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5-Fluorouracil and Low-Dose Recombinant Interferon-α-2a in Patients With Hormone-Refractory Adenocarcinoma of the Prostate

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BACKGROUND. The effectiveness of a chemotherapy regimen including 5-fluorouracil (5-FU) and recombinant interferon-α-2a (rIFN-α-2a) was evaluated in hormone-refractory prostate cancer patients.

METHODS. Patients received a continuous intravenous infusion of 5-FU at 600 mg/m^2/day for 5 days (D1–D5), followed by a bolus injection of 5-FU on D15 and D22. Patients received intramuscular injection of rIFN-α-2a at 3 million IU on D1, D3, D5, D15, and D22. This schedule was repeated every 4 weeks.

RESULTS. Between 1993 and 1995, 23 patients with hormone refractory prostate cancer were enrolled in this study. Two of five patients with nodal disease exhibited partial responses according to the NPCP criteria. Fourteen of 17 patients with bone disease showed stable disease. Of 21 patients assessible for response, 9 patients had a decrease in the PSA level greater than 50% of baseline. Bone pain disappeared partially or completely in 8 of 14 patients with this symptom at entry. The median overall survival was 18 months. The associate toxicity was well tolerable.

CONCLUSIONS. Combination chemotherapy of 5-FU and low dose rIFN-α-2a in patients with hormone-refractory prostate cancer proved feasible, and with acceptable toxicity. *Prostate 35:56–62, 1998.*

KEY WORDS: **prostate cancer; hormone-refractory; chemotherapy; 5-FU; interferon**

INTRODUCTION

Castration and estrogens have been recognized as effective therapies for advanced prostate cancer since the 1940s [1]. Several surgical and pharmacological maneuvers, all with the common aim of decreasing endogenous androgen levels or blocking its actions, have been employed as the primary treatment [2]. Although high initial response rates to such hormonal therapy occur, most patients will eventually have progressive disease. Once hormone refractory cancer occurs, therapeutic options are limited for these patients. Second-line hormonal treatment brings only temporary benefits to a relatively small number of patients [3]. Chemotherapy has shown only minor effectiveness in this clinical setting; side effects may represent a major concern in the average prostate cancer patient with extensive bone metastases, advanced age, and, not infrequently, associated systemic diseases [4]. Considering the poor life expectancy of hormone-refractory prostate cancer patients (about 6–12 months), specific, effective and less toxic chemotherapy regi-

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mens are needed for these patients, especially for younger (less than 70 years) patients [5].

5-Fluorouracil (5-FU) is an antimetabolic anticancer drug commonly used for breast and gastrointestinal malignancies. Clinical trials in patients with prostate cancer using 5-FU as a single agent administrated either as a bolus injection or by continuous infusion have shown limited efficacy [6]. Since a positive interaction has recently been reported between 5-FU and interferon-α (IFN-α) in patients with advanced colorectal carcinomas [7], clinical trials utilizing this combination chemotherapy have been conducted in patients with hormone refractory prostate cancer [8,9]. However, these studies demonstrated that combination chemotherapy with 5-FU and IFN-α caused significant morbidity at the doses of both drugs used in these treatment regimens. It is therefore considered that an attempt to ameliorate the increase of treatment-related toxicity is necessary.

Although several clinical trials employing 5-FU and IFN-α have been performed for a variety of cancers, the optimum dose of 5-FU or IFN-α and optimum schedule of combination have not yet been defined. Our preclinical studies demonstrated that, in a hormone-refractory prostate cancer cell line, higher concentrations (1,000, 10,000 IU / ml) of rIFN-α-2a did not always bring about an increase in 5-FU cytotoxicity, compared with lower concentration (100 IU / ml) [10]. We therefore conducted a clinical trial employing 5-FU in combination with a lower dose of rIFN-α-2a than that reported previously for patients with hormone-refractory prostate cancer. The purpose of the present study was to study the efficacy and the toxicity profile of this combination chemotherapy.

MATERIALS AND METHODS

Patients

Between September 1993 and November 1995, a total of 23 patients with metastatic prostate cancer with evidence of progression during primary hormonal treatment were entered into the present study. As primary hormonal treatment, any treatment that impaired testosterone production or activity, or both, was accepted. Judgment of progression was according to the National Prostatic Cancer Project (NPCP) criteria for response [11]. Briefly, patients had new sites or an increase in size of metastases on bone scans, or new soft tissue metastases with a 25% or greater increase in the perpendicular diameters of the measurable lesions or the development of new lesions.

