Phase II Study of Dolastatin-10 in Patients with Hormone-refractory Metastatic Prostate Adenocarcinoma

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ABSTRACT

Dolastatin-10 is a natural, cytotoxic peptide with microtubule-inhibitory and apoptotic effects. It has demonstrated in vitro and in vivo efficacy in the DU-145 human prostate cancer model. A Phase II clinical trial was designed in patients with hormone-refractory prostate cancer. Dolastatin-10 was administered at a dose of 400 µg/m² i.v. every 3 weeks. Dose escalation to 450 µg/m² was permitted. Toxicity evaluation was conducted every 2 weeks, and assessment of response was done at the end of every two cycles. Sixteen patients were enrolled between October 1998 to December 1999. The median age was 71 years (range, 59–79 years). Median prostate-specific antigen value was 108 ng/ml (range, 15.3–1672 ng/ml). Of the 15 eligible patients, 7 were Caucasian and 8 were African-American. Eight patients had bone-only metastases, and seven had measurable disease with or without bone metastases. A total of 56 cycles have been administered. Only 2 patients required dose adjustment because of toxicity, and in 5 patients, dose escalation was feasible to 450 µg/m². The major toxicities observed were grade 3 and 4 neutropenia in 5 patients and grade 3 neuropathy in 1 patient. All 15 patients are evaluable for response. Three patients demonstrated stable disease; 2 of these had bone disease, and 1 had nodal metastasis. All others had disease progression. Dolastatin-10 is very well tolerated in this elderly, pretreated population but lacks significant clinical activity as a single agent.

INTRODUCTION

In the year 2000, it is estimated that 180,400 men will be diagnosed with prostate cancer, and 31,900 men will die of the disease (1). The vast majority of these deaths are secondary to metastatic disease for which androgen deprivation continues to be the therapeutic standard. Historically, a variety of agents have been evaluated in HRPC with objective response rates of <10%. Recognizing the morbid course of HRPC, studies have evaluated the palliative effects of chemotherapy. The demonstration of a palliative benefit led to the approval of mitoxantrone and prednisone as standard treatment for symptomatic disease (2–4). Several estramustine-based combinations using either etoposide, vinblastine, or the taxanes have elicited higher response rates (30–50%) in Phase II trials (5–8). The impact of some of these combinations on overall survival is currently being evaluated in randomized trials.

Dolastatins are natural cytotoxic pseudopeptides extracted from the marine shell-less mollusk Dolabella auricularia. These compounds were first isolated by Pettit et al. (9). The dolastatin family has demonstrated antineoplastic, bactericidal, and fungicidal properties (10, 11). Within the family, dolastatin-10 and dolastatin-15 exhibit the most promising antiproliferative actions, and synthetic analogues of these are currently under evaluation in clinical trials. These antimitotic agents exhibit inhibition of microtubule assembly and induction of apoptosis in numerous malignant cell lines (12). In vitro growth inhibition and in vivo efficacy were demonstrated against small lung cell cancer cell lines (13, 14). Turner et al. (15) studied the effects of dolastatin-10 on the DU-145 human prostate cancer cell lines. Complete growth inhibition was observed in vitro at concentrations of 1 nm. Cell cycle arrest in G2-M phase and α-tubulin depolymerization correlated with the growth inhibition. Similar results were observed in the PC3 and LNCaP human prostate cancer cell lines (15). In vivo efficacy was demonstrated at a 5-µg dose of dolostatin-10 administered i.p. every 4 days in athymic mice. Dolastatin-10 decreased the number and size of tumors on the diaphragms of mice and prevented invasion of the musculature, as compared with the prostate tumors implanted in mouse controls (15). The modulation of apoptotic pathways by bcl-2 phosphorylation was shown on immunoblot analysis (13, 14). Bcl-2 is expressed in ~65% of HRPC specimens and appears to play a role in development of resistance to therapy (16, 17). These promising preclinical results, together with the properties of microtubule inhibition, bcl-2 phosphorylation, and apoptosis induction, led to this Phase II clinical trial of dolastatin-10 in HRPC.

