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A phase II trial of irinotecan in hormone-refractory prostate cancer

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Summary

Irinotecan is a DNA topoisomerase I inhibitor that has a wide spectrum of activity against human tumors in both preclinical and clinical studies. To evaluate the efficacy of irinotecan in hormone-refractory prostate cancer, we conducted a phase II study in 15 men with metastatic, PSA-progressive disease after primary androgen deprivation. Irinotecan was administered at a dose of 125 mg/m^2 weekly for four weeks followed by a two-week rest period; cycles were repeated every six weeks. Response was assessed by evaluation of serial changes in the serum PSA. None of fifteen patients had a decline in PSA of greater than 50%; eight patients had stable disease as a best response. None of three patients with measurable disease had a partial or complete response. Toxicity was primarily hematologic and gastrointestinal, with 40% of patients requiring dose modification due to granulocytopenia and 20% requiring intravenous fluid supplementation after development of diarrhea. There were no treatment-related deaths. We conclude that irinotecan in the dose and schedule used in this trial does not have significant activity against hormone-refractory prostate cancer.

Introduction

The treatment of hormone-refractory prostate cancer (HRPC) poses a difficult clinical challenge. A variety of approaches have been used, including secondary hormonal manipulations [1], estramustine [2], use of investigational drugs such as suramin [3], and palliative care alone. In addition, numerous cytotoxic chemotherapy regimens have been investigated. Most single agents have reported response rates of less than 20% [4], although some regimens, for example mitoxantrone with prednisone [5] or estramustine in conjunction with anti-microtubule agents [6–9], may yield responses in 30–60% of patients. However, no therapy has yet demonstrated a survival benefit, and there remains no clear standard of care for patients with HRPC.

Irinotecan (CPT-11) is a semi-synthetic derivative of camptothecin that is a potent inhibitor of topoisomerase I, a nuclear enzyme that plays an essential role in DNA replication and transcription [10]. Irinotecan has a broad spectrum of antitumor activity in preclinical models [11] and has demonstrated efficacy in patients with 5-flourouracil-resistant metastatic colon cancer [12]. The drug is currently being evaluated in a wide range of human malignancies. Irinotecan also inhibits the growth of prostate cancer cell lines *in vitro* and *in vivo* [13]. Based on these observations, we conducted a phase II trial of irinotecan in patients with HRPC. Our data indicate that irinotecan, in the dose and schedule used in this study, does not have significant activity against HRPC.

Methods

Patient selection

Between May 1997 and April 1998 15 eligible patients were enrolled at UCLA Medical Center and through the UCLA Community Oncology Network. All patients had a pathologic diagnosis of prostate cancer and documented metastatic disease by bone scan, MRI, CT, or X-rays. Patients had progressive disease after primary hormonal therapy (bilateral orchiectomy

or use of an LHRH agonist) as documented by a rising PSA level measured on two separate occasions at least two weeks apart. Since the primary endpoint of the study was evaluation of changes in PSA levels, patients had to have a PSA value of at least 5 ng/dL. Patients receiving an antiandrogen had to discontinue the drug at least 4 (flutamide) or 6 (bicalutamide) weeks prior to study entry to exclude the antiandrogen withdrawal syndrome. Patients also had to have a performance status of 0–2 on the ECOG performance scale and a life expectancy of at least 12 weeks; no radiation therapy for at least 3 weeks or strontium-89 for at least 12 weeks prior to entry; no surgery for at least 2 weeks prior to entry; adequate marrow function including pretreatment granulocyte count $\geq$ 1500/mm^3, hemoglobin $\geq$ 9.0 g/dL, and platelet count $\geq$ 100,000/mm^3; and adequate renal and hepatic function with serum creatinine $\leq$ 2.0 mg/dL, serum bilirubin $\leq$ 1.5 mg/dL, and aspartate transaminase (AST) $\leq 3\times$ the upper limit of normal, unless the liver was involved with tumor, in which case the AST had to be $\leq 5\times$ the upper limit of normal. Patients could not have received any prior cytotoxic chemotherapy for prostate cancer. In addition, patients were excluded if they had a history of myocardial infarction within the previous six months or congestive heart failure requiring therapy, uncontrolled diabetes mellitus, a history of prior malignancy (except adequately treated basal cell or squamous cell skin cancer) within the previous five years, central nervous system metastases, or Gilbert's disease. All patients receiving an LHRH agonist continued to receive this agent throughout the course of the study. All patients gave written informed consent in accordance with federal, state, and institutional guidelines.