Patients were eligible if they had a performance status (PS) of ≤3, according to the Eastern Cooperative Oncology Group (ECOG) scale and a life expectancy of at least 3 months. The patients had to have adequate hematologic function (absolute neutrophil count >3,000 and platelet count >120,000), adequate hepatic function (bilirubin ≤1 mg / dl and serum glutamic pyruvic transaminase 2 times or less the upper limit of normal value) and adequate renal function (creatinine less than 1.5 mg / dl). Patients were not concurrently receiving other specific anticancer drugs, except luteinizing hormone-releasing hormone (LH-RH) analogues or oral estrogens, or both, which were continued to maintain plasma testosterone within the castrate level in those patients with no prior orchiectomy. For patients receiving antiandrogens, chlormadinone acetate, or flutamide, these drugs were discontinued at least 4 weeks before initiation of therapy. Patients with a history of any other cancer and who had received radiation therapy within 28 days of study entry were not eligible.

Treatment

After having given signed, informed consent, patients who fulfilled the eligibility criteria were treated with 5-FU in combination with low-dose rIFN-α-2a. Combination chemotherapy consisted of the intravenous continuous infusion of 5-FU, 600 mg / m^2 / day for 5 days (D1–D5), followed by a bolus injection of 5-FU at 600 mg / m^2 / day on days 15 and 22. Patients also received an intramuscular injection of rIFN-α-2a (3 million IU) daily on days 1, 3, 5, 15, and 22. This schedule was repeated every 4 weeks.

Evaluation and Follow-up Study

Patients were followed during the study at least once weekly with a complete blood count with differential, platelet count, urinalysis, and analyses of electrolytes, serum bilirubin, serum glutamic pyruvic transaminase, lactate dehydrogenase, and alkaline phosphatase. Serum prostate-specific antigen (PSA) was monitored at least every course. A history and physical examination (with performance status) were repeated before each course. Tumor size, response of each lesion and overall response were measured every 4 weeks. Radiological studies, including a bone scan and computed tomography (CT), were performed for every course.

Response Criteria

Responses were categorized based on the NPCP criteria [11]. A complete response (CR) required disappearance of all evidence of tumors for ≥4 weeks. Osteolytic or mixed bone lesions should show reossification by radiography or improvement by bone scan

and the patient should be free of all symptoms. A partial response (PR) required that the sum of the product of the largest perpendicular diameters decrease by ⩾50% but less than 100% for ⩾4 weeks. Bone scans were not used as criteria to document this response, as they could not demonstrate any new areas of change consistent with metastases. Stable disease (SD) was defined as a decrease in measurable disease of less than 50% but more than 25% for ⩾12 weeks. Progressive disease (PD) was defined as development of new sites or an increase in size of metastases on bone scans or new soft tissue metastases with a 25% or greater increase in the perpendicular diameters of the measurable lesions or the development of new lesions.

Toxicity was graded according to World Health Organization (WHO) criteria [12] by physical examination, direct questioning, and measurement of hematologic and biochemical parameters. The decrease in serum PSA was calculated from baseline to the point at which the lowest value was recorded.

Statistical Methods

Survival times were calculated from the date the patient was entered into the present study until the date of death or last follow-up. The Kaplan–Meier method was used to calculate the probability of survival as a function of time [13].

RESULTS

The pretreatment characteristics of the patients entered into the present study are listed in Table I. Two patients did not complete the initial cycle of therapy because of unacceptable toxicity (1 patient) and withdrawal of consent (1 patient). Twenty-three patients were assessable for toxicity, and 21 patients were assessible for response. They received a total of 66 cycles of therapy (mean, 3: range, 2–5). The mean follow-up duration was 17.8 months (range, 8–33 months).

