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Continuous-infusion fluorodeoxyuridine with leucovorin and high-dose interferon: a phase II study in metastatic renal-cell cancer

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Summary. A total of 25 patients with metastatic renal cancer were treated on a phase II protocol with 5 days of continuous-infusion fluorodeoxyuridine (FUDR), (0.1 mg/ kg daily) together with high-dose oral leucovorin (100 mg 4 h) and daily ×6 high-dose interferon-α2b (30×10^6 IU/m^2). Despite the good performance status of the patients and the inclusion of 14 previously untreated patients in the cohort, no response was observed among the 20 evaluable patients. Toxicities included high fever, moderate anemia, transient leukopenia, transient and mild elevations of transaminases, and moderate to severe nausea, vomiting, diarrhea, and mucositis. There were also two episodes each of confusion, fluid retention, and pancreatitis and one episode of increased creatinine levels. During the study three deaths occurred, two of which were possibly therapy-related. Despite previous reports of activity of FUDR in metastatic renal cancer, the present regimen cannot be recommended.

Introduction

Treatment of metastatic renal-cell carcinoma with chemotherapy has generally been an unsuccessful endeavor, with the median survival being approximately 9 months. No chemotherapeutic regimen has achieved a reproducible objective response rate of greater than 15%. Recently, the role of fluoropyrimidines has been reexamined and response rates of 10%–30% have been reported [3, 4, 9, 10, 12, 20, 22, 28]. Fluorouracil (5-FU) interferes with cellular metabolism through two mechanisms. It can be incorporated into RNA and either inhibit RNA processing or, through its activation to fluorodeoxyuridine monophosphate (FdUMP), inhibit thymidylate synthetase (TS) and thus DNA synthesis.

Fluorodeoxyuridine (FUDR) is a committed metabolite whose main mechanism of action is inhibition of TS. The inhibition of TS by both 5-FU and FUDR is greatly enhanced by the presence of reduced folates such as leucovorin (LV), the mechanism involved being stabilization of the ternary complex of FdUMP, LV, and TS [13]. Increased toxicity, usually manifesting as increased mucositis, has clearly been demonstrated for the combination of fluoropyrimidines and LV [14, 15]. A greater response rate as well as better survival have also been demonstrated for the combination as compared with single-agent 5-FU in metastatic colon cancer [7].

Extensive experience with interferon-α treatment in metastatic renal-cell cancer has revealed that the response rate is about 10%–15% [1, 19, 21]. More recently it has been noted that interferon-α augments the cytotoxicity of 5-FU in cell lines [26]. Increased toxicity is also noted in patients treated with this combination [11, 26], perhaps occurring through an interferon-mediated increase in 5-FU levels [2, 16]. Numerous trials are currently examining this combination in an effort to increase response rates in colon, head and neck, and other malignancies.

To examine the clinical interaction between fluoropyrimidines, reduced folates, and interferon-α, we initiated and recently completed two phase I trials. The first trial was performed with FUDR and LV [24] and the second with FUDR, LV, and interferon-α [25]. We defined the maximum tolerable dose (MTD) as being 30×10^6 IU/m^2 interferon given daily for 6 days together with concomitant oral administration of LV at 100 mg q 4 h and 5 days of continuous infusion of FUDR at 0.1 mg/kg daily. The dose-limiting toxicity was severe flu-like symptoms and fatigue attributed to the interferon. Higher doses of FUDR were accompanied by severe mucositis and diarrhea. Because objective responses were seen in renal cancer patients in the phase I trials and due to the previous positive responses noted in single-agent FUDR trials, we initiated a phase II study using the recommended doses for

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Table 1. Patients' characteristics

Number of patients	25
Median age (range)	54 (30–69) years
Performance status:	
0	4
1	17
2	4
Sex (M/F)	18/7
Previously treated:	
IFN-γ	2
IL-2/IFN-α	6
IL-2/LAK	1
OKT-3	1
Cyclophosphamide/CDDP	1
Prior nephrectomy	18
Sites of disease:	
1 only	8[a]
2	10
⩾3	7
Time to metastatic disease[b]:	
At diagnosis	13
0–12 months	1
12–24 months	3
>24 months	8

IFN-γ, Gamma-interferon; IFN-α, alpha-interferon; IL-2, interleukin 2; LAK, lymphokine-activated killer cells; OKT-3, anti-CD3 monoclonal murine antibody; CDDP, cisplatin

