A Phase II Trial of Interferon-α and 5-Fluorouracil in Patients with Advanced Renal Cell Carcinoma

A Southwest Oncology Group Study

Laurence Elias, M.D.[1]
Brent A. Blumenstein, Ph.D.[2]
Julie Kish, M.D.[3]
Robert C. Flanigan, M.D.[4]
James L. Wade, M.D.[5]
Bruce A. Lowe, M.D.[6]
John Wendall Goodwin, M.D.[7]
E. David Crawford, M.D.[8]

[1] Cancer Research and Treatment Center, University of New Mexico, Albuquerque, New Mexico.

[2] Southwest Oncology Group Statistical Office, Fred Hutchinson Cancer Research Center, Seattle, Washington.

[3] Division of Hematology/Oncology, Henry Ford Hospital, Detroit, Michigan.

[4] Department of Urology, Loyola University Medical Center, Maywood, Illinois.

[5] Central Illinois CCOP, Springfield, Illinois.

[6] Department of Surgery, Division of Urology, Oregon Health Science Center, Portland, Oregon.

[7] Ozarks Regional CCOP, Springfield, Missouri.

[8] Department of Surgery, Division of Urology, University of Colorado Health Science Center, Denver, Colorado.

Supported in part by the following PHS Cooperative Agreement grant numbers awarded by the National Cancer Institute, DHHS: CA38926, CA32102, CA45807, CA46113, CA45560, CA04920, CA37981, CA35261, CA27057, CA12213, CA20319, CA45377, CA46441, CA32734, CA46136, CA46282, CA16385, and CA35431.

Address for reprints: Southwest Oncology Group (SWOG-9122), Operations Office, 14980 Omicron Drive, San Antonio, TX 78245-3217.

Received February 22, 1996; revision received May 23, 1996; accepted May 23, 1996.

BACKGROUND. Renal cell carcinoma is a common neoplasm that is often refractory to treatment. It is occasionally responsive to immunomodulating agents including interferon-α, which enhances the effects of 5-fluorouracil upon cells. Combinations of these two drugs have been most frequently tested in patients with gastrointestinal cancers, with some promising results. Because interferon-α has activity for renal cell carcinoma, a trial of this combination in patients with this malignancy was undertaken.

METHODS. The Southwest Oncology Group performed a Phase II clinical trial of the combination of 5-fluorouracil and interferon-α for recurrent or metastatic renal cell carcinoma. Eligibility criteria included no prior treatment with medications for cancer, a performance status of 2 or better, and bidimensionally measurable disease. The regimen studied consisted of 5-fluorouracil, 750 mg/M^2/day, by continuous intravenous infusion on Days 1–5, and interferon-α-2b (Intron A), 5 $\times$ 10^{6}U/M^2/day, subcutaneously on Days 1, 3, and 5, repeated every 21 days.

RESULTS. Forty eligible patients were treated; twenty of the 40 underwent a nephrectomy. The regimen was tolerable: 3 patients had Grade 4, and 17 had Grade 3 toxicity. There were 5 partial responses (13% with 95% confidence limits of 4–27%). Median progression free survival for all 40 patients was 4 months and median overall survival was 15 months from the time of registration.

CONCLUSIONS. The combination of 5-fluorouracil and interferon-α given by this schedule, although tolerable and occasionally yielding responses, is not an improvement over existing therapies. ***Cancer* 1996; 78:1085–8.**

KEYWORDS: interferon-α, 5-fluorouracil, renal cell carcinoma, human, cancer clinical trial.

Renal cell carcinoma (RCC) is a relatively common form of cancer that continues to present a major challenge.[1] Its natural history is characterized by a high rate of primary unresectability, and synchronous or subsequent metastases that are relatively refractory to chemotherapy. Although there is substantial evidence of RCC susceptibility to immune system modulation, it has not yet been possible to develop strategies that are helpful to a majority of patients.

In recent years, a large body of in vitro evidence has been presented indicating significant synergistic effects of interferon-α and 5-fluorouracil.[2] The mechanism of interaction has been analyzed, with most investigations pointing toward thymidylate synthetase inhibition[3–6] as the prime locus, although alternative mechanisms have been implicated in other studies.[7–9] Several Phase II clinical trials based upon these results in patients with colon and other gastro-

intestinal carcinomas suggested significant activity of this synergistic combination.[2,10–13] However, enthusiasm for this approach has waned, based upon results of larger, multicenter randomized trials[14,15] that failed to substantiate significantly augmented antitumor activity.

