The Prostate 52:264–268 (2002)

SWOG-9510: Evaluation of Topotecan in Hormone Refractory Prostate Cancer: A Southwest Oncology Group Study

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BACKGROUND. Prostate cancer is the most common malignancy in American men, and as many as 70% of those initially treated for localized disease will ultimately progress and be considered candidates to receive therapy for metastatic cancer [1,2]. Although most will respond initially to hormone manipulation, essentially all will fail and require additional therapy. No standard chemotherapy approach has been shown to prolong survival significantly, and new agents are desperately needed. Topotecan is a new topoisomerase-1 inhibitor whose early investigation suggested possible activity in hormone-refractory prostate cancer.
METHODS. In this phase II trial, patients having failed one or two prior androgen ablative therapies were treated with 21-day continuous intravenous infusions of topotecan at a dose of 0.5 mg/m^2 per day every 28 days.
RESULTS. Twenty-six eligible patients were entered on the study. There were no confirmed tumor responses. Median survival was 9 months. The most common toxicities were hematologic, with 8 of 24 assessable patients experiencing grade 4 toxicity.
CONCLUSION. Topotecan infusions at this dose are ineffective in the management of hormone-refractory prostate cancer. *Prostate 52: 264–268, 2002.*

KEY WORDS: **hormone refractory prostate cancer; topotecan; clinical trial**

INTRODUCTION

Prostate cancer is the most common malignancy in American men and kills approximately 40,000 patients each year. Although many men with this tumor will have an indolent course and succumb to other processes, a large percentage will present with or develop metastatic disease after initial therapy and would benefit from effective therapy to control metastatic disease and its debilitating symptoms [1,2]. In the vast

Grant sponsor: National Cancer Institute; Grant numbers: DHHS: CA38926, CA32102, CA04919, CA46113, CA20319, CA35431, CA63844, CA35281, CA58861, CA37981, CA45807, CA96429, CA12213, CA45560, CA14028, CA76462.

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Received 15 August 2001; Accepted 29 March 2002
DOI 10.1002/pros.10118

majority of such patients, androgen deprivation dramatically improves symptoms and lowers prostate specific antigen (PSA), but unequivocal evidence that endocrine therapy prolongs survival is lacking, and cure is not a reasonable expectation. The median duration of response to androgen ablation is 12–18 months, at which time essentially all responders relapse. Second-line hormonal therapy benefits the minority of patients. PSA decline or symptom improvement is documented in 20–25% of men after withdrawal of antiandrogens, administration of megestrol acetate, glucocorticoids, bicalutamide, and ketoconazole, but no survival increase has been documented after any second-line endocrine therapy [3–5].

Clinical trials of conventional cytotoxic chemotherapeutic agents in the treatment of hormone-refractory prostate cancer have been disappointing. Yagoda and Petrylak [6] reviewed 26 studies completed between 1988 and 1991 and found an overall response rate of only approximately 9%, and no indication of any prolongation in average survival. More recent studies have combined the most promising of the single agents, including mitoxantrone, estramustine, and taxanes. Although these reports suggest that combination chemotherapy may increase the response rate among hormone-refractory prostate cancer patients, no current treatment clearly improves survival to any meaningful extent [7,8].

Topotecan is a semisynthetic analogue of camptothecin, a plant alkaloid derived from the stem wood of the Chinese tree *Camptotheca acuminata*. Its mechanism of action is the inhibition of the enzyme topoisomerase I, important in DNA replication where it produces reversible single-strand breaks to relieve the torsional strain ahead of the replication fork, allowing the free replicating DNA strand to proceed.

In preclinical studies, topotecan demonstrated activity in chemorefractory murine colon carcinomas, in B16 melanoma, Lewis lung carcinoma and L1210 leukemia [9,10]. In human tumor cloning assays, it has activity against ovary, breast, renal, gastric, and lung carcinoma cells [11,12]. Early data suggest that the drug activity is more related to target enzyme level rather than to cell proliferative rate, an indication that slower-growing prostate cancer might be susceptible to topotecan administration [13]. Phase I studies have indicated that topotecan has activity in ovarian, non-small cell lung cancer, colorectal, renal cancer, and acute leukemia, other tumors often regarded as chemorefractory [14,15]. Consistent with its known S-phase–specific mechanism of action, drug delivery by continuous infusion in these models is more effective than short-term administration [16]. Consequently the Southwest Oncology Group initiated a phase II trial to assess the activity of continuous intravenous infusion of topotecan in the treatment of hormone-refractory prostate cancer.