Table II lists the spectrum and severity of side effects observed during the trial. Gastrointestinal toxicity was common. Oral mucositis, usually occurring shortly after the conclusion of 5-FU continuous infusion, was observed in nine patients, three of whom experienced grade 3, according to WHO criteria. Ten patients and eight patients experienced anorexia and nausea/vomiting, respectively. Diarrhea was encountered in eight patients; one patient suffered grade 3 diarrhea. Grade 3 leukocytopenia was encountered in 1 (4%) of the 23 patients. Symptoms of flu-like syndrome characteristic of rIFN-α-2a were observed uniformly and were controllable. In most patients, tachyphlaxis to these symptoms developed. We also observed severe neurotoxicity in one patient (4%). Hand-foot syndrome related to 5-FU treatment was noted in six patients (26%) during the second and third cycles. There were no chemotherapy-related deaths.

Objective responses in bone and soft tissue metastases, PSA change, and survival are correlated in Table III. Two (40%) of five patients with nodal disease obtained PR (duration of response: 9 months and 11

TABLE I. Patient Characteristics

Characteristics	n	%
No. registered	23	
Age (years):		
Median	65	
Range	56–81	
Performance status (PS)		
0	7	31
1	12	52
2	3	13
3	1	4
Prior treatment		
Surgical castration	9	39
Medical castration	12	52
Estrogen	6	26
Antiandrogen		
Chlormadinone acetate	10	43
Flutamide	3	13
Chemotherapy		
Estramustine phosphate	11	48
Tegafur-uracil	6	26
Cisplatin	1	4
Radiation	4	17
Prostatectomy	2	9
Site of metastasis		
Bone	19	83
Soft tissue		
Lymph nodes	5	22
Pelvic soft tissue	1	4
PSA value at study entry (ng/ml)[a]		
Median	55.1	
Range	2.5–1040	

[a]Delfia PSA kit: cutoff value, 1.98 ng/ml.

TABLE II. Toxicity Observed During Any Cycle

	Grade (WHO criteria)					% of
Toxicity	0	1	2	3	4	grade 3 or more
Leukocytopenia	10	3	9	1	—	4
Thrombocytopenia	21	2	—	—	—	0
Mucositis	14	3	3	3	—	13
Anorexia	13	4	4	2	—	9
Nausea/vomiting	15	5	3	—	—	0
Diarrhea	15	4	3	1	—	4
Neurologic	22	—	—	1	—	4

TABLE III. Comparison of Clinical Response, PSA, and Survival in Patients With Hormone-Refractory Prostate Cancer

Pt no.	Pretreatment PSA (ng/ml)	PS	No of cycle	Response Bone	Soft tissue	PSA (% decrease)	Survival (mos)
1	45	0	3	SD		69	31[a]
2	11.1	0	3	SD		85	33[a]
3	137	2	4	PD		62	13
4	20.3	1	3	SD		31	20
5	69.1	2	3	PD		Increase	9
6	2.5	0	3		PR	—	30[a]
7	26.3	1	3	SD		Increase	29[a]
8	11.4	1	2	SD		85	10
9	809	3	5		PR	93	18
10	56.1	1	3	PD		Increase	9
11	77.2	1	3		PD	Increase	24
12	70.4	0	4	SD		96	27[a]
13	101	0	3	SD		80	10
14	1,040	1	3	SD		41	12
15	154	1	3	SD		51	18
16	860	1	3	SD		Increase	10
17	37.9	1	3	SD	SD	No change	18[a]
18	23.1	0	3	SD		Increase	12
19	61	1	4	SD		No change	17[a]
20	6.7	0	2		PD[b]	67	8
21	266.3	1	3	SD		No change	15[a]

[a]Survivor.
[b]Lymph node (SD) and pelvic soft mass (PD).
PS, performance status; PD, progressive disease; PSA, prostate-specific antigen.

months, respectively). Both patients had a decrease in PSA levels (93% and 44%, respectively). Among the 17 patients with evaluable bone disease, there were no objective responses. Fourteen patients (82%) showed stable disease, eight of whom showed a decrease in PSA levels, ranging from 31% to 96%. Of the 21 patients assessable for response, nine patients (43%) had a decrease in the PSA level greater than 50% of baseline. None of the PSA responses was attributed to antiandrogen withdrawal.

Eight (57%) of 14 patients who suffered significant bone pain at entry into the present study had partial or complete disappearance of this symptom. No patients exhibited a decrease in performance status during the treatment; in addition, five patients showed improvement of performance status with the relief of bone pain. The median overall survival assessible for response was 18 months. The survival curve is shown in Figure 1.