The elusiveness of a regimen of proven clinical value despite continued confirmation of this drug combination's biologic interactions indicated that alternative directions should be explored. Basic and clinical studies have suggested that scheduling of the two drugs may be critical.[3,16–18] There has been interest in testing this approach in RCC because of its modest level of responsiveness to interferon-α alone, and intriguing preliminary results of combination therapy.[19] In this trial, we tested a regimen that was comprised of 5-day 5-fluorouracil intravenous (i.v.) infusions, in combination with interferon-α subcutaneously on Days 1, 3, and 5, repeated every 21 days in patients with metastatic or recurrent RCC not previously treated with chemotherapy.

MATERIALS AND METHODS

Eligibility criteria included histologically proven RCC, either metastatic or recurrent, with bidimensionally measurable disease, and no pericardial effusions, massive ascites, or brain metastases. Patients must have had an Eastern Cooperative Oncology Group performance status of 2 or better, and not received prior chemotherapy or biologic regimens. Patients also had to meet standard criteria for acceptable levels of hematologic, renal, and hepatic organ function. Informed consent was obtained from all patients.

Treatment was comprised of 5-fluorouracil, 750 mg/M^2/day, by continuous i.v. infusion on Days 1 through 5, and interferon-α-2b (Intron A; Schering Corporation, Kenilsworth, NJ), 5 $\times$ 10^{6}U/M^2/day, by subcutaneous injection on Days 1, 3, and 5, with cycles repeated every 21 days. Dosages were adjusted for SWOG Grade 3 or 4 toxicities, with stomatitis, diarrhea, or palmar-plantar erythrodysesthesia specifically leading to 5-fluorouracil adjustments, and systemic symptoms resulting in interferon adjustments. Discontinuation of therapy was required for disease progression or unacceptable toxicity.

X-rays and scans necessary for the evaluation of tumor response were required every 6 weeks. Scoring a patient as attaining complete response required complete disappearance of all evidence of disease at two consecutive evaluations. A partial response score required a 50% or greater decrease of the sum of the products of the perpendicular diameters of all measurable lesions at two consecutive evaluations, and no progression of evaluable (nonmeasurable) lesions.

TABLE 1
Toxicities

	Alpha-IFN and 5-FU (n = 40)					
	Grade					
Toxicity	0	1	2	3	4	5
Alopecia	34	6	0	0	0	0
Anemia	26	0	9	4	1	0
Anorexia	23	17	0	0	0	0
Anxiety/depression	27	11	2	0	0	0
Chills	14	14	12	0	0	0
Constipation	36	3	1	0	0	0
Cough	31	8	1	0	0	0
Desquamation	37	2	0	1	0	0
Diarrhea	26	10	2	2	0	0
Dyspnea	32	0	8	0	0	0
Erythema	35	3	2	0	0	0
Fever without infection	12	9	17	2	0	0
GI (other)	38	0	1	1	0	0
Gastritis/ulcer	39	0	0	0	1	0
Granulocytopenia	33	3	2	1	1	0
Headache	27	9	3	1	0	0
Hypertension	35	4	0	1	0	0
Leukopenia	29	8	3	1	0	0
Malaise/fatigue/lethargy	10	15	13	2	0	0
Myalgia/arthralgia	29	9	1	1	0	0
Nausea	11	19	6	4	0	0
Numbness/other PNS	35	0	5	0	0	0
Pain	30	7	3	0	0	0
Pharynx/esophagitis	27	7	4	2	0	0
Pulmonary edema	39	0	0	1	0	0
Skin rash/urticaria	34	4	2	0	0	0
Stomatitis	16	12	9	3	0	0
Thrombocytopenia	38	1	0	1	0	0
Vision	39	0	0	1	0	0
Vomiting	22	10	6	2	0	0
Weight loss	36	2	2	0	0	0
Maximum grade any toxicity						
Number	1	4	15	17	3	0

IFN: interferon; 5-FU: 5-fluorouracil; GI: gastrointestinal; PNS: parasympathetic nervous system.
Only toxicities affecting 10% or more of patients or at Grade 3 or higher level are listed.

RESULTS

A total of 40 patients were registered to this study, all of whom were subsequently confirmed to be eligible. The median age was 56 years (range, 36–82 years), and there were 26 men and 14 women. The study group included 20 patients with prior nephrectomy, and all but 5 had a performance status of 0 or 1. All patients were evaluable for toxicity (Table 1). Three patients had Grade 4 toxicity: granulocytopenia, gastritis/ulcer (treatment discontinued due to toxicity), and anemia (further treatment refused). Seventeen of the 40 patients had Grade 3 toxicities as their worst grade, notably anemia (4 patients), and 1 patient each with proctitis (gastrointestinal-other) and desquamation.

