, PR, or progression.

Statistical Analysis

At the end of the trial the posterior mean of the dose-toxicity parameter, α, and, correspondingly, the DLT at each dose level, were calculated using the logistic dose-toxicity model and exponential prior distribution on α that were used to conduct the trial. The recommended dose level for future study was based on choosing the highest dose level that met the target toxicity rate of 30%. All analyses were performed using SAS software (SAS Institute Inc., Cary, NC).

RESULTS

Patient Characteristics

Thirty-three eligible patients were registered from February 10, 2002 to November 11, 2003. Patient characteristics are summarized in Table 1. All patients were male and 97% were white. ECOG performance status was 0-1. The median age was 66 years (range, 49-82 years). Thirty-one had detectable cancer by either bone scan, CT, or both. All patients had hormone-refractory disease with elevated PSA and a median number of prior hormonal therapies of 2 (range, 1-4 therapies). The majority (67%) had received prior chemotherapy (median number of regimens, 1; range, 0-3 regimens). Ten patients (30%) had previously received docetaxel and 12 (36%) had received estramustine.

Toxicity

Of 33 patients enrolled in the study, 31 were evaluable for toxicity (Table 2). Patient 1 completed the first

TABLE 1
Patient Characteristics

Characteristic	Value
Total no. of patients enrolled	33
Total no. of patients evaluable	31
Median no. of cycles per patient	3 (range, 1–7)
Median age in years	66 (range, 49–82)
Median ECOG performance status	0 (range, 0–1)
Sites of disease (no. of patients)	
Bone only	13
CT only	4
Both bone scan and CT	14
PSA only	2
Median PSA	82.7 (range, 6.8–2558)
Prior local therapy (no. of patients)	
Radical prostatectomy	15
Definitive RT	11
Radical prostatectomy w/salvage RT	8
Other	2
Prior systemic therapy (no. of patients)	
Median no. of hormonal modalities	2 (range, 1–4)
Median no. of chemotherapy modalities	1 (range, 0–3)
No. of patients on vaccine trial	4
Palliative RT (no. of patients)	
External beam	9

ECOG: Eastern Cooperative Oncology Group; CT: computed tomography; PSA: prostate-specific antigen; RT: radiation therapy.

TABLE 2
Toxicity (Grade 3/4)*

Lymphopenia	3
Neutropenia	2
Neutropenia/fever	0
Anemia	1
AST/ALK-P elevation	1
Nausea/vomiting	1
Fatigue	1
Diarrhea	1
SOB	2
Hyperkalemia	1
Clotting	2
Incontinence	1

AST: aspartate aminotransferase; ALKP: alkaline phosphatase; SOB: shortness of breath.
* Toxicity was assessed using National Cancer Institute Common Toxicity Criteria (version 2.0).

cycle but never returned for follow-up. Patient 12 received 1 dose of vinorelbine and died unexpectedly 2 weeks later of a hemorrhagic cerebrovascular accident that was determined to be unrelated to therapy. DLTs included 1 patient with atrial fibrillation and nausea (dose level of 60 mg/m^2), 2 patients with vomiting (both at a dose of 70 mg/m^2), and 1 patient with a myocardial infarction (at a dose of 70 mg/m^2) who was found to have previously unsuspected, severe 3-vessel coronary artery disease. Another patient developed urinary obstruction and <Grade 2 elevated liver function tests (at a dose of 70 mg/m^2). His symptoms were due to disease progression and were not believed to be DLTs. One patient developed an episode of congestive heart failure and fatigue (at a dose of 70 mg/m^2) after abruptly discontinuing his diuretic therapy. Two patients developed thrombosis, 1 mentioned above with a myocardial infarction and another with a deep vein thrombosis who continued therapy with anticoagulation until disease progression. Toxicities by dose level are summarized in Table 3.

TABLE 3
Dose Level and Dose-Limiting Toxicity

Level	Dose	Prior DLT Estimate	No. of DLT/ Patients	Posterior DLT Estimate
1	30	10%	0/0	3.9%
2	40	15%	0/0	6.6%
3	50	20%	0/5	9.6%
4	60	25%	1/9	13%
5	70	30%	3/17	16.8%

DLT: dose-limiting toxicity.