[a] Lung, 3; bone, 2; visceral, 1; nodal, 2

[b] From the time of initial nephrectomy

Table 2. Toxicity of the present regimen

	CALGB grade			
	1	2	3	4
Hemoglobin	10	9	1	0
WBC	3	14	6	0
Liver-function tests	12	6	2	0
Nausea/vomiting	8	4	3	1
Fever	0	21	4	0
Diarrhea	7	4	6	1
Mucositis/stomatitis	9	5	5	0
Dermatitis	0	3	0	0
Confusion	0	2	0	0
CHF/edema	0	1	1	0
Pancreatitis	2	0	0	0
Other	1 case of increased creatinine, 1 case of GI bleeding at a disease site, 1 skin abscess, 2 possible toxic deaths			

CALGB, Cancer and Leukemia Group B; CHF, congestive heart failure; WBC, white blood count

FUDR, LV, and interferon-α2b in patients with metastatic renal cancer.

Patients and methods

Patients. A total of 25 patients with histologically documented metastatic renal-cell cancer were entered in the study. Eligibility requirements included a performance status of 0–2, a life expectancy of greater than 8 weeks, adequate hematologic and metabolic parameters (WBC, >3.0/μl; platelets, >100,000/μl; total bilirubin, <1.6 mg/dl; creatinine, <2.0 mg/dl; and SGOT and SGPT levels of <3 times the normal values), and documentation of measurable or evaluable disease within 2 weeks of the beginning of treatment. Two patients had only evaluable disease. Because of a lack of other potentially effective treatment, patients who had undergone prior chemo- or immunotherapy were eligible; however, an a priori decision was made to enroll 14 previously untreated patients to ensure adequate evaluation of this regimen. Antecedent chemo- or radiotherapy had to have been completed at least 3 weeks prior to the initiation of therapy and could not have included 5-FU or FUDR. All patients were more than 18 years old and gave their written informed consent.

Treatment follow-up. Patients received 100 mq oral LV q 4 h for a total of 36 doses (6 days). At 4 h after the beginning of LV treatment, FUDR (0.1 mg/kg daily) was given by continuous infusion for 5 days. Interferon-α2b (Intron, 30×10^6 IU/m^2) therapy was begun simultaneously with the FUDR infusion and was given subcutaneously daily for six doses. Complete blood counts; platelet counts; electrolyte, blood urea nitrogen (BUN), and creatinine values; and liver-function tests were obtained prior to each treatment, on day 5, and at the follow-up examination carried out 2 weeks after the start of each treatment. Subsequent cycles were given at 28-day intervals. The FUDR dose was reduced by 50% for grade 3 or 4 mucositis and by 25% for neutropenic fever encountered during the previous cycle, Reevaluation was performed after two cycles of therapy. Patients with progressive disease were removed from the study; the administration of additional cycles of therapy to patients with responding or stable disease was left to the discretion of the attending physician. Toxicity was graded according to Cancer and Leukemia Group B (CALGB) consensus guidelines. To be evaluable for response, patients had to have completed at least two cycles of treatment unless therapy had to be discontinued due to progressive disease. All patients were analyzed for toxicity and survival.

Results

The characteristics of the 25 patients entered in the study from June to December of 1991 are shown in Table 1. Importantly, there was an adequate representation of patients with good prognostic indicators for survival [6]. The median performance status was 1 (symptomatic, but no activity limitations), 8 patients had only 1 site of metastatic disease (3 in the lung only), 8 had experienced a progression-free interval lasting more than 2 years, and 14 had undergone no prior treatment.

No objective response was observed among 20 evaluable patients (9 previously untreated, 11 previously treated; 95% confidence interval, 0–17%). The toxicity of this regimen is shown in Table 2. All patients developed a fever to greater than 38°C and four patients developed a fever exceeding 40°C. The leukopenia (median nadir, 2.7/μl) resolved as soon as interferon had been discontinued and was not associated with clinical signs of infection. Anemia was mild and no significant thrombocytopenia was noted. The elevations in transaminases were also transient, resolving by the time of the follow-up clinic visit on day 14.

Table 3. Reasons for stopping treatment

Progressive disease	13
Death	3
Patient's refusal	5
Physician's refusal	4

Median number of cycles, 2; range, 1–6

Nausea and vomiting was considered to be severe in four patients. Mucositis, stomatitis, and diarrhea were the most serious common toxicities, but they usually resolved by the 3rd week and no cycles were delayed. Mild cases of hand-foot syndrome were observed in three patients. We also encountered several toxicities that have previously been attributed to high-dose interferon [8]. There were two episodes each of pancreatitis, mental confusion, and volume overload that was presumably cardiogenic in nature.