TABLE 2
Characteristics of Responders

Age	Sex	PS	Prior nephrectomy	Metastatic sites	Fully confirmed	Duration response (mos)
62	M	1	Yes	Lung, bone, chest wall	Yes	2.5
78	F	1	Yes	Lung, lymph nodes	Yes	8
45	M	2	Yes	Bone, lymph nodes, pericardium	No	7.5
61	F	1	No	Kidney, lung, bone	No	13.5
71	F	0	No	Kidney, lymph nodes	Yes	8

M: male; F: female; PS: performance status.

Grade 1 and 2 toxicities were most commonly associated with known interferon systemic effects. Some mild episodes of nausea, vomiting, anorexia, and stomatitis also occurred.

Response was not assessable for six patients due to patient refusal prior to first planned assessment or failure to submit data; these patients are assumed to have not had a response. There were 5 partial responses (13%; 95% confidence interval, 4–27%), 2 of which were not fully documented. Both patients considered to have incompletely documented responses met partial response criteria of measurable disease, but had abnormal initial bone scans that were not repeated at the time response was scored. Neither patient had bone pain when the measurable disease response was recorded or when removed from protocol. One patient's bone abnormality was in a single rib ipsilateral to a thoracotomy site. One of these patients also initially had a 2 cm × 2.5 cm retrotracheal lymph node on chest computed tomography scan that was not seen on the first follow-up scan but measured 1 cm × 1 cm or less on 3 subsequent scans. A second mass on the scan regressed from 5 cm × 4 cm before the study to 2.5 cm × 2.5 cm on the third scan to undetectable on the fourth scan. Table 2 provides detailed information on the responding patients. Responses occurred both among patients with (three patients) and without (two patients) prior nephrectomies. Median progression free survival of all 40 patients was 4 months (95% confidence interval, 3–6 months), and median overall survival was 15 months (95% confidence interval, 9–18 months) from time of registration.

DISCUSSION

The combination of 5-fluorouracil and interferon-α was herein studied using a moderately intensive but intermittent schedule, with 5-fluorouracil given by continuous infusion over 5 days, and interferon-α given 3 times during the infusion, repeated every 3 weeks. The response rate observed was modest, and not a clear improvement compared with interferon-α alone. Most trials of interferon-α monotherapy have employed more intensive and continuous dosing, so it is conceivable that both drugs employed here contributed to those responses that were observed. Other studies of this combination in RCC have been performed utilizing various schedules, modes of administration, and dosages. These studies have reported slightly better response rates of 23%[20] and 24%.[21] However, another trial by Murphy et al. utilized a dose and schedule similar to that of Wadler et al.,[10] and reported no responses among 14 patients.[22] Although dosage and scheduling are probably important, and might be further optimized, combining these drugs with other third agents now seems to be a more promising avenue for future development in RCC. Sella et al. reported a 33% response rate to a combination of mitomycin C, 5-fluorouracil, and interferon-α.[19] More recently, Atzpodien et al. reported a 48.6% response rate to a combination of interleukin-2 interferon-α, and 5-fluorouracil.[23] A similar response rate of 47% was reported by Sella et al.,[24] using the same drugs with different scheduling and dosages. Efforts are underway by the Southwest Oncology Group to explore and confirm these newer directions.

REFERENCES

1. Yarbro JW, Bornstein RS, Mastrangelo MJ, editors. Renal cell carcinoma. *Semin Oncol* 1995;22:1–94.
2. Wadler S, Schwartz EL. Biologic agents as biochemical modulators: pharmacologic basis for the interaction of cytotoxic chemotherapeutic drugs and interferon. *Cancer Chemother Pharmacol* 1994;35:21–30.
3. Elias L, Crissman HA. Interferon effects upon adenocarcinoma 38 and HL-60 cell lines: antiproliferative responses and synergistic interactions with halogenated pyrimidine antimetabolites. *Cancer Res* 1988;48:4868–73.
4. Elias L, Sandoval JM. Interferon effects upon fluorouracil metabolism by HL-60 cells. *Biochem Biophys Res Commun* 1989;163:867–74.
5. Schwartz EL, Hoffman M, O'Connor CJ, Wadler S. Stimulation of 5-fluorouracil metabolic activation by interferon-α in human colon carcinoma cells. *Biochem Biophys Res Commun* 1992;182:1232–9.