Dose escalation and the associated toxicities at each level and for each patient are described in Table 4. Six patients were enrolled at the starting vinorelbine dose of 50 mg/m^2. The dose was then increased to 60 mg/m^2 beginning with the seventh patient. The dose was escalated to 70 mg/m^2 after Patient 11. After the initial dose increase to 70 mg/m^2, 3 patients developed DLT. Therefore, when the dose for Patient 17 was assigned, the TITE-CRM algorithm estimated that the 70 mg/m^2 dose level had exceeded the target toxicity level and Patient 17 was assigned to a dose of 60 mg/m^2. The next 4 subjects (Patients 17-20) were treated at the 60 mg/m^2 dose, after which the vinorelbine dose for the final 13 subjects was reescalated to 70 mg/m^2 without further dose modification during the course of the trial.

Response

Of the 33 patients enrolled, 29 were evaluable for a response (Table 5). The 2 patients who were not evaluable for toxicity were not evaluable for response. Patient 8 developed dose-limiting atrial fibrillation and nausea during his first cycle of therapy. Patient 21 developed rapidly progressive disease with ureteral obstruction after 1 cycle of therapy and was subsequently taken off study. His rapid disease progression required intervention and interruption of therapy. Neither patient had adequate therapy administered to allow assessment of response.

Five patients (17.2%; 95% confidence interval, 5.9-

TABLE 4
Dose Escalation and Toxicities

Dose Level, mg/m^2	Patient No.	Non-DL Toxicity (Grade 3-4)*	DL Toxicity
50	1 (Not evaluable)		
	2	Lymphopenia	
	3		
	4	Lymphopenia	
	5		
	6		
60	7		
	8		Atrial fibrillation Nausea
	9		
	10		
	11		
	17		
	18		
	19		
	20	DVT	
70	12 (Not evaluable)		
	13		Vomiting
	14		Vomiting
	15		Myocardial infarction
	16		
	21		
	22	Anemia, diarrhea, SOB	
	23		
	24		
	25		
	26		
	27	Lymphopenia, neutropenia	
	28	Pain	
	29		
	30		
	31		
	32		
	33	SOB	

DL: dose level; DVT: deep vein thrombosis; SOB: shortness of breath.
* Toxicity was assessed using National Cancer Institute Common Toxicity Criteria (version 2.0).

TABLE 5
Response

≥50% PSA Response		5
	Response by vinorelbine dose	
	50 mg/m^2	0
	60 mg/m^2	2
	70 mg/m2	3
Stable disease		7
Progressive disease		17
Patient withdrawal from study		7
No. of patients entering observation		5
Median duration of observation period		48 days (range, 14–66 days)

PSA: prostate-specific antigen.

35.8%) had a PSA response during the course of their therapy and entered the observation stage per protocol. The median duration of observation before requiring the resumption of therapy was 48 days (range, 14-66 days). One patient experienced another PSA response after being restarted on therapy and underwent a second period of observation, ultimately developing disease recurrence and progression on further therapy. The second patient withdrew after entering the observation phase as he had relocated to another state. The third was restarted on therapy but withdrew after developing urinary obstruction despite developing another PSA response. One failed to return for further therapy due to his debilitated condition at the time of disease progression, and the last patient received an additional 4 cycles of therapy and then withdrew from the study due to symptoms of fatigue.

The median number of cycles administered to each patient was 3 (range, 1-7 cycles). At a median follow-up of 9 months, 13 patients (45%) had died. The median survival of all patients enrolled was 18.6 months.

DISCUSSION

Therapy for HRPC remains palliative and the efficacy of a regimen needs to be balanced against the toxicity. Our aim in designing an oral regimen given in an intermittent fashion was to minimize toxicity and to emphasize the quality of life for patients in this setting. We elected to use the TITE-CRM[14,15] for the dose escalation of oral vinorelbine. The TITE-CRM assumes a simple model for the time to occurrence of toxic response as a function of dose, and allows information from all patients enrolled in the trial to be employed when assigning a new patient to a dose level. This method has several potential advantages over the "traditional" 3 or 6 subjects per cohort design that is used for Phase I studies.

