A Phase II Study of Continuous Infusion 5-Fluorouracil in Advanced Hormone Refractory Prostate Cancer

An Illinois Cancer Center Study

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Background. **5-Fluorouracil (5-FU) has been previously associated with therapeutic benefit in hormone refractory prostate cancer. However, no previous study has administered 5-FU as a prolonged continuous infusion, which may be the optimal schedule for this cell-cycle specific agent.**

Methods. **Therefore, 25 patients were treated with 5-FU administered as a continuous intravenous infusion at a dose of 1000 mg/m^2/day for 5 days every 28 days. Eligibility required disease defined by bidimensionally measurable lesions or evaluable lesions on bone scan or radiograph with elevated serum levels of prostate-specific antigen (PSA), no severe cytopenias, and an Eastern Cooperative Oncology Group performance status less than 3. Prior chemotherapy was not allowed. Dose modifications were specified for mucositis and hematologic toxicity.**

Results. **Eighteen of 22 patients were evaluable for response and toxicity, whereas 4 were evaluable for toxicity alone. Toxicity was significant using this dose and schedule and included episodes of sudden death (one patient), paroxysmal supraventricular tachycardia (one patient), and congestive heart failure (one patient). Other Grade 3 toxicities included stomatitis (two patients) and diarrhea (one patient). Significant myelosuppression did not occur. Objective responses were not observed, but 12 patients experienced stable disease with a median duration of 4 months.**

Conclusions. **Infusional 5-FU can not be recommended for the treatment of advanced hormone refractory prostate cancer. *Cancer* 1993; 72:1965–8.**

Key words: continuous infusion, prostate cancer, chemotherapy, 5-fluorouracil.

The treatment of advanced hormone refractory prostate cancer is a common therapeutic dilemma faced by the medical oncologist. Although secondary hormonal maneuvers occasionally achieve clinically meaningful remissions,[1,2] the duration of remission is usually less than 6 months. Still, chemotherapy is frequently only administered after the failure of second-line hormone therapy. Many chemotherapeutic agents have been tested in this disease with stabilization and remission rates of approximately 25%.[3] However, no chemotherapeutic agent alone or in combination has improved the survival of patients with this disease.

5-Fluorouracil (5-FU) is a commonly used antineoplastic agent with activity in tumors of the head and neck, breast, and gastrointestinal tract. In addition, 5-FU has been shown in vitro to inhibit deoxyribonucleic acid synthesis and 5-alpha reductase activity in the prostatic cell.[4] Most studies of 5-FU for advanced hormone refractory prostate cancer have suggested only a modest benefit.[5,6] However, 5-FU has usually been administered as an intravenous bolus either once per week or every 3 weeks. It is now recognized that 5-FU is a cell-cycle specific agent. Therefore, administration by continuous intravenous infusion may maximize the

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therapeutic efficacy against a relatively indolent neoplasm with a long doubling time.[7,8] The Piedmont Oncology Association reported a Phase II trial using a high dose (4000 mg/m^2) of 5-FU administered via a 24-hour continuous infusion.[9] Objective responses were not observed, but 33% of patients had stable disease. More commonly, 5-FU is administered as a 5-day infusion at more modest doses (1000 mg/m^2/day). This dose and schedule in colorectal carcinomas yields similar response rates as the bolus 5-FU schedules combined with the modulators leucovorin or alpha-interferon.[10] Thus, the Illinois Cancer Center performed a Phase II study of continuous infusion 5-FU in patients with hormone refractory prostate cancer.

Methods

Patients with histologically documented metastatic prostate carcinomas refractory to hormonal therapy were eligible. Patients were required to have bidimensionally measurable lesions or evaluable lesions on bone scan or radiograph with elevated serum levels of prostate-specific antigen (PSA), no pre-existing severe cytopenias, and an Eastern Cooperative Oncology Group performance status less than or equal to 2. Prior chemotherapy was not permitted. Patients with symptomatic coronary artery disease or those who had received radiation therapy within 28 days of study entry were not eligible. Concurrent chemotherapy or steroid therapy was not permitted.