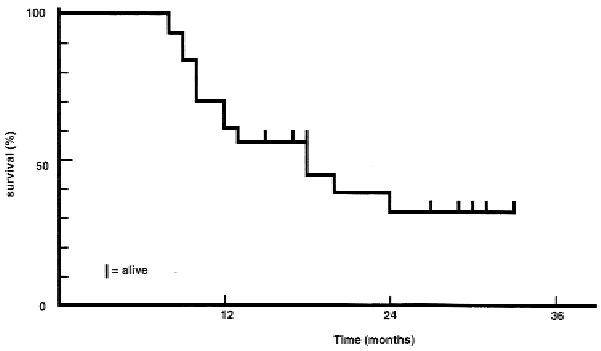

Fig. 1. Overall survival curve in patients assessible for response.

DISCUSSION

Treatment of advanced prostate cancer after hormonal failure is still controversial; at the moment, no effective secondary therapy has been proposed. Considering the limited life expectancy (6–12 months) and the devastating triad of bone pain, fatigue, and cachexia that affect most patients, there remains an urgent need to identify an effective second-line therapy. The present study demonstrated that, according to NPCP criteria for response [11], two of five patients with nodal disease obtained PR and that one patient with nodal disease and 14 patients with bone metas-

tases had stable disease. In addition, about 40% of patients had a more than 50% decrease in post-therapy PSA levels. The median overall survival of patients assessable for response was 18 months. The associated toxicity was significant but well tolerable and reversible.

5-FU has been shown to inhibit deoxyribonucleic acid synthesis and 5α-reductase activity in the prostatic cell in vitro [14]. Clinical trials in patients with hormone-refractory prostate cancer employing 5-FU as a single agent administered either as a bolus injection or by continuous infusion have reported only a modest benefit [6,15]. In fact, Kuzel et al. [6] reported that no objective responses were observed in patients treated with 5-FU administered as a continuous intravenous infusion at a dose of 1,000 mg/m^2/day for 5 days every 28 days.

IFN-α, originally described as an antiviral agent, has also been investigated as a potential anticancer drug because of its antiproliferative and cytotoxic effects, ability to activate specific components of the immune system, and relatively modest toxicity. It has been approved by the Food and Drug Administration (FDA) for the treatment of patients with hairy cell leukemia, acquired immunodeficiency syndrome (AIDS)-related Kaposi sarcoma, and condylomata acuminate. Modest but reproducible antitumor activity was also shown against tumors such as melanoma and renal cell carcinoma, which are unresponsive to conventional cytotoxic chemotherapy. However, this drug has minimal antitumor activity against hormone-refractory prostate cancer. In fact, only two responses (5%) were observed in 40 patients treated with rIFN-α administered intramuscularly at a dose of 10 million IU/m^2 three times weekly [16].

Several preclinical studies have demonstrated that IFN-α may enhance the cytotoxicity of 5-FU in a greater-than-additive manner in a variety of human cancer cell lines. The underlying mechanisms have varied in different cancer cell lines and include increased anabolism of 5-FU to 5-fluorouridine (FUR), inhibition of thymidine kinase activity, possible alteration of the pharmacokinetics of 5-FU, and enhanced natural killer (NK) cell-mediated lysis of tumor targets [17]. Since a high response rate in patients with previously untreated advanced metastatic colorectal cancer was reported by Wadler et al. [7], consecutive phase II studies employing the combination of 5-FU and IFN-α have been undertaken and shown a modest response rate for colorectal cancer, suggesting that there is clinical synergism between these two drugs. Clinical trials examining 5-FU and IFN-α for hormone-refractory prostate cancer have also been conducted [8,9]. Daliani et al. reported that, in patients treated with the combination chemotherapy, objective responses were not observed and only 17% of patients showed a greater than 50% decrease in serum PSA. They observed significant toxic side effects [9]. Similar results have been noted by Dreicer et al. [8]. The present study showed that 2 patients and 14 patients had PR and SD, respectively, and that 43% of patients assessable for response had a decrease in PSA level greater than 50% of baseline. The median overall survival observed in the present study was longer than that in other studies. In addition, treatment-related toxicity of the present study was somewhat milder than that observed in other studies. Although it is impossible to deny that there are some differences in patient selection and response criteria between the present study and others, the results obtained here appear to be at least partially due to the treatment schedule and to dosages of drugs administered.

