Treatment of Carcinoma of the Esophagus with 5-Fluorouracil and Recombinant Alfa-2a-Interferon

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Background. **Combinations of 5-fluorouracil (5FU) and recombinant alfa-2a-interferon (IFN) are synergistic in vitro and have demonstrated activity in colorectal carcinoma, renal cell carcinoma, and urothelial tumors.**

Methods. **A Phase II trial of the combination of 5FU, 750 mg/m^2 daily × 5 followed by weekly bolus therapy, and IFN, 9 MU subcutaneously three times per week, was initiated in patients with esophageal carcinomas. Patients were required to have biopsy-proven squamous cell or adenocarcinoma of the esophagus, locally advanced or metastatic disease beyond the scope of surgical resection, and adequate performance status, renal, hepatic, and bone marrow function.**

Results. **Twenty-one patients were enrolled; one patient was inevaluable for response because he had received prior chemotherapy, but was evaluated for toxicity. Eleven patients had metastatic disease, and 10 had locally advanced disease. Thirteen patients had squamous cell carcinoma and 8 adenocarcinoma. Toxicities were acceptable with no serious diarrhea and only two cases of serious stomatitis, although a greater than expected incidence of neurologic toxicity was observed. There were five responders (25%) including two patients with advanced or locally advanced disease rendered pathologically free of disease. One patient, initially considered surgically unresectable, was able to undergo a total thoracic esophagectomy after responding to treatment with 5FU/IFN, at which time only a single microscopic focus of carcinoma in situ was found. She remains alive and free of disease at 18+ months. A second patient who presented with metastatic disease and nearly complete obstruction of the esophagus regained normal swallowing function after treatment with 5FU/IFN; rebiopsy of all lesions revealed the patient to be pathologically free of disease. He survived over 2 years.**

Conclusions. **This regimen employing a single cytotoxic agent has activity in esophageal carcinoma. Strategies employing biochemical modulation deserve additional investigation in the treatment of esophageal carcinoma. *Cancer* 1993; 71:1726–30.**

Key words: esophagus, 5-fluorouracil, interferon, biochemical modulation.

Carcinoma of the esophagus has a poor prognosis with only about 5% of patients surviving disease-free for 5 years.[1–5] This may be accounted for by the rich lymphatic drainage of this organ with unpredictable routes of spread, extensive local growth, and a strategic location contiguous to vital structures which complicate attempts at extirpative surgery.[6] Not only is survival compromised by this disease, but quality of life often suffers because of intractable obstructive symptoms, malnutrition, weight loss, and pain.

At least six chemotherapeutic agents have been shown to have activity against esophageal carcinomas,[7] and combinations of chemotherapeutic agents have demonstrated response rates of 17–55%,[8] but without survival benefits. Based on in vitro studies demonstrating synergy for the combination of 5-fluorouracil (5FU) and recombinant alfa-2a-interferon (IFN),[9] a broad-based Phase II trial of this regimen was initiated in patients with advanced gastrointestinal malignancies. In patients with colorectal carcinoma, response rates of 63% were achieved in a single institution trial[10] and 42% in a trial by the Eastern Cooperative Oncology Group (ECOG).[11] Based on these encouraging results, this regimen was investigated in patients with esophageal carcinoma. Preliminary results from two independent clinical trials[12,13] were presented in 1990 which

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demonstrated activity for this regimen. Our trial has been expanded to a larger group of patients and confirms the activity for this regimen previously noted.

Materials and Methods

Eligibility

Patients were required to have biopsy-proven, measurable locally advanced or metastatic squamous cell or adenocarcinoma of the esophagus beyond the scope of surgical resection. All patients were ambulatory (ECOG performance status 0–2) with adequate hepatic, renal and bone marrow function, and have fully recovered from prior surgery. Patients were excluded for prior chemotherapy or immunotherapy, active infection, severe coexisting disease, inadequate nutrition or poor life expectancy. All patients were required to give written informed consent meeting institutional and federal guidelines.