Three deaths also occurred during the study. The first occurred during internal fixation of a long bone pathologic fracture on day 10 of cycle one in a man who experienced a sudden intraoperative respiratory arrest that was presumably due to a fat embolism. The second patient died 4 weeks after undergoing his second cycle of therapy with ascites, renal failure, and fever. Although this death was presumably due to rapidly progressing bilateral renal cancers, we felt that it might have been therapy-related. The third death occurred suddenly in a 59-year-old man 2 days after the second cycle of therapy had been completed. The patient had known lung metastasis, coronary artery disease, and a depressed ejection fraction; thus, this death was also judged to have possibly been therapy-related.

The median number of cycles given was 2 (range, 1–6); therapy of 13 patients was discontinued because of progressive disease, 3 patients died, and 5 patients refused further therapy because of the toxicity they experienced. In 4 patients, additional therapy was discontinued after the second possibly therapy-related death had been reported (Table 3). At a median follow-up period of 5 months, median survival has not yet been reached.

Discussion

Interferon given at a variety of doses and schedules consistently produces a 10%–15% response rate in metastatic renal cancer [1, 19, 21]. Recent reexamination of single-agent 5-FU and FUDR has shown response rates of 10%–30% [3, 4, 9, 10, 12, 20, 22, 28]. The biochemical interaction of LV, interferon, and 5-FU or FUDR led us to initiate this protocol. In two previous studies using interferon and 5-FU or FUDR in patients with metastatic renal cancer, a response rate of 30% was reported [5, 23], although this was not confirmed in a third trial [17].

We also failed to replicate these high response rates using fluoropyrimidine-based therapy. Patient selection may have biased the previous trials or our own study. The dose of interferon used in the present investigation was significantly higher than that tested in the previous studies. It is unlikely that this would adversely affect the antitumor activity of the interferon itself [18]. In phase I studies using a small series of patients, it has been reported that low-dose interferon is more effective than high-dose interferon in modulating the response to 5-FU [27]. This finding, however, has not been confirmed in carefully designed phase II or III studies. The pharmacokinetic modulation of 5-FU by LV has also been reported to be abrogated by interferon in one study [2]. We could not replicate these findings using our pharmacokinetic data from the phase I study performed prior to the current investigation (Vokes et al., manuscript in preparation). Moreover in some of the previous studies, FUDR was given in a circadian-timed manner, but it is not known whether this is important in obtaining responses. The severe side effects experienced by our patients demonstrate that the maximal dose intensity was used. Thus, we must conclude that despite the multiple interactions as well as the previous promising reports, the combination of FUDR, LV, and high-dose interferon-alpha used in the present trial is associated with significant toxicity and is inactive against metastatic renal-cell carcinoma.

References

1. Creagan ET, Twito DI, Johansson SL, et al (1991) A randomized prospective assessment of recombinant leukocyte interferon with and without aspirin in advanced renal adenocarcinoma. J Clin Oncol 9: 2104
2. Czejka M, Jager W, Schuller J, et al (1991) Pharmacokinetic aspects of the combination of interferon-alpha-2b and folic acid with fluorouracil. Arzneimittelforschung 41: 860
3. Damascelli B, Marchiano A, Spreafico C, et al (1990) Circadian continuous chemotherapy of renal cell carcinoma with an implantable, programmable infusion pump. Cancer 66: 237
4. Dexeus FH, Logothetis CJ, Sella A, et al (1991) Circadian infusion of floxuridine in patients with metastatic renal cell carcinoma. J Urol 146: 709
5. Dimopoulos MA, Dexeus FH, Jones E, et al (1991) Evidence for additive anti-tumor activity and toxicity for the combination of FUDR and interferon alpha-2b in patients with metastatic renal cell carcinoma (abstract). Proc Assoc Cancer Res 32: 1112
6. Elson PJ, Witte RS, Trump DL (1988) Prognostic factors for survival in patients with recurrent or metastatic renal cell carcinoma. Cancer Res 48: 7310
7. Erlichman C, Fine S, Wong A, Elhakin T (1988) A randomized trial of fluorouracil and folic acid in patients with metastatic colorectal carcinoma. J Clin Oncol 6: 469
8. Foon KA, Roth MS, Bunn PA (1987) Interferon therapy of non-Hodgkin's lymphoma. Cancer 59 [Suppl 3]: 601
9. Geoffrois L, Conroy T, Hubert J, et al (1991) Circadian modified FUDR infusion in patients with metastatic renal cell cancer (abstract). Proc Am Soc Clin Oncol 10: 595
10. Hrushesky WJ, Roemeling R von, Lanning RM, Rabatin JT (1990) Circadian-shaped infusions of floxuridine for progressive metastatic renal cell carcinoma. J Clin Oncol 8: 1504
11. Kemeny N, Younes A, Seiter K, et al (1990) Interferon alpha-2a and 5-fluorouracil for advanced colorectal carcinoma. Assessment of activity and toxicity. Cancer 66: 2470
12. Kish JA, Neefe JR, Flanigan R (1991) Efficacy of low dose continuous infusion 5-fluorouracil in recurrent/metastatic renal cell carcinoma. A Southwest Oncolgy Group study (abstract). Proc Am Assoc Cancer Res 32: 1107
13. Lockshin A, Danenberg PV (1980) Biochemical factors affecting the tightness of 5-fluorodeoxyuridylate binding of human thymidylate synthetase. Biochem Pharmacol 30: 247

