Phase II Clinical Trial with 5-Fluorouracil, Recombinant Interferon-α-2b, and Cisplatin for Patients with Metastatic or Regionally Advanced Carcinoma of the Esophagus

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BACKGROUND. Recombinant interferon-α (IFN) augments the cytotoxicity of both 5-fluorouracil (5-FU) and cisplatin in vitro. A Phase II study of 5-FU and IFN resulted in response rates of 25–27% in patients with metastatic esophageal carcinoma.

METHODS. A Phase II trial was initiated to determine the clinical utility of a three-drug combination (FIP) in patients with regionally advanced or metastatic esophageal carcinoma. Eligibility included biopsy-proven Stage III or IV squamous cell carcinoma or adenocarcinoma of the esophagus with no prior chemotherapy, adequate performance status, nutritional status, bone marrow, hepatic and renal function, and signed informed consent. Patients were treated in the exact sequence of IFN ⇒ cisplatin ⇒ 5-FU. Patients received 5-FU, 750 mg/m^2/day for 5 days followed by weekly bolus therapy at the same dose; cisplatin, 100 mg/m^2 on Day 1, followed by weekly therapy, 25 mg/m^2 over the course of 1 hour; and IFN, 10 MU subcutaneously 3 times/week beginning on Day 1. All patients received sargramostim (granulocyte-macrophage colony-stimulating factor, *Escherichia coli*-derived), 5 μg/kg subcutaneously 5 times/week. No patients received radiotherapy.

RESULTS. Twenty-four patients were enrolled; 23 were eligible, and 1 was excluded on pathology review (patient was found to have a leiomyoblastoma). The demographics of the population were: median age, 63 years (range, 43–73 years); 18 male patients; squamous cell carcinoma: adenocarcinoma ratio, 22:1; and Stage III:IV ratio, 10:13. Grade 3–4 National Cancer Institute Common Toxicity Criteria toxicities included: leukopenia (13), thrombocytopenia (14), and infection (9). Grade 3 diarrhea, mucositis, and vomiting occurred in 6 patients, 4 patients, and 1 patient, respectively. There were two instances of sudden death, likely related to tumor progression. Major responses occurred in 15 of 23 patients (65%; 95% confidence interval, 43%, 85%) (1 complete response, 14 partial responses). The median survival was 8.6 months; with a median follow-up of 26 months, estimated 30-month survival was 31%.

CONCLUSIONS. This regimen, although moderately toxic, has substantial activity in metastatic and regionally advanced squamous cell carcinoma of the esophagus. Further investigations should be conducted to determine the role of IFN in the treatment of esophageal carcinoma. ***Cancer* 1996; 78:30–4.**
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Once beyond the scope of surgical excision, carcinoma of the esophagus has a poor prognosis, with only approximately 5% of patients

surviving disease free for 5 years. The primary explanation for this is that the vast majority of patients already have metastatic spread of their disease regionally or distantly at the time of diagnosis. This accounts for the high failure rate for surgery[1] and radiation therapy,[2] and reinforces the importance of chemotherapy as a therapeutic modality in the treatment of these patients.

The fluorinated pyrimidine, 5-fluorouracil (5-FU), has only modest single agent activity in the treatment of advanced esophageal cancer;[3] however, two Phase II clinical trials have demonstrated nearly doubling of objective response rates when 5-FU was employed in combination with the biologic response modifier, recombinant interferon-α (IFN).[4,5] Cisplatin is probably the most active single agent in the treatment of carcinoma of the esophagus,[6] and in preclinical tumor model systems has been shown to act synergistically with interferon;[7] thus, it is reasonable to combine 5-FU, IFN, and cisplatin in a therapeutic regimen for the treatment of these patients. To better define the response rates and toxicities of this regimen, a Phase II trial was initiated in patients with advanced and regionally advanced carcinoma of the esophagus.

TABLE 1
Demographic Characteristics

	No. of patients
Entered	24
Evaluable	23[a]
Male/female	18:5
Age (yrs)	
Median	63
Range	43–73
Performance status 0:1	7:16
Squamous cell carcinoma:adenocarcinoma	22:1
Stage	
III	10
IV	13
Location	
Upper thoracic	3
Midthoracic	14
Lower thoracic	5
Distal esophagus	1
Prior chemotherapy	0
Prior radiation therapy	0
Prior surgery	1

[a] One patient was found to have a leiomyoblastoma at a retrospective pathology review.

PATIENTS AND METHODS

Study Design

This was a prospective, single institution, Phase II clinical trial. The aims of the study were to determine the objective response rates, toxicities, and survival of patients with metastatic or regionally advanced carcinoma of the esophagus treated with 5-FU, IFN-α-2b (IFN-α-2b), and cisplatin. This trial was initiated in 1992, after approval by the Institutional Review Board of the Montefiore Medical Center, Bronx, New York.