Study Design

A clinical trial was initiated in January 1988 to determine the efficacy of a previously studied regimen developed at The Albert Einstein College of Medicine[10] in patients with advanced and locally advanced esophageal carcinoma. Accrual goals and statistical analysis met standard National Cancer Institute (NCI) criteria for Phase II studies.[14] Recombinant IFN was supplied by Hoffman-LaRoche (Nutley, NJ). 5FU was obtained commercially. Patients received a continuous infusion of 5FU 750 mg/m^2 daily for 5 days followed by weekly bolus therapy at the same dose. IFN, 9 MU subcutaneously, was administered on days 1, 3, and 5, then three times weekly. Patients were taught to self-administer the drug. Doses of 5FU were reduced by 25% for grade 2–3 myelosuppression, grade 2–3 stomatitis or for watery diarrhea. The dose of IFN was reduced by 50% for grade 2–3 neurologic toxicities or a two-level decrease in performance status. For grade 4 toxicities, patients were removed from study. Toxicities were assessed according to the NCI Common Toxicity Criteria.[15]

Patients were evaluated at baseline and every 6 weeks with esophagram, endoscopy, and computed tomographic (CT) scan of the primary and metastatic lesions. For patient with clearly measurable disease on esophagram or CT scan, all three studies were not required. Standard ECOG response criteria were employed[16] with the exception that complete response required disappearance of all measurable and evaluable disease radiographically and by physical examination and biopsy-proven confirmation of absence of disease. All patients had bidimensionally measurable disease, and the esophagram was not employed as a sole criterion for determining response. For patients in whom response was measured by esophagram, confirmation by a reference radiologist was required, and these results were used solely to support a determination of response which always required bidimensionally measurable disease. All patients enrolled in this trial were evaluable with the exception of a single patient determined retrospectively to be ineligible. Partial response required symptomatic or subjective improvement in addition to objective improvement. Study end points were disease progression or unacceptable toxicity.

Results

Demographic Characteristics

Patient characteristics are shown in Table 1. Twenty-one patients were entered onto a clinical trial. One patient was inevaluable for response because he received prior chemotherapy for a gastric lymphoma. The patient characteristics are representative of the population with esophageal carcinoma at our institution. Although the majority of the patients had a squamous cell histologic type, eight (38%) had an adenocarcinoma reflecting the increasing representation of this histologic type among patients with esophageal carcinoma. Poor prognostic factors included 11 patients with distant metastases, 4 with performance status of 2, and 2 who recurred after radiation therapy.

Toxicity

The toxicities observed are shown in Table 2. The most serious toxicity was a hemorrhage from the esophagus in a patient with a normal platelet count. Bleeding was controlled by cauterizing the lesion. Two patients had serious infections in the absence of neutropenia requiring administration of parenteral antibiotics; one of these was associated with thrombocytopenia. No patients had nadir sepsis. One patient had stomatitis requiring parenteral hydration. No patients experienced severe diarrhea. Neurologic toxicities included the following: weakness (4), dizziness (3), transient confusion (3), depression (1), and falling (1). All neurologic toxicities resolved after withholding treatment. Whereas one third of patients (7) experienced a grade 3 or 4 toxicity, this was considered acceptable in light of the very poor prognosis for this disease.

With a single exception, all patients experienced fatigue requiring reduction in the dose of IFN with a median time to dose reduction of 9 weeks. Likewise, 20 of 21 patients required dose reductions of 5FU, primarily for hematologic toxicity or diarrhea.

Table 1. Patient Characteristics

Characteristic	No.
Entered patients	21
Eligible patients	20*
Age (yr)	
Median	60
Range	45–80
Male:female	16:5
Performance status	
0	6
1	11
2	4
Presenting symptoms	
Obstruction	15
Weight loss	3
Pain	2
Mass	1
Stage	
Locally advanced	10
Distant metastases	11
Histology	
Squamous cell carcinoma	13
Adenocarcinoma	8
Primary site	
Cervical	1
Upper/midthoracic	12
Distal/GE junction	8
Distant metastases	
Nonregional lymph nodes	4
Lung	4
Liver	3
Ascites	2
Differentiation	
Well	1
Moderate	4
Poor	11
N/A	5
Prior treatment	
Surgery	5
Radiation therapy	2

N/A: not available; GE: gastroesophageal.
* One patient ineligible because of prior chemotherapy.

Table 2. Toxicity

	Grade*			
Toxicity	*1*	*2*	*3*	*4*
Leukopenia	5†	7	4	0
Thrombocytopenia	4	1	1	1
Anemia	4	9	4	0
Hemorrhage	0	2	1	1
Infection	1	3	0	2
Fever	2	11	0	0
Nausea/vomiting	6	3	1	0
Diarrhea	5	5	0	0
Stomatitis	3	7	1	1
Neurologic	7	3	3	0
Rash	5	0	0	0

*NCI Common Toxicity Criteria.
† Number of patients with toxicity at that grade (total = 21).