PATIENTS AND METHODS

Patient Eligibility. Patients with metastatic (D1 or D2) HRPC were eligible for this study. Documentation of clinical or PSA progression during administration of hormone therapy was required. All patients were required to have had primary gonadal suppression with or without androgeners. Patients with elevated PSA had to demonstrate a rising trend with three successive elevations at a minimum interval of 2 weeks. For patients lacking measurable disease, the minimum PSA value for enrollment on the study was 10 ng/ml. No prior chemotherapy was permitted. A maximum of three prior hormonal manipulations were permitted, with androgen withdrawal considered as one

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3 The abbreviations are: HRPC, hormone-refractory prostate cancer; PSA, prostate-specific antigen; GNRH, gonadotrophin releasing hormone.
Patients had to be off flutamide and any other hormones, including steroids for at least 4 weeks and off bicalutamide for at least 6 weeks. No prior treatment with strontium-89 or other therapeutic radioisotope was allowed. A minimum of 4 weeks since prior radiation therapy was required. Good performance status (0–2 by Southwest Oncology Group criteria) was necessary, with adequate bone marrow, hepatic, and renal function (absolute neutrophil count ≥1500/mm³, hemoglobin ≥8 g/dl, platelet count >100,000/mm³, serum bilirubin ≤2 mg/dl, and serum creatinine ≤1.5 mg/dl). Continuation of GnRH agonist was permitted. Patients with a prior malignancy other than nonmelanoma skin cancers had to be disease free for 5 years. A signed informed consent was obtained from every individual enrolled in the protocol.

**Treatment Plan.** Dolastatin-10 was administered at a starting dose of 400 μg/m² by iv bolus every 3 weeks. There was a provision for dose escalation to 450 μg/m² after two cycles if ≤ grade one toxicity was observed. Dose reduction was required for absolute neutrophil count nadir ≤500/mm³ or platelet nadir ≤50,000/mm³. At the time of each scheduled treatment, dolastatin-10 was administered only if absolute neutrophil count ≥1000/mm³ and if the platelet count was ≥100,000/mm³. Otherwise, treatment was held until hematological recovery to these minimum levels, and subsequent cycles were started at a dose reduction. A one level, dose reduction was necessary for grade 2 neuropathy (dose, 300 μg/m²), and a two-level dose decrease was required for grade 3 or 4 neuropathy (dose, 225 μg/m²). Other nonhematological toxicities were managed at the discretion of the treating physician and did not mandate specific dose adjustments.

**Evaluation and Response.** Patients were evaluated weekly for toxicity. Measurable disease was assessed, and bone scans were repeated every three cycles. Patients were taken off protocol if there was disease progression, treatment delay of ≥4 weeks, administration of any other antitumor therapy, or patient refusal. The National Cancer Institute common toxicity criteria version 2.0 were used to grade toxicity. Measurable disease response was assessed using standard criteria for solid tumors (18). Bone metastases were considered nonevaluable disease, and its status did not affect response assessment, except in the determination of complete response (must be absent) or progressive disease (new lesions). Complete clinical response was defined as disappearance of all measurable and evaluable disease for a minimum of 4 weeks, no new lesions, and normalization of PSA (≤4 ng/ml). PSA was measured prior to each cycle every 3 weeks and every 2 weeks as necessary to document a response. A “PSA partial response” for patients with metastatic bone disease and PSA-only progression was defined as ≥50% reduction in PSA sustained for three successive determinations performed 2 weeks apart. PSA progression was defined as two values at least 2 weeks apart with ≥50% increase over nadir PSA. Patients who did not meet the above criteria of response and progression were considered to have stable disease. The time to treatment failure was calculated from the date of registration to date of progressive disease or to date off treatment because of toxicity, refusal, or death. Response rate assessment and toxicity evaluation were the primary end points of the study. Time to treatment failure and overall survival were secondary end points. A two-stage study design was used with provisions for early stopping for demonstrated efficacy or the lack thereof. Fifteen patients were to be enrolled initially, and if ≤1 response was observed, then the study would be terminated. If >5 responses were observed, then the regimen would be pursued further in a larger study. If two to four responses occurred, then an additional 15 patients were to be accrued.