6. Chu E, Koeller DM, Johnston PG, Zinn S, Allegra CJ. Regulation of thymidylate synthase in human colon cancer cells treated with 5-fluorouracil and interferon-γ. *Mol Pharmacol* 1993;43:527–33.
7. Grem JL, McAtee N, Murphy RF, Balis FM, Steinberg SM, Hamilton JM, et al. A pilot study of interferon alpha-2a in combination with fluorouracil plus high-dose leucovorin in metastatic gastrointestinal carcinoma. *J Clin Oncol* 1991; 9:1811–20.
8. Houghton JA, Morton CL, Adkins DA, Rahman A. Locus of interaction among 5-fluorouracil, leucovorin and interferon-α2a in colon carcinoma cells. *Cancer Res* 1993;53:4243–50.
9. Reiter Z, Ozes OM, Blatt LM, Taylor MW. A dual anti-tumor effect of a combination of interferon-α or interleukin-2 and 5-fluorouracil on natural killer cell-mediated cytotoxicity. *Clin Immunol Immunopathol* 1992;62:103–11.
10. Wadler S, Schwartz EL, Goldman M, Lyver A, Rader M, Zimmerman M, et al. Fluorouracil and recombinant alpha-2a-interferon: an active regimen against advanced colorectal carcinoma. *J Clin Oncol* 1989;7:1769–75.
11. Wadler S, Wiernik PH. Clinical update on the role of fluorouracil and recombinant interferon alpha-2a in the treatment of colorectal carcinoma. *Semin Oncol* 1990;17:16–21.
12. Wadler S, Lembersky B, Atkins M, Kirkwood J, Petrelli N. Phase II trial of fluorouracil and recombinant interferon alpha-2a in patients with advanced colorectal carcinoma: an Eastern Cooperative Oncology Group study. *J Clin Oncol* 1991;9:1806–10.
13. Wadler S, Fell S, Haynes H, Katz HJ, Rozenblit A, Kaleya R, et al. Treatment of carcinoma of the esophagus with 5-fluorouracil and recombinant alpha-2a-interferon. *Cancer* 1993;71:1726–30.
14. Kocha W. 5-Fluorouracil (5FU) plus interferon alfa-2a (Roferon-A) versus 5-fluorouracil plus leucovorin (LV) in metastatic colorectal cancer—results of a multicentre multinational phase III study. *Proc Am Soc Clin Oncol* 1993;12:193.
15. York M, Greco FA, Figlin RA, Einhorn L, Man T, Cockey L, et al. A randomized phase III trial comparing 5-FU with or without interferon alfa 2a for advanced colorectal cancer. *Proc Am Soc Clin Oncol* 1993;12:200.
16. Cascinu S, Del Farro E, Fedeli A, Grianti C, Foglietti G, Olivieri Q, et al. Cytokinetic effects of interferon in colorectal cancer tumors: implications in the design of the interferon/5-fluorouracil combinations. *Cancer Res* 1993;53:5429–32.
17. Ragnhammar P, Blomgren H, Edler D, Lundell G, Magnusson I, Sonnenfeld T. Different dose regimens of 5-fluorouracil and interferon-α in patients with metastatic colorectal carcinoma. *Eur J Cancer* 1995;31A:315–20.
18. Greenblatt MS, Mangalik A, Ferguson J, Elias L. Phase I evaluation of therapy with four schedules of 5-fluorouracil by continuous infusion combined with recombinant interferon α. *Clin Cancer Res* 1995;1:615–20.
19. Sella A, Logothetis C, Dexeus F, Amato R, Kolbourn R, Fitz K, et al. Increased response rate with the combination of chemotherapy 5-fluorouracil (T-FU) and mitomycin-C (MMC) with interferon (Roferon) in patients with metastatic renal cell carcinoma. *Amer Soc Clin Oncol* 1990;9:146.
20. Haarstad H, Jacobsen AB, Schjlseth SA, Risberg T, Fossa SD. Interferon-alpha, 5-FU and prednisone in metastatic renal cell carcinoma: a phase II study. *Ann Oncol* 1994;5:245–8.
21. Schuth J, Goldschmidt AJ, Tunn UW. Response in patients with metastatic renal cell carcinoma (RCC) during the treatment with alpha interferon in combination with 5-fluorouracil. In: Biologic Response Modifiers, 2nd International Congress, San Diego, California, Jan 29–31, 1993:49.
22. Murphy BR, Rynard SM, Einhorn LH, Loehrer PJ. A phase II trial of interferon alpha-2A plus fluorouracil in advanced renal cell carcinoma. A Hoosier Oncology Group Study. *Invest New Drugs* 1992;10:225–30.
23. Atzpodien J, Kirchner H, Hanninen EL, Deckert M, Fenner M, Poliwoda H. Interleukin-2 in combination with interferon-alpha and 5-fluorouracil for metastatic renal cell cancer. *Eur J Cancer* 1993;29A(Suppl 5):S6–8.
24. Sella A, Zukiwski A, Robinson E, Kilbourn R, Ellerhorst J, Amato R, et al. Interleukin-2 (IL-2) with interferon-alpha (IFN-alpha) and 5-fluorouracil (5-FU) in patients (pts) with metastatic renal cell cancer (RCC). *Proc Annu Meet Am Soc Clin Oncol* 1994;13:A733.