5-FU was administered as a 5-day continuous infusion via a peripheral vein or through a central indwelling catheter at a dosage of 1000 mg/m^2/day every 28 days. Patients were to be examined at least monthly so that response and toxicity could be assessed. Complete blood counts, serum chemistries, prostatic acid phosphatase, and serum PSA levels were to be obtained before study and before each cycle. Lesion measurements or bone scan/radiographs documenting evaluable disease were to be obtained every other month. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria.

Response criteria for the study were based on Eastern Cooperative Oncology Group criteria for measurable lesions and on National Prostatic Cancer Project criteria for evaluable lesions. Complete response required complete disappearance of all clinically detectable tumor and osteoblastic lesions for at least 28 days, return to normal of elevated levels of serum prostatic acid phosphatase and serum PSA, recalcification of all osteolytic lesions, normalization of any abnormal biochemical markers, and absence of cancer-related weight loss greater than or equal to 10%. Partial response required at least a 50% reduction in the product of the longest diameters of the indicator lesions or sums of the products of multiple indicator lesions for a minimum of 28 days (for patients with measurable disease), return to normal of elevated levels of serum prostatic acid phosphatase and PSA, no increase in size of osteoblastic lesions, recalcification of one osteolytic lesion if any present, a 50% reduction in number of abnormal foci of uptake on bone scan, and no cancer-related weight loss greater than or equal to 10% and no deterioration of performance status from baseline. Progressive disease was defined as (1) the appearance of new areas of malignant disease by bone scan or radiograph; (2) death attributed to neoplastic disease after a minimum of one cycle of chemotherapy (5 days); (3) for measurable disease an increase in product of longest diameters or sum of products greater than 25% over smallest size documented earlier; (4) for evaluable disease an increase in extent of disease judged to exceed 25% over minimum tumor burden previously; (5) development of ureteral obstruction; or (6) an increase in bone pain requiring radiation therapy. Stable disease included patients with tumor indicator changes less than those defined for partial response or not as great as for progressive disease. PSA levels were monitored, but increases alone did not constitute progressive disease.

Results

Between February 1990 and June 1992, 25 patients were enrolled in this study. All patients were required to give written informed consent, as approved by the institutional review boards at all participating institutions. Three patients were found to be ineligible because of either previous chemotherapy (two patients) or withdrawal before receiving chemotherapy (one patient). Characteristics of eligible patients are summarized in Table 1. All patients had failed systemic hormonal therapy with either orchiectomy or gonadotropin releasing hormone (GRH) agonists. Patients who had not undergone orchiectomy were required to continue the GRH agonist therapy during this trial. Of the 22 eligible patients, 18 were evaluable for both toxicity and response (received one full cycle of 5-FU), and 4 were only evaluable for toxicity (did not complete one cycle).

Toxicity

Mild anemia, nausea/vomiting, leukopenia, and stomatitis were common side effects. Table 2 lists the spectrum and extent of side effects observed during the trial. Hematologic toxicity was not a major toxicity. Severe neutropenia (less than 500/μl) or thrombocytopenia (less than 20,000/μl) did not develop in any patient.

Table 1. Patient Characteristics

No.	22
Age (yr)	
Median	69
Range	54–79
ECOG performance status	
0	3
1	16
2	3
Previous hormonal therapy	
Orchiectomy	11
Orchiectomy + flutamide	2
Orchiectomy + diethylstilbesterol	1
GRH	1
GRH + flutamide	1
Unknown	2
Site of disease	
Bone only	22
Entry PSA	
Median	88
Range	8.9–11,700

ECOG: Eastern Cooperative Oncology Group; GRH: gonadotropin releasing hormone agonist; PSA: prostate-specific antigen.

Several patients received erythrocyte transfusions during the course of the trial. The most common side effect requiring dose adjustment was Grade 2–4 stomatitis. Two of the four patients evaluable only for toxicity were removed from study because of Grade 3 or 4 cardiac toxicity. One patient developed a supraventricular arrhythmia with hypotension during the administration of the first cycle of 5-FU, and one patient developed congestive heart failure requiring termination of the first cycle of chemotherapy. A third patient died unexpectedly 3 weeks after the first cycle of 5-FU. The exact cause of death was not determined, and no autopsy was performed.