### RESULTS

**Patient Characteristics.** Sixteen patients were registered between October 1998 and December 1999. One patient was deemed ineligible because of PSA elevation alone in the absence of detectable metastases. Patient characteristics are summarized in Table 1. The median age of the patients was 71 years (range, 59–79 years). Median baseline PSA was 108 ng/ml (15.3–1672 ng/ml). The majority of the patients (75%) had three prior hormonal interventions. All patients had progressed on primary gonadal suppression. Four patients had orchectomy, and 10 patients continued to be on a GnRH agonist. One patient was off the GnRH agonist because of progression while on therapy and had subsequently received ketoconazole and hydrocortisone with documented disease progression. Seven patients had prior radiation therapy (three, definitive to the prostate, and four, palliative).

**Treatment Administered and Toxicity Data.** A total of 56 cycles of dolastatin-10 were administered with a median of 3 cycles/patient (range, 2–10 cycles). Dose escalation was feasible in five patients. Two patients required dose reductions because of grade 4 neutropenia. One patient required a one-dose level decrease, and one needed a two-dose level reduction. The latter patient received 10 cycles of dolastatin-10.

A comprehensive list of toxicities is included in Table 2.
Although the major toxicity observed was grade 3 and 4 neutropenia in 50% of the patients, no hospital admissions were necessary for febrile neutropenia. Only two patients had severe neutropenia in the first two courses. Grade 3 neuropathy was noted in one patient. There were no treatment-related deaths.

**Response.** Fifteen eligible patients were evaluable for response. There were no objective responses. Stable disease was documented in 3 of 15 patients (20%) for a duration of 10, 16, and 28 weeks. Two of these patients had stabilization of PSA and no development of new bone metastases. One patient had stabilization of lymph node measurements and PSA values. The PSA data in all patients with stable disease is depicted in Fig. 1. All other patients had disease progression. Median follow-up duration at the time of this report is 10 months (range, 4–15 months). Six patients have died, and median survival has not been reached. The patients with stable disease are alive at 5, 7, and 12 months since starting dolastatin-10.

**DISCUSSION**

Traditional guidelines for pursuing new agents in clinical oncology have required the demonstration of clinical activity in Phase II settings. However, there are several examples in prostate cancer where two single agents, individually having minimal impact, have been combined to produce significant antitumor effects. Single-agent trials involving vinblastine, paclitaxel, and etoposide each demonstrated low activity (19–21) for a duration of 10, 16, and 28 weeks. Two of these patients had stabilization of PSA and no development of new bone metastases. One patient had stabilization of lymph node measurements and PSA values. The PSA data in all patients with stable disease is depicted in Fig. 1. All other patients had disease progression. Median follow-up duration at the time of this report is 10 months (range, 4–15 months). Six patients have died, and median survival has not been reached. The patients with stable disease are alive at 5, 7, and 12 months since starting dolastatin-10.

Table 3 Clinical efficacy of chemotherapy: single agent versus combination

<table>
<thead>
<tr>
<th>Agent (Ref.)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of patients</th>
<th>Response</th>
<th>Med TTP</th>
<th>Med Surv</th>
</tr>
</thead>
<tbody>
<tr>
<td>VP-16 (21)</td>
<td>24</td>
<td>Obj-8%</td>
<td>NR</td>
<td>6.8 mths</td>
</tr>
<tr>
<td>E + VP-16 (5)</td>
<td>42</td>
<td>Obj-50%</td>
<td>PSA-52%</td>
<td>NR</td>
</tr>
<tr>
<td>Vinb (19)</td>
<td>39</td>
<td>Obj-20%</td>
<td>6.2 mths</td>
<td>NR</td>
</tr>
<tr>
<td>E + Vinb (22)</td>
<td>36</td>
<td>Obj-28%</td>
<td>PSA-61%</td>
<td>3.5 mths</td>
</tr>
<tr>
<td>Vinb (23)</td>
<td>98</td>
<td>Obj-6%</td>
<td>PSA-3%</td>
<td>2.2 mths</td>
</tr>
<tr>
<td>E + Vinb (23)</td>
<td>95</td>
<td>Obj-20%</td>
<td>PSA-25%</td>
<td>3.7 mths</td>
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<td>Tax (20)</td>
<td>23</td>
<td>Obj-4.3%</td>
<td>9 mths</td>
<td>9 mths</td>
</tr>
<tr>
<td>E + Tax (6)</td>
<td>36</td>
<td>Obj-44%</td>
<td>PSA-53%</td>
<td>5 mths</td>
</tr>
</tbody>
</table>