Response

Response to therapy is shown in Table 3. Five patients (25%) had an objective response to therapy lasting 5+, 5, 5, 9, and 16+ months, respectively. Two patients (10%) were pathologically free of disease at the time of surgery or rebiopsy. The first patient was a 50-year-old man who presented with three fixed supraclavicular lymph nodes, a 6-cm mediastinal mass, and a near-obstructing lesion of the esophagus for which a biopsy was performed; it was found to be squamous cell carcinoma. A gastrostomy tube was placed because the obstruction was severe enough to prevent adequate nutritional intake. After 2 weeks of therapy with 5FU/IFN, the gastrostomy tube was removed and the patient was able to eat normally. After 3 months the supraclavicular lymph nodes disappeared and the esophagram normalized. The esophagus underwent rebiopsy and was found to be pathologically free of disease. At 9 months, the mass in the mediastinum persisted on CT scan. Multiple biopsies of the mediastinal mass were performed which revealed necrotic material with no evidence of viable tumor. The patient remained in response for 9 months. After recurrence, he received radiation therapy and further chemotherapy and survived 25 months.

The second patient was a 51-year-old woman who presented with obstructive symptoms. An endoscopic biopsy was positive for squamous cell carcinoma. On radiographic studies the lesion was greater than 8 cm in length with mediastinal adenopathy present. The lesion was considered too extensive for surgical resection, and the patient was treated with 5FU/IFN. At 6 months the patient's symptoms had resolved and the mass had decreased sufficiently in size to permit an esophageal resection. A total thoracic esophagectomy was performed which revealed dense fibrosis with a single nest of squamous cell carcinoma in situ. The specimen was otherwise pathologically without evidence of invasive carcinoma, including multiple lymph nodes which were negative. The patient remains alive and free of disease at 18+ months.

Table 3. Response (n = 20)

	No. (%)	
Complete response	2 (10)	5 (25)
Partial response	3 (15)	
Minor response	1 (5)	
Stable disease	3 (15)	
Progression	11 (55)	

A third patient presented with an adenocarcinoma of the gastroesophageal junction with massive ascites and involvement of the falciform ligament. At 6 weeks the lesion had resolved completely on CT scan and the ascites was absent. The patient was eating normally and was asymptomatic. The fourth and fifth responders had squamous cell carcinomas with distant metastases which regressed in size with symptomatic improvement.

Discussion

This study yielded several encouraging findings. Responses were observed in 25% of the patients entered onto this trial, and two of these responders were pathologically confirmed to be free of disease after treatment. Of interest, one of these patients had been deemed inoperable because of the extent of her lesion before initiation of chemotherapy and after treatment with 5FU/IFN had a near complete response allowing her to have an esophagectomy. The sole remaining disease was a microscopic focus of carcinoma in situ which was excised rendering her pathologically free of disease. She remains alive and asymptomatic at 18 months. A second patient presented with metastatic disease and nearly complete obstruction of the esophagus requiring placement of a gastrostomy tube and, after treatment with 5FU/IFN, achieved normal deglutition and complete resolution of disease, allowing survival for over 2 years. In contrast, in a Phase II trial conducted by the ECOG, treatment of 23 patients with esophageal carcinoma with 5FU, 500 mg/m^2 daily $\times$ 5 every 5 weeks, resulted in four responses (17%) with no complete responses and only two patients surviving 36 weeks.[17]

Toxicities on this trial generally were not more severe than those observed with 5FU alone in patients with esophageal carcinoma and were considered acceptable in light of the generally poor prognosis for this disease.[17] The exception to this observation, however, was the greater number of cases of neurologic toxicity observed compared with previous trials in patients with colorectal carcinoma.[10,11] This may relate to the greater debility of this patient population and more fulminant course of their disease. Of interest, the incidence of severe stomatitis and diarrhea were markedly less than previously reported[10,11]; however, this may be solely a function of the shorter duration of treatment for many of these patients.

Our results confirm the observations of Kelsen et al.[18] who employed a similar regimen for the treatment of patients with esophageal carcinoma and observed a response rate of 27%. The incidence and grade of toxicities were similar, essentially confirming the tolerability of this regimen in patients with esophageal carcinoma, who generally are malnourished, debilitated, and prone to infections.

The mechanism of synergy for 5FU and IFN remains unclear and may result from effects at the cellular level[19–23] or from augmented pharmacokinetic effects.[24–27] Recent results in vitro demonstrate that IFN augments the anabolism of 5FU to its active metabolite, fluorodeoxyuridylate (FdUMP), by stimulating activity of the enzyme, thymidine phosphorylase.[28] The results of this clinical trial suggest that biochemical modulation may be a viable strategy in the treatment of esophageal carcinoma and deserves further investigation.

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