Response

Eighteen patients were assessable for response. No complete responses and no partial responses were observed. Twelve patients experienced stable disease with a median duration of 4 months as determined by symptoms and objective results of bone scans. Only three of these patients experienced a decline in their PSA levels during their treatment, none as great as 50% of pretreatment levels. All others had gradual increases in PSA.

Discussion

5-FU is a commonly used antineoplastic agent for the treatment of adenocarcinomas. Prolonged infusions have been associated with significant response rates in neoplasms of the breast, head and neck, and gastrointestinal tract. In vitro, there is evidence for alteration in deoxyribonucleic acid synthesis and 5-alpha reductase activity in prostate cell lines.[4] Early trials using 5-FU as a single agent with bolus administration suggested response rates of 20–25%.[3] These trials were performed before the kinetic advantages of prolonged infusions of 5-FU were recognized and before the availability of PSA monitoring. Thus, this trial was carried out to further study 5-day infusions of 5-FU in hormone refractory prostate cancer.

No objective responses were observed in the 18 patients assessable for response. The lack of even as much as a 50% decrease in PSA levels further suggests that this agent has no clinical activity in this disease. Stable disease was observed based on bone scan findings and symptom control, but the relatively short duration suggests that these patients may simply have had biologically more indolent disease, rather than a benefit from the therapy.

Toxicity was significant in this population. In particular, cardiotoxicity was frequently observed. Cardiotoxicity has been associated previously with infusions of 5-FU.[11,12] The incidence of significant adverse cardiac events of all types reported from a recent large prospective trial was approximately 7.6%.[12] In this trial the incidence of cardiotoxicity ranged from 9.1% to possibly as high as 13.6% if the patient with sudden death is included. The mechanism(s) by which 5-FU effects the heart have not been clearly elucidated, but may involve thrombogenic complications,[13] vasospastic changes[14] or direct antimyocardial effects.[12] This trial was designed for older male patients, a population at

Table 2. Toxicity Observed During Any Cycle

	Grade			
Symptoms	*1*	*2*	*3*	*4*
Anemia	7	4	1	
Nausea/vomiting	4	1		
Stomatitis	5	3	2	1
Diarrhea	2		1	
Leukopenia	5	2		
Thrombocytopenia	4			
Cardiac				
PSVT				1
CHF			1	
Dysuria	1			
Anorexia	1			
Altered sensorium	1			
Alopecia	1			

PSVT: paroxysmal supraventricular tachycardia; CHF: congestive heart failure.

significant risk for underlying cardiac disease. Thus, the higher incidence in this trial may be related to subclinical pre-existent atherosclerotic disease. Alternatively, there may be a greater risk of inducing a hypercoaguable state due to the underlying metastatic adenocarcinoma which is further exacerbated by 5-FU.

Attempts to enhance bolus 5-FU efficacy in colorectal tumors using combinations of 5-FU with alpha-interferon or leucovorin recently have been described. Using these strategies, bolus 5-FU appears to be as effective as infusional 5-FU. Furthermore, long-term low-dose infusions of 5-FU may be the most dose-intense way to administer the agent. These approaches may warrant further study in prostate cancer, but there is little reason to be encouraged. Synergistic benefits are unlikely, as a recent Phase II trial of recombinant human alpha-interferon in hormone refractory prostate carcinoma demonstrated little antitumor effect and substantial toxicity.[15] Additionally, the mechanism of enhanced antitumor effect using the combinations appears to relate to alterations in metabolism and clearance of 5-FU, similar to infusing 5-FU. Therefore, given the lack of response, and the development of significant toxicity, infusional 5-FU can not be recommended for the treatment of hormone refractory prostate cancer. New drugs with novel mechanisms of action or combinations of drugs exploiting the biology of hormone refractory prostate cancer cell need to be developed.

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