<sup>a</sup> Ref, references; E, estramustine; VP-16, etoposide; Vinb, vinblastine; Tax, paclitaxel; Med, median; TTP, time to progression; Surv, survival; Obj, objective; PSA response &gt;50% decrease in PSA maintained for at least three consecutive values at least 2 weeks apart; mths, months; NR, not reported.

Dolastatin-10 shares some characteristics of the above agents. It has demonstrated microtubule inhibition with cell arrest in metaphase (24). However, it occupies a site distinct from the Vinca alkaloids and induces formation of tubulin aggregates that are distinct from those triggered by vinblastine (25, 26). Additionally, dolastatin-10 has shown apoptosis induction via bcl-2 phosphorylation, similar to that demonstrated by paclitaxel and docetaxel (13, 14, 27). Finally, there are some data to indicate that dolastatin-10 functions better as a potentiator of other agents than as a single agent. Studies in chronic lymphocytic leukemia, non-Hodgkin’s lymphoma, and Waldenstrom’s macroglobulinemia cell lines indicate synergy between dolastatin-10 and bryostatin 1 (28–30). Drawing a parallel from the enhanced efficacy of combinations of tubulin inhibitors, there is a rationale for evaluation of dolastatin-10 in combination with other agents. Preclinical investigations of dolastatin-10 in combination with other agents would be worthwhile.

Phase I trials of dolastatin-10 in a variety of advanced solid tumors have shown minimal myelosuppressive effects (31, 32). There was no relation between hematological toxicity and systemic exposure to dolastatin-10 in one of these trials (32). Our experience in this trial confirms that grade 4 neutropenia of brief duration was observed in one-third of patients with no episodes of febrile neutropenia at the recommended Phase II dose. Also, no cases of severe thrombocytopenia or anemia were seen, and the incidence of neuropathy was low.
Despite the lack of significant clinical activity in an advanced metastatic prostate cancer population, the mechanism of action and favorable toxicity profile of dolastatin-10, coupled with ease of administration, make it a potentially attractive agent in a combination chemotherapy development strategy. The observation of stable disease in 3 of 15 patients may warrant further evaluation of this agent. Treatment of patients in earlier stages and treatment of asymptomatic prostate cancer patients with relatively lower tumor burden may be worthy of investigation.

ACKNOWLEDGMENTS

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REFERENCES

Erratum

In the article by Soh et al., which appeared in the October, 2000, issue of *Clinical Cancer Research* (pp. 4136–4141), the concentrations of sulindac sulfide, sulindac sulfone, CP248, CP461, KT5720, and Rp-8-pCPT-cGMPS in the text and figures should always be “μM” instead of “mM.” On page 4137, lines 4 and 5 should read “18 ml Tris-AcrylM column with a 0-1 M NaAc gradient” instead of “180 ml Tris-AcrylM column with a 0-1 M NaAc gradient.”

Correction

In the article by U. Vaishampayan et al., which appeared in the November, 2000 issue of *Clinical Cancer Research* (pp. 4205–4208), the first author’s name should read “Ulka Vaishampayan,” instead of “Uika Vaishampayan,” and the sixth author’s name should read “John Wright,” instead of “Jeremy Wright.”
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