First, it allows subjects to be continuously recruited throughout the trial, without recruitment pauses between dose levels. The duration of > 1.5 years to complete enrollment for this study reflects the restricted criteria inherent in our trial and the population base available to participate at our institution. Second, the target toxicity rate for the trial is variable. The traditional Phase I design has a fixed implied rate of 33%. For this study, we chose 30% as the target rate. Third, the TITE-CRM design is potentially more accurate at determining the maximum tolerated dose (MTD) than the traditional design. An analysis with 500 simulations based on the posterior toxicity rates estimated for each of the 5 dose levels from our study (Table 3) shows that the traditional design correctly identifies the 70 mg/m^2 dose as the MTD only 51.4% of

the time. In contrast, 500 simulations of the TITE-CRM design using the same toxicity estimates found that the 70 mg/m^2 dose level was correctly identified as the MTD 100% of the time. The improved level of precision does not appear to be based on the increased sample size for a TITE-CRM trial. Whereas the traditional design would also accrue 30 patients if 6 patients were needed for each of the 5 dose levels, the average sample size for the traditional design over the 500 simulations was 18.9 subjects with a mode of 18. To test the impact of the increased sample size on the precision of the MTD estimate, we repeated the 500 TITE-CRM simulations using only 18 patients. The correct MTD was identified 97.2% of the time. Fourth, a larger proportion of patients are able to be treated at doses that are potentially therapeutic. This should allow for better response estimates at the MTD dose. Conversely, there is the risk that the TITE-CRM-designed trials may expose more patients to doses above the MTD. Our findings suggested otherwise, because the regimen was well tolerated, with minimal toxicity. However, timely reporting of toxicities is crucial to avoid potential unnecessary risk. Finally, the TITE-CRM design incorporates information for the entire time that a subject is enrolled in the study. An appraisal of cumulative toxicities is not usually considered with a traditional design, which assesses DLT only during the first cycle of therapy. Of the 4 DLTs from our study, 1 did not occur until the second cycle of therapy.

This method performed well in this trial. The primary goal of the study was to determine a tolerable dose of oral vinorelbine combined with estramustine. We had estimated a toxicity rate of 30% at the 70 mg/m^2 dose based on experience with these agents individually. The occurrence of DLT at this dose was lower than anticipated (Table 4). The combination of oral vinorelbine and estramustine did not have any significant increase in immediate or cumulative toxicity. The recommended Phase II dose of oral vinorelbine is 70 mg/m^2 in combination with estramustine.

Seventeen patients in the trial were treated at the proposed Phase II dose with an overall response rate of 14%. The response rate is disappointing when compared with trials utilizing intravenous vinorelbine in combination with estramustine in HRPC. Of 4 trials employing this combination, the PSA response rates ($\geq$50% decline) ranged from 24% to 71%.[10,11,16,17] Prior chemotherapy was an exclusion criterion in all the trials of intravenous vinorelbine and this may account for the difference in response rates. Many of the 29 patients evaluable for response were heavily pretreated, having received a median of 2 hormone modalities and 1 chemotherapy regimen; 36% had previously received estramustine and 30% had received docetaxel. The other difference that could account for the decreased response rate is the route of administration. However, the oral form of vinorelbine compared favorably with the intravenous formulation in advanced breast cancer patients.[12] Of the 29 patients evaluable for response, only 5 patients went on to the observation phase, with 3 resuming therapy when they developed evidence of progression by PSA criteria.

Other oral regimens that have been employed in the treatment of HRPC have shown more promising results. A Phase II trial combining oral cyclophosphamide, diethylstilbestrol, and prednisone showed that 15 of 36 patients (42%) evidenced a decline in PSA of $\geq$50%. Quality of life (QOL) evaluations from 17 patients showed a significant improvement in responders and no decline in QOL in nonresponders.[18] Two Phase II trials of oral etoposide and estramustine have shown response rates ranging from 22% to 50% by PSA criteria.[19,20] Therefore, the overall strategy of using oral chemotherapy in this setting is reasonable, and further exploration of this approach is warranted.

Conclusions

The results of this Phase II study suggest that this combination has minimal activity in pretreated patients with HRPC. The combination was well tolerated, with little significant toxicity. Given the minimal level of activity, this regimen is unlikely to provide significant benefit to men with prostate cancer despite the low overall rate of toxicity. Other combinations or novel agents will be required to further test the utility of this trial design.