Although several preclinical studies showed that IFN-α might modulate that cytotoxic effect of 5-FU in a concentration- and schedule-dependent fashion [18], the optimum dose of 5-FU or IFN-α and optimum schedule of this combination chemotherapy have not yet been defined. Thus, we initially examined in vitro cytotoxicity with various combinations of these drugs in order to design the most effective combination regimens. This preclinical study demonstrated that, in the hormone-refractory prostate cancer cell line PC-3, the presence of rIFN-α-2a at 100 IU/ml induced a two-fold increase in 5-FU cytotoxicity, compared with control, and that higher doses of rIFN-α-2a (1,000, 10,000 IU/ml) did not always bring about the increase in 5-FU cytotoxicity [10]. Recently, a clinical study employing different dose regimens for 5-FU and IFN-α for treatment of patients with advanced colorectal cancer was conducted to clarify the optimal doses of these drugs [19]. This study demonstrated that a regimen which consisted of 5-FU (750 mg/m^2; continuous infusion on D1–D5, followed by bolus injection on D12 and D19) and IFN-α (3 million IU on D1–D5, followed by 5 million IU on D11–D13 and D18–D20) might be more effective than one consisting of 5-FU (750 mg/m^2; continuous infusion on D1–D5, followed by weekly bolus injection) and IFN-α (5 million IU on D1, D3, and D5, followed by 9 million IU given weekly), suggesting that a higher dose of IFN-α does not always bring about a higher objective response rate in a clinical setting. Moreover, Czejka et al. [20] reported that there is no significant difference in pharmacokinetics of 5-FU between two doses of preadministered IFN-α (5 million IU and 9 million IU). These results suggest that, in the biochemical modulation of 5-FU by IFN-α, administration of a higher dose (9 million IU) of IFN-α, which was used in a previous report, does not necessarily enhance the cytotoxic effects of 5-FU against hormone-refractory prostate cancer.

The treatment-related toxicity in the present study was also different from those of others. With regard to neurotoxicity, known to be one of the peculiar toxic effects of IFN-α, Daliani et al. [9] reported that 80% of patients suffered severe neurotoxicity. By contrast, the present study showed that severe neurotoxicity occurred in only 4% of patients. It is possible that the difference in treatment-related toxicity between the two studies results from the difference in the dose of IFN-α-administered. As most patients with prostate cancer are aged men, administration of a higher dose of IFN-α (9 million IU) might result in more toxic effects and aggravated performance status. In general, performance status is one of the important prognostic factors in patients treated with cytotoxic chemotherapy. Therefore, significant aggravation of performance status during chemotherapy, such as 5-FU/IFN-α combination chemotherapy, may reduce its efficacy, aggravating the prognosis. Aggravation of performance status during the treatment was not observed in the present study; in addition, five patients showed improvement of performance status with the relief of bone pain. The fact that this combination chemotherapy did not result in significant aggravation of performance status may have resulted in the better overall survival, compared with the overall survival shown by Daliani et al. [9].

To attempt to ameliorate treatment-related toxicity, Glazier et al. [21] recently reported the results of their clinical trial of 5-FU/rIFN-α-2b combination chemotherapy combined with allopurinol, which is known to modify 5-FU toxicity in patients with hormone-refractory prostate cancer. However, objective responses were not observed. PSA values and symptoms improved temporarily in only 3 of 10 patients (30%). Their results suggest that reduction in the toxic effect of 5FU against normal tissues may result in reduction in the cytotoxic effect of this drug on malignant tissues, resulting in diminution of the treatment efficacy. Therefore, in order to ameliorate treatment-related toxicity, a reduction in the dose of IFN-α appears to be more appropriate than modification of 5-FU toxicity by allopurinol.

CONCLUSIONS

Within the limitations of the present pilot study, combination chemotherapy of 5-FU and a low dose of rIFN α-2a in patients with hormone refractory prostate cancer proved to be feasible, with acceptable toxicity. The effects on survival of this combination chemotherapy still remain to be proven. Further studies are needed to confirm these results in a large patient population with a randomized trial between 5FU alone and 5FU in combination with a low dose of rIFN α-2a.

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