PATIENTS AND METHODS

Patient Population

Patients with a SWOG criteria performance status of 0–2 and a histologic diagnosis of metastatic adenocarcinoma of the prostate unresponsive or refractory to hormone therapy were eligible for the study. They must have failed at least one, but not more than two, prior androgen ablative therapies, and PSA must have risen after 1 month after cessation of all hormone therapy other than maintenance leuprolide. Patients were required to have bidimensionally measurable or evaluable disease. Baseline PSA ≥ 20 was considered evaluable disease. No prior chemotherapeutic agents or biologic response modifiers and no concomitant radiotherapy were permitted. Eligible patients were required to have adequate organ function as defined by a granulocyte count $> 1{,}500$ mm^3 and platelet count of $> 100{,}000$ mm^3, normal hepatic function, and a serum creatinine < 1.6 mg/dl. Prior radiation was allowed if it encompassed less than 25% of the bone marrow volume and had to be completed at least 3 weeks before entry on the study. Patients with prior nonskin malignancies were excluded. All patients gave written, informed consent.

Treatment Plan

After insertion of a semipermanent venous access device, topotecan was administered as a continuous intravenous infusion of 0.5 mg/m^2 per day for 21 days, followed by a 7-day rest period. Treatment cycles were continued at 28-day intervals until disease progression (after a minimum of two cycles), unacceptable toxicity, or patient decision to withdraw. All patients were followed until death.

Toxicity

Toxicity was evaluated according to the standard Southwest Oncology Group criteria.

Dose Modifications

Infusions were suspended for the rest of the cycle for ANC $< 1{,}000$ mm^3, platelet count of $< 50{,}000$ mm^3, unresolvable Grade 3 toxicity or any Grade 4 toxicity. Routine, prophylactic use of colony stimulating factors was prohibited. Dose reduction to 0.4 mg/m^2 per day was undertaken for nadir ANC $< 500/$mm^3, platelet count $< 50{,}000/$mm^3 or any Grade 3 or greater toxicity. If, after dose reduction, nadir ANC was again $< 500/$mm^3 or platelet count was $< 50{,}000/$mm^3, the

patient was withdrawn from the protocol therapy. No dose escalation was permitted.

Study Design

Initially 20 patients were to be accrued. If at least one of the first 20 patients responded, then an additional 20 patients would be accrued. Five or more responses out of 40 patients would be considered evidence warranting further study of the regimen, provided other factors such as toxicity and survival also appeared favorable. This design has a significance level of 5% and a power of 92%.

Response Criteria

Response to treatment was assessed after every cycle with PSA level and after every second cycle with radiologic evaluation. Standard solid tumor response criteria were used. Complete response was defined as the total disappearance of all measurable and evaluable disease, with no new disease, no disease-related symptoms and no evidence of nonevaluable disease, including the resolution of all abnormal serum markers and lab values. PSA must have declined to < 4.0 ng/ml.

Partial response was defined only in those with measurable disease and required a 50% or greater decrease from baseline in the sum of products of perpendicular diameters of all measurable disease, no progression of evaluable disease, and no appearance of new disease.

Progression was defined as a 50% increase or an increase of 10 cm^2 (whichever was smaller) in the sum of products of all measurable lesions over the smallest sum obtained, clear worsening of evaluable disease, reappearance of any lesion which had disappeared, the appearance of any new lesion or a 50% increase over minimum PSA obtained. PSA $\geq$ 4ng/ml after previous normalization was also considered to be progression.

RESULTS

Demographic Data

A total of 31 patients were entered on the trial between November 1, 1996, and January 1, 1998. Of these patients, five were ineligible and one was not analyzable because no protocol treatment was ever received, for a total of 25 patients to be included in the analysis of this study (Table I). Patients were ineligible for the following reasons: rising PSA in the 42 days before registration was not documented in two patients; PSA level was obtained over 42 days before registration in one patient; in one patient, no prestudy chest radiograph was obtained; and one patient did not have a testosterone level obtained within 28 days of registration.

TABLE I. Baseline Demographics for 25 Evaluable Patients*

Median age (range) years	68	(54–83)
Median PSA (range) ng/ml	135	(20–3724)
Mean hematocrit (range)	35.2	(25.2–46.5)
Mean Gleason score (range)	7.2	(6–10)
Gleason score 8–10 (%)	11	(44)
Visceral involvement (%)	6	(24)
Performance status 0–1(%)	21	(84)
Prior orchiectomy (%)	15	(60)
>1 prior hormone (%)	8	(32)
Prior radiation (%)	16	(64)

*PSA, prostate specific antigen.

The median age was 68.0 years (range, 54–83 years). Eighteen patients were white, 4 were African American, 2 were Hispanic, and 1 was Asian. Twenty-one patients had a performance status of 0–1, 4 had performance status of 2. Six patients had visceral involvement. Median PSA was 135 ng/ml (range, 20–3724 ng/ml).