Eligibility

Patients were required to have histologically confirmed squamous cell carcinoma or adenocarcinoma of the esophagus. Patients with lesions of the gastroesophageal junction were ineligible. Patients were required to have metastatic disease or regionally advanced disease deemed incurable with surgery, radiation therapy, or combined modality therapy.[8] Lesions were required to be measurable in two dimensions. All patients were fully ambulatory (Eastern Cooperative Oncology Group [ECOG] performance status 0 or 1), had no prior chemotherapy or radiation therapy, had adequate bone marrow function (defined as a leukocyte count of >4000 cells/mm^3 and platelet count of >100,000 cells/mm^3; liver function (defined as a total bilirubin of <1.5 mg/dL, serum aspartate transaminase < 3 times the upper limit of normal, and serum alkaline phosphatase < 3 times the upper limit of normal), and normal renal function (defined as a serum creatinine < 2.0 mg/dL), and no uncontrolled comorbid disease. Patients were precluded from having inadequate coloric intake (<1500 kcal/day), a recent surgical procedure, or clinical evidence of brain metastases. All patients gave informed written consent, which met all local, state, and federal guidelines.

Treatment Plan

IFN and sargramostim (*Escherichia coli*-derived granulocyte-macrophage colony-stimulating factor) were supplied by the Schering Corporation (Kenilworth, NJ). 5-FU and cisplatin were obtained commercially. The sequence of drug administration was always IFN-⇒cisplatin⇒5-FU, with cisplatin administered immediately after IFN. 5-FU was administered intravenously at 750 mg/m^2 daily for 5 days beginning on Day 1, then at 750 mg/m^2 every week, beginning on Day 15. Cisplatin was administered intravenously at 100 mg/m^2 over the course of 2 hours on Day 1, then at 25 mg/m^2 over the course of 1 hour each week immediately before the 5-FU bolus, beginning on Day 15. IFN was administered at 10 MU subcutaneously each week on Day 1, immediately before the cisplatin, then on Days 3 and 5. Sargramostim was administered at 5 μg/kg subcutaneously on Days 7–13, then on Days 2–5 each week beginning the day after administration of chemotherapy.

Standard National Cancer Institute Common Tox-

TABLE 2
Toxicities

	NCI CTC Grade[a]				
	0	1	2	3	4
Leukopenia	2	4	5	10	3
Granulocytopenia[a]	13	0	2	6	2
Thrombocytopenia	3	2	5	9	5
Anemia	2	0	10	11	1
Infection	7	1	7	8	1
Fever	3	1	19	1	0
Fatigue[a]	5	3	7	8	0
Diarrhea	6	6	6	6	0
Vomiting	3	8	12	1	0
Mucositis	7	7	6	4	0
Neurologic	6	6	5	6	1
Dermatologic	18	2	4	0	0
Renal	11	5	7	1	0
Hepatic	5	6	5	6	2
Alopecia	15	9	0	—	—

NCI CTC: National Cancer Institute Common Toxicity Criteria.
[a] According to National Cancer Institute Common Toxicity Criteria.

TABLE 3
Response to Therapy

	n = 24
Complete response	1
Partial response	14
Stable disease	4
Progressive disease	4
Not evaluable	1

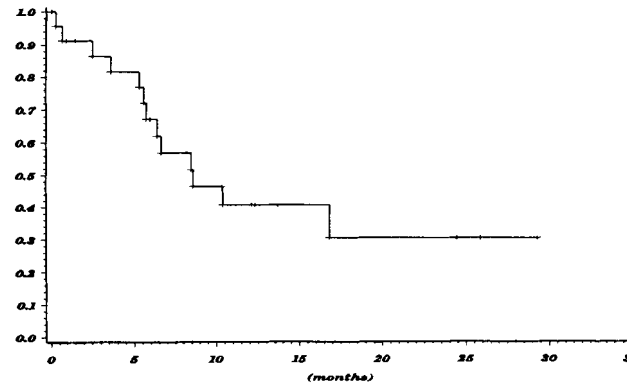

FIGURE 1. Survival of patients treated with 5-fluorouracil, interferon-α and cisplatin. The median survival was 8.6 months.

icity Criteria were employed to assess toxicities.[9] The dose of IFN was reduced by 50% for Grade 3 neurotoxicity or for a 2-level decrease in performance status. The dose of 5-FU was held and then reduced by 25% for Grade 2–3 stomatitis, Grade 3 diarrhea, or Grade 3 myelosuppression. Cisplatin was held for a rise in serum creatinine to >2 mg/dL. Patients were removed from study for Grade 4 nonhematologic toxicity, progressive disease, suspension of treatment for >4 weeks, or patient preference.