14. Machover D, Goldschmidt E, Chollet P (1986) Treatment of advanced colorectal and gastric adenocarcinomas with 5-fluorouracil and high-dose folinic acid. J Clin Oncol 4: 685
15. Madajewicz S, Petrelli N, Rustum YM, et al (1984) Phase I–II trial of high-dose calcium leucovorin and 5-fluorouracil in advanced colorectal cancer. Cancer Res 44: 4667
16. Meadows LM, Walther P, Ozer H (1991) Alpha-interferon and 5-fluorouracil: possible mechanisms of anti-tumor action. Semin Oncol 18 [Suppl 7]: 71
17. Murphy B, Rynard S, Einhorn L, Loehrer PJ (1991) A phase II trial of interferon alpha-2A plus 5-fluorouracil in advanced renal cell carcinoma: a Hoosier Oncology Group study (abstract). Am Fed Clin Res 39: 747A
18. Muss HB (1991) Interferons – clinical applications – renal cell carcinoma. In: Devita VT, Hellman S, Rosenberg SA (eds) Biologic therapy of cancer. J. B. Lippencott, Philadelphia, p 298
19. Quesada JR, Rios A, Swanson D, et al (1985) Antitumor activity of recombinant-derived interferon alpha in metastatic renal cell carcinoma. J Clin Oncol 3: 1522
20. Richards F II, Cooper MR, Jackson DV, et al (1991) Continuous 5-day intravenous FUDR infusion for renal cell carcinoma. A phase I–II trial of the Piedmont Oncology Association (abstract). Proc Am Soc Clin Oncol 9: 545
21. Sarna G, Figlin R, De Kernion JB (1987) Interferon in renal cell carcinoma: the UCLA experience. Cancer 59: 610
22. Schulof F, Lokich J, Wampler G, et al (1991) Phase II trial of protracted infusional 5-FU for metastatic renal cell carcinoma (abstract). Proc Am Soc Clin Oncol 9: 544
23. Sella A, Logothetis DJ, Fitz K, et al (1992) Phase II study of interferon-α and chemotherapy (5-fluorouracil and mitomycin C) in metastatic renal cell cancer. J Urol 147: 572
24. Vokes EE, Raschko J, Vogelzang NJ, et al (1991) Five day infusional fluorodeoxyuridine (FUDR) with oral leucovorin (LV): a phase I study. Cancer Chemother Pharmacol 28: 69
25. Vokes EE, Ratain MJ, O'Brien S, et al (1991) Five day infusional fluorodeoxyuridine with oral leucovorin and escalating doses of interferon alpha-2b: a clinical and pharmacokinetic study (abstract). Proc Am Assoc Cancer Res 32: 177
26. Wadler S, Wiernik PH (1990) Clinical update on the role of fluorouracil and recombinant interferon alpha-2a in the treatment of colorectal carcinoma. Semin Oncol 1 [Supp 1]: 16
27. Wadler S, Goldman M, Lyver A, Wierick PH (1990) Phase I trial of 5-fluorouracil and recombinant α2a-interferon in patients with advanced colorectal carcinoma. Cancer Res 50: 2056
28. Wilkinson M, Stagg R, Grobman B, et al (1990) A phase II study of constant rate FUDR infusion in patients with metastatic renal cell cancer (abstract). Proc Am Soc Clin Oncol 9: 538