REFERENCES

1. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. *CA Cancer J Clin.* 2004;54:8–29.
2. Tannock IF, Osoba D, Stockler MR, et al. Chemotherapy with mitoxantrone plus prednisone or prednisone alone for symptomatic hormone-resistant prostate cancer: a Canadian randomized trial with palliative end points. *J Clin Oncol.* 1996;14:1756–1764.
3. Kantoff PW, Halabi S, Conaway M, et al. Hydrocortisone with or without mitoxantrone in men with hormone-refractory prostate cancer: results of the Cancer and Leukemia Group B 9182 study. *J Clin Oncol.* 1999;17:2506–2513.
4. Petrylak DP, Tangen CM, Hussain MH, et al. Docetaxel and estramustine compared with mitoxantrone and prednisone for advanced refractory prostate cancer. *N Engl J Med.* 2004; 351:1513–1520.
5. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med.* 2004;351:1502–1512.
6. Speicher LA, Barone L, Tew KD. Combined antimicrotubule activity of estramustine and taxol in human prostatic carcinoma cell lines. *Cancer Res.* 1992;52:4433–4440.

7. Hudes GR, Greenberg R, Krigel RL, et al. Phase II study of estramustine and vinblastine, two microtubule inhibitors, in hormone-refractory prostate cancer. *J Clin Oncol.* 1992;10: 1754–1761.
8. Seidman AD, Scher HI, Petrylak D, Dershaw DD, Curley T. Estramustine and vinblastine: use of prostate specific antigen as a clinical trial end point for hormone refractory prostatic cancer. *J Urol.* 1992;147:931–934.
9. Binet S, Chaineau E, Fellous A, et al. Immunofluorescence study of the action of navelbine, vincristine and vinblastine on mitotic and axonal microtubules. *Int J Cancer.* 1990;46: 262–266.
10. Carles J, Domenech M, Gelabert-Mas A, et al. Phase II study of estramustine and vinorelbine in hormone-refractory prostate carcinoma patients. *Acta Oncol.* 1998;37: 187–191.
11. Sweeney CJ, Monaco FJ, Jung SH, et al. A phase II Hoosier Oncology Group study of vinorelbine and estramustine phosphate in hormone-refractory prostate cancer. *Ann Oncol.* 2002;13:435–440.
12. Freyer G, Delozier T, Lichinister M, et al. Phase II study of oral vinorelbine in first-line advanced breast cancer chemotherapy. *J Clin Oncol.* 2003;21:35–40.
13. Goodman SN, Zahurak ML, Piantadosi S. Some practical improvements in the continual reassessment method for phase I studies. *Stat Med.* 1995;14:1149–1161.
14. O'Quigley J, Shen LZ. Continual reassessment method: a likelihood approach. *Biometrics.* 1996;52:673–684.
15. Cheung YK, Chappell R. Sequential designs for phase I clinical trials with late-onset toxicities. *Biometrics.* 2000;56:1177–1182.
16. Smith MR, Kaufman D, Oh W, et al. Vinorelbine and estramustine in androgen-independent metastatic prostate cancer: a phase II study. *Cancer.* 2000;89:1824–1828.
17. Borrega P, Velasco A, Bolanos M, et al. Phase II trial of vinorelbine and estramustine in the treatment of metastatic hormone-resistant prostate cancer. *Urol Oncol.* 2004;22:32–35.
18. Hellerstedt B, Pienta KJ, Redman BG, et al. Phase II trial of oral cyclophosphamide, prednisone, and diethylstilbestrol for androgen-independent prostate carcinoma. *Cancer.* 2003;98:1603–1610.
19. Pienta KJ, Fisher EI, Eisenberger MA, et al. A phase II trial of estramustine and etoposide in hormone refractory prostate cancer: a Southwest Oncology Group trial (SWOG 9407). *Prostate.* 2001;46:257–261.
20. Sumiyoshi Y, Hashine K, Nakatsuzi H, Yamashita Y, Karashima T. Oral estramustine phosphate and oral etoposide for the treatment of hormone-refractory prostate cancer. *Int J Urol.* 2000;7:243–247.