A two-stage accrual strategy was planned, but patient enrollment was stopped after none of the first fifteen patients achieved a partial response by PSA criteria.

Evaluations

All patients underwent a screening evaluation within 21 days of the first treatment. Required observations at screening included a complete history and physical examination, ECOG performance status, radiologic studies (bone scan, x-rays, CT scan, or MRI as indicated for identification of measurable or evaluable disease), chest x-ray, and electrocardiogram. Within 7 days of first treatment patients underwent laboratory studies including PSA, complete blood count, serum chemistry profile, and urinalysis; documentation of analgesic intake; and completion of the FACT-P quality of life questionnaire.

Patients were seen once weekly for follow-up while on study. Complete blood count, analgesic consumption, and vital signs were recorded weekly. Every 6 weeks a complete physical examination, serum chemistry profile, PSA level, ECOG performance status, and FACT-P questionnaire were obtained. Radiologic studies were repeated every 12 weeks as clinically indicated to assess disease state.

Treatment plan

Irinotecan was given over 90 minutes intravenously in doses of 125 mg/m^2 weekly for 4 weeks followed by a 2-week rest period. Cycles were repeated every 6 weeks. Patients received standard antiemetics (excluding dexamethasone and other steroids) and were aggressively treated for diarrhea according to a standardized protocol with empiric antimotility agents (loperamide). *During* a treatment course, patients experiencing any NCI grade 2 toxicity had the dose of irinotecan reduced one dose level (dose levels were 125, 100, 75, and 60 mg/m^2) for all remaining doses during that treatment course. Patients experiencing grade 3 or higher toxicity had a dose omitted and could re-start treatment at one dose level lower upon resolution of toxicity to grade 2 or less, except in the case of grade 4 hematologic toxicity, in which case treatment was resumed at 2 dose levels lower upon resolution of toxicity to grade 2 or less.

Dose modifications of the *next* course of treatment were based on the worst toxicity observed during the preceding course. Patients experiencing grade 3 or grade 4 hematologic toxicity had doses reduced one or two dose levels, respectively. For grade 2 non-gastrointestinal or grade 3 gastrointestinal toxicity, doses were reduced one dose level. For all other grade 3 or grade 4 toxicities doses were reduced two dose levels. Patients who experienced toxicity requiring dose modification to levels below 60 mg/m^2 were taken off study. Dose modifications are summarized in Table 1.

Toxicity and response criteria

Toxicity was graded according to the revised common toxicity criteria (Cancer Therapy Evaluation Program, National Cancer Institute). Protocol treatment was administered until disease progression or the toxicity was unacceptable to the patient. The primary efficacy

Table 1. Dose modifications for irinotecan

	Dose modification during a course of treatment		
		Non-hematologic toxicity[a]	
NCI toxicity grade	Hematologic toxicity[a]	Non-GI toxicity	GI toxicity[b]
0	None	None	None
1	None	None	None
2	↓ One dose level[c]	↓ One dose level	↓ One dose level
3	Omit dose[d]	Omit dose[e]	Omit dose[d]
4	Omit dose[e]	Omit dose[e]	Omit dose[e]
Febrile neutropenia	Omit dose		
	Dose modifications for the next course of treatment		
		Non-hematologic toxicity	
NCI toxicity grade	Hematologic toxicity	Non-GI toxicity	GI toxicity
0	↑ One dose level	↑ One dose level	↑ One dose level
1	None	None	None
2	None	↓ One dose level	None
3	↓ One dose level	↓ Two dose levels	↓ One dose level
4	↓ Two dose levels	↓ Two dose levels	↓ Two dose levels
Febrile neutropenia	↓ Two dose levels		