Treatment

Fifteen patients were removed from treatment for progressive disease, 7 because of unacceptable toxicity, 1 patient refused to continue therapy, and 2 patients died while on study from causes not believed to be treatment-related. (One died of heart failure 1 day after starting therapy. He had triple vessel coronary disease. The other died of progressive disease.) Of the 15 patients removed from treatment for progression, 3 had rise in PSA as the only indication of worsening disease. Thirteen patients completed at least two cycles of therapy (range, 1–6).

Toxicity

Twenty-four patients could be assessed for toxicity. The one patient not assessable for toxicity is the eligible and evaluable patient who died of heart failure 1 day after initiating therapy, hence no toxicity notation was done. There were no treatment-related deaths. Eight patients experienced grade 4 toxicity (1 epistaxis, 6 granulocytopenia, and 1 leukopenia without granulocytopenia). Eleven patients experienced grade 3 toxicity as their worst grade: most commonly anemia (9 patients), thrombocytopenia (8 patients), leukopenia (7 patients), and 1 each experienced hematuria, confusion, infection, and nausea (Table II).

TABLE II. Number of Patients and Degree of Toxicity

	Grade		
Toxicity	1/2	3	4
Alopecia	3	0	0
Anemia	14	9	0
Confusion	23	1	0
Diarrhea	32	0	0
Epistaxis	2	0	1
Fatigue	13	0	0
Fever	5	0	0
Hematuria	1	1	0
Leukopenia	10	7	5
Nausea	13	1	0
Neutropenia	4	3	6
Stomatitis	4	0	0
Thrombocytopenia	9	8	0
Vomiting	7	0	0
Weakness	3	0	0
Max grade any toxicity	5	11	8

Response

Nine patients had inadequate tumor-response assessment and are considered nonresponders. Five patients had stable disease, no patient had a documented complete or partial response. Four patients (16%) had a decline of PSA by 50% from baseline. Only one of these patients had stable disease by standard response criteria. At the time of reporting, all but one patient have died. The median survival for the group was 9 months.

DISCUSSION

Effective therapy for hormone-refractory prostate cancer has been elusive; progress in this area has been hampered by a dearth of effective agents and by the inherent difficulty in measuring tumor response in the majority of prostate cancer patients whose evident metastatic disease is limited to bony structures. Recently, however, reports have indicated that change in serum PSA is a reliable indicator of tumor response in patients with hormone refractory prostate cancer [17]. In addition, a variety of new agents have been evaluated in these patients, and response rates have been encouraging [18,19].

Our study allowed evaluation of PSA change from baseline for tumor response measurement in patients without traditional bidimensionally measurable disease. Change in PSA could be used to define a complete response, but no ''partial PSA response'' was defined. By using these criteria, our study has demonstrated that topotecan administered as a 21-day infusion of 0.5 mg/m^2 per day to men with hormone-refractory prostate cancer is of no therapeutic benefit and is associated with significant, largely hematologic toxicity. The median survival of 9 months in this group, somewhat less than seen in similar contemporary series, further indicates that topotecan offered no significant benefit. A review of the demographic features of our patient population at study entry does not reveal an obvious explanation for the poor response rate seen in this study. Median age, Gleason score, and intensity of prior therapy are in line with prior SWOG trials. However, ours is not the first study failing to demonstrate topotecan activity in the treatment of hormone refractory prostate cancer. Hudes et al. evaluated 30-min infusions daily for 5 consecutive days in 37 patients. One response was seen in the first 14 patients treated, allowing continued accrual, but the final reported response rate was only 2.9% [13].

As anticipated, the major toxicity from topotecan infusion in our study was hematologic. Nearly two thirds of assessable patients experienced grade 3 or 4 hematologic toxicity. Six of 40 administered cycles (16%) required dose modification or delay in treatment. Whether growth factor support would allow better adherence to treatment dose and schedule is unknown. One published report of a Phase I study allowing granulocyte colony stimulating factors support in conjunction with 5-daily 30-min topotecan infusions, suggests it would not [14]. The relatively young age of our population (median, 68 years) and their overall good performance status would indicate that patient selection was not an important variable in our inability to demonstrate activity of topotecan in this setting. The large number of patients whose response was not adequately assessed is troubling and not readily explained. The baseline demographic features of this group are not significantly different from the others. Several were removed from the study for early toxicity before tumor assessment was required. It is also possible that the logistics of the study treatment and evaluation with an unfamiliar drug may have been overly burdensome for either the treating physicians or the patients themselves.

Based on our results, we conclude that topotecan administered as a 21-day continuous infusion every 28 days is an ineffective and moderately toxic treatment for patients with hormone refractory prostate cancer.

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