Prior to initiation of therapy, all patients were evaluated by physical examination, computed tomography scan of the chest and abdomen, esophagogastroscopy, and upper gastrointestinal series. Standard ECOG response criteria[10] were employed to assess response to therapy. Response to therapy was the primary study endpoint. A 2-stage trial design was employed to assess the true response rate of this regimen with the planned initial accrual of 14 patients, then enrollment of up to 16 additional patients if ≥1 response was observed among the first 14.[11]

RESULTS

Demographic Characteristics

As shown in Table 1, 24 patients were enrolled in this trial. One patient was ineligible; at a retrospective pathology review, he was found to have a leiomyoblastoma. All other patients, with the exception of a single patient with adenocarcinoma, had squamous cell carcinoma. No patients had tumors of the gastroesophageal junction, and no patients had received prior chemotherapy or radiation therapy.

Toxicities

As shown in Table 2, the predominant toxicities were hematologic. Unlike our comparable experience with 5-FU plus IFN in the absence of cisplatin, thrombocytopenia was the most significant toxicity resulting in delay in treatment and dose reduction with this regimen. Fatigue resulted in dose reduction in the IFN dose in nearly every patient. Neurologic toxicities included dizziness (five patients), gait disturbance (five patients), hearing loss (one patient), and hallucinations (one patient). There were two instances of sudden death, likely related to disease progression involving the heart and great vessels.

Response to Treatment

As shown in Table 3, 15 of 23 patients (65%; 95% confidence interval, 43%, 85%) achieved a major response (1 complete response, 14 partial responses) to treatment. This included 4 of 10 patients with Stage III disease and 11 of 13 patients with Stage IV disease. The median response duration was 2+ months. With a median follow-up of 26 months, the median survival for all patients was 8.6 months (Fig. 1), with 40% of

patients surviving at 1 year and 30% surviving at 2 years.

DISCUSSION

The high response rates observed and the favorable survival for this group of patients confirms the activity previously observed among a smaller group of patients with epidermoid carcinoma.[12] In that trial, 27 of 37 assessable patients had tumors of the distal esophagus, whereas in our trial, only 1 of 23 patients had a distal tumor. In both trials, the majority of patients had distant metastases (30 of 40 and 13 of 23, respectively) as opposed to locoregional disease. Furthermore, the survival among patients with epidermoid carcinoma in the prior trial, 45 weeks,[12] was similar to that observed for patients with epidermoid carcinoma in our trial. Thus, this is likely to be a highly active regimen in patients with epidermoid carcinomas.

Most of the regimens designed for the treatment of advanced esophageal carcinoma have employed combination chemotherapy. Biochemical modulation has not heretofore been an important therapeutic strategy. Thus, it is of interest that a regimen based on modulation of the fluoropyrimidine by interferon should be active. Recently, the mechanism by which IFN interacts with 5-FU has been carefully delineated in in vitro tumor models. Specifically, IFN augmented the cytotoxicity of 5-FU[13] in human colon cancer cell lines, and this was associated with induction of thymidine phosphorylase, the rate-limiting enzyme in the anabolism of 5-FU to its active anabolite,[14–16] and this in turn was associated with an increase in DNA double strand breaks.[17] Induction of thymidine phosphorylase by IFN has recently been documented in vivo as well.[18] Although IFN also augments the cytotoxicity of cisplatin in vitro, the mechanism by which this occurs has not been clearly defined.

Although these preliminary results are encouraging, a randomized trial will be required to confirm the utility of this regimen. It is of interest that in the ECOG trial employing single agent therapy,[3] whose study population was not strictly comparable to ours and which included only patients with metastatic disease, survival was nevertheless inferior to that observed in our trial, regardless of whether the patients were fully ambulatory (15 weeks), had not had prior radiation (20 weeks), or did not have visceral involvement (14 weeks). Furthermore, in that trial, regardless of whether patients received 5-FU, doxorubicin, or methotrexate, 95% of all patients had died by 36 weeks, whereas in our trial 55% of patients were still alive at 36 weeks. Only two combination chemotherapy regimens have been adequately studied in patients with advanced carcinoma of the esophagus. The combination of cisplatin, vindesine, and bleomycin has resulted in response rates > 50% in the neoadjuvant setting,[19] but is not extensively employed because vindesine remains an experimental agent. The combination of 5-FU and cisplatin has resulted in response rates of 30% in patients with metastatic disease, and 50–60% in patients with regionally advanced disease.[20] Whether the addition of IFN can augment the response rates and survival observed with the combination of 5-FU and cisplatin will require a randomized trial. Because of the substantial activity observed, this regimen warrants further examination.

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