[a] Dosage not adjusted for anemia, lymphocytopenia, or alopecia
[b] GI toxicity includes nausea, vomiting, diarrhea, and mucositis/stomatitis and is scored after maximal medical management (e.g., antiemetics, antimotility agents)
[c] Dose levels: 125, 100, 75, and 60 mg/m^2
[d] Upon resolution of toxicity to grade 2 or less, treatment to be resumed at one lower dose level and maintained at that level for the remainder of the course
[e] Upon resolution of toxicity to grade 2 or less, treatment to be resumed at two lower doses and maintained at that level for the remainder of the course

endpoints of the trial included changes in PSA levels and/or measurable disease. For PSA data, a complete response (CR) was defined as normalization of the PSA for at least 4 weeks. A partial response (PR) was a decline in PSA by 50% for at least 4 weeks. Progressive disease (PD) was considered a 25% or greater increase in PSA measured on two separate occasions at least two weeks apart. Stable disease was present if patients did not meet criteria for CP, PR, or PD.

For patients with measurable disease, complete response required disappearance of all measurable and evaluable disease, no new lesions, and no evidence of nonevaluable disease. A partial response required a $\geq$ 50% decrease in the sum of the products of the longest perpendicular diameters of all measurable lesions, no progression of evaluable disease, and no new lesions. Progressive disease was a $\geq$ 25% increase in the sum of products of measurable lesions, reappearance of any lesion which had disappeared, or appearance of any new lesion.

Exploratory analyses were conducted to assess the clinical benefit of the therapy and included determination of changes in performance status as measured on the ECOG scale, analgesic consumption, time to disease progression, and survival.

Results

The pretreatment characteristics of the 15 patients enrolled in the study are shown in Table 2. All fifteen patients were evaluable for toxicity and response.

All patients had a rising PSA after orchiectomy or use of an LHRH agonist. Twelve patients had dis-

Table 2. Patient characteristics

Characteristic	No. of patients
Number enrolled	15
Median age, years (range)	68 (48–85)
ECOG performance status	
0	4
1	10
2	1
PSA, ng/mL	
Median	109
Mean	151
Range	17–650
Sites of disease	
Bone	12
Lymph nodes	3
Lung	0
Soft tissue	0
Prostate bed/bladder	2
Prior therapy	
Prostatectomy	3
Radiation to prostate	6
Orchiectomy	5
LHRH agonist	10
Antiandrogen	13
Ketoconazole	4
Aminoglutethimide	1
Hydrocortisone	5
Megestrol acetate	1
Diethylstilbestrol	1
Radiation to metastases	3
Strontium-89	1

Table 3. Treatment results

Patient	# of cycles	PSA levels (ng/mL)	
		baseline	off-study
1	2	316	786
2	2	109	129
3	2	146	193
4	1	81	70
5	4	24	28
6	2	650	685
7	2	132	422
8	1	95	153
9	2	74	380
10	5	19	29
11	1	212	234
12	2	116	201
13	1	17	17
14	2	62	75
15	1	211	690

ease detectable only in bone, while 3 had lymph node metastases that were measurable. Thirteen patients had received therapy with an antiandrogen at some point in their disease course, and all discontinued it at least 4 (flutamide) or 6 (bicalutamide) weeks prior to protocol therapy; none experienced a withdrawal decline in PSA. Six patients received at least one form of secondary hormonal therapy prior to ironotecan treatment, 3 had prior radiation to bone metastases, and 1 had received strontium-89.

Ten patients received two or more cycles of therapy, and 5 patients received one cycle. Of the 5 patients who received one cycle of treatment, two discontinued treatment due to the development of progressive disease by PSA criteria, two were taken off study at their request due to toxicity (diarrhea), and one was removed due to a rapid decline in performance status. The median dose intensity per cycle for those patients receiving more than one cycle of therapy was 78% of the scheduled dose (125 mg/m^2 weekly) over the first two cycles of therapy, reflecting the necessity to reduce doses for hematologic or gastrointestinal toxicity.

Response

Changes in PSA level were evaluated as the primary marker of antitumor activity (Table 3). No patient obtained a 50% reduction in PSA. Of the 15 patients, 7 (47%) had increases in PSA by $\geq$ 25% after at least one cycle of treatment, while 8 (53%) had stable disease as a best response by PSA protocol criteria. One patient (#10) had a stable PSA for four cycles but developed progressive disease after a fifth cycle of treatment. Two of the eight patients with stable disease had slight declines in PSA (11% and 18%, respectively), while the remainder had increases in PSA $\leq$ 25%. None of the three patients with measurable disease had a partial or complete response in these lesions. The median time to PSA progression was 8 weeks.

Clinical parameters including performance status and analgesic consumption were not primary response endpoints of the study but were evaluated to assess potential clinical benefits. One patient with minor symptoms had an improvement in ECOG performance status from 1 to 0; this patient had stable disease by

Table 4. Toxicities ≥ grade 2 (worst any cycle)

Toxicity	Number with toxicity		
	Grade 2	Grade 3	Grade 4
Granulocyte	2	4	0
Platelet	0	0	0
Hemoglobin	4	0	0
Fatigue	7	1	0
Nausea/vomiting	5	0	1
Diarrhea	4	2	1

PSA criteria after two cycles of therapy. All other patients had stable (n = 7) or worse (n = 7) performance status. In addition, of eight patients requiring routine narcotic analgesic use for pain at baseline, none had a decrease in analgesic consumption while receiving the study drug. One patient not requiring analgesics at entry was utilizing ibuprofen after two cycles of therapy; this patient had a 70% increase in PSA. The remaining six patients did not require analgesics at any point in the trial.

Seven patients (47%) have died (survival range, 4–16 months), while eight patients remain alive (survival range, 7–17+ months).

Toxicity

No unexpected drug-related side effects were encountered in the study, and there were no therapy-related deaths. As anticipated, the most common toxicities were hematologic and gastrointestinal (Table 4). Six patients (40%) experienced granulocytopenia severe enough to warrant dose modification; four had grade 3 and 2 had grade 2 toxicity. There were no episodes of febrile neutropenia or other infectious complications, however, and no significant thrombocytopenia was encountered.

Gastrointestinal toxicity consisted primarily of nausea, vomiting, and diarrhea (Table 4). Nausea occurred in 6 patients (40%), but was severe (grade 4) in only one (7%); three patients (20%) had grade 2 vomiting. All patients were instructed to take empiric loperamide with the development of loose stools or diarrhea, but 6/15 (40%) developed grade 2 or grade 3 diarrhea. Two patients received outpatient intravenous fluid hydration to prevent volume depletion. One patient was admitted for dehydration after continuing to use laxatives, stool softeners, and multiple enemas despite the development of loose stools during a cycle of therapy.

Eight patients (53%) experienced fatigue during at least one cycle of therapy, but this was mild in all but one.

Discussion

The development of effective new therapies for hormone-refractory prostate cancer is essential, since currently available treatments have not demonstrated a survival benefit. The evaluation of new agents is complicated by the fact that the majority of patients have disease limited to bone; in this study, 12/15 patients (80%) had bone-only metastases, a finding typical in clinical trials for HRPC. Recently, however, use of changes in serum PSA has emerged as a relatively reliable indicator of antitumor effect for cytotoxic compounds. Kelly and colleagues noted that a 50% decline in PSA level two months after therapy was associated with improved outcome in patients treated with a variety of systemic agents, an observation confirmed in an independent data set [14]. More recently, investigators at the University of Michigan analyzed PSA responses in 114 patients treated with estramustine and etoposide on sequential clinical trials. Their data also suggest that a decline of PSA of ≥ 50% correlates with improved survival [15].

In the current trial we used changes in serum PSA as the primary endpoint in assessing treatment response, requiring at least a 50% decrease to achieve a partial response. By this criterion, there were no objective responses in 15 patients. In addition, none of 3 patients with measurable disease had a partial response by traditional criteria. It is unlikely that the patients in this study had exceptionally advanced or resistant disease: fourteen of 15 had an ECOG performance status of 0 or 1; less than 50% had been treated with secondary hormonal manipulations; only three had received prior radiation to bony metastases; and none had received prior chemotherapy. Furthermore, the median PSA was comparable to that reported in other recent trials investigating cytotoxics for HRPC [5–9,16–18]. Thus, the patients enrolled in this trial appear to be representative of those with HRPC for whom cytotoxic chemotherapy is considered an appropriate treatment option.

It has also been suggested that measures of clinical benefit, such as improvements in performance status or quality of life, changes in pain level or an-

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