Phase II Clinical Trial of 13-Cis-Retinoic Acid and Interferon-α-2a in Patients with Advanced Esophageal Carcinoma

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BACKGROUND. Interferon in combination with 5-fluorouracil has been shown to be active in squamous cell carcinoma (SCC) and adenocarcinoma (AC) of the esophagus. 13-cis-retinoic acid (CRA) has chemopreventive activity in SCC of the head and neck, and, in combination with interferon, has antitumor activity in SCC of the skin and cervix.

METHODS. The activity and toxicity of CRA and interferon-α-2a (IFN) in patients with advanced esophageal carcinoma was evaluated in a Phase II single institution trial. Patients had unresectable or metastatic AC or SCC of the esophagus. One prior chemotherapy regimen was allowed. IFN was given by daily subcutaneous injection at a dose of 3 million U and CRA was taken orally at a dose of 1 mg/kg/day in 2 divided doses. Treatment was given in cycles of 4 weeks and continued until documented disease progression.

RESULTS. Of the 19 patients entered, 15 were evaluable for response and toxicity. One patient was evaluable for response only and one patient was evaluable for toxicity only. Evaluable patients were predominantly male (15 patients), and had AC (13 patients). All had AJCC Stage IV disease and 12 were pretreated. Patients completed an average of two cycles of therapy (range, one to six cycles) prior to progression of disease. National Cancer Institute Common Toxicity Criteria Grade 3/4 toxicity was notable for nausea (25%) and fatigue (31%). No major objective responses were recorded. Eleven patients with AC and 3 patients with SCC had rapid progression of disease. One patient with AC was found to have a minor response for 22 weeks and 1 patient with AC had stable disease for 45 weeks.

CONCLUSIONS. This regimen had no significant activity in patients with advanced AC of the esophagus. Further evaluation of IFN plus CRA, using this dose and schedule, is not recommended. In comparison with prior trials of this therapy, a surprising amount of severe nausea and fatigue was observed in this trial. ***Cancer* 1999;85:1213–7.**

KEYWORDS: esophageal carcinoma, 13-cis-retinoic acid, interferon-α, adenocarcinoma.

In 1997, approximately 12,500 Americans were diagnosed with esophageal carcinoma. With current treatment modalities, 5-year survival is only 5–10%. In metastatic disease, trials with cisplatin and 5-fluorouracil (5-FU) have demonstrated a 25–35% major response rate. Response duration often is ≤5 months with a median survival of 4–8 months.[1,2] New therapeutic drugs therefore are needed.

Interferon-α-2a (IFN) has shown antitumor activity in a number of gastrointestinal malignancies. Significant clinical responses were reported for IFN in combination with 5-FU in colorectal carcinoma.[3] We performed a Phase II trial of IFN and 5-FU in patients with

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metastatic or unresectable esophageal carcinoma, and reported results comparable to those of cisplatin-based regimens with a major response observed in 10 of 37 patients (27%).[4] Our subsequent trial with 5-FU, cisplatin, and IFN showed a 53% response in 24 evaluable patients. However, the median response duration of 5 months was brief.[5]

A number of clinical trials have shown the efficacy of retinoids as chemopreventive and chemotherapeutic agents. Hong et al. reported a decrease in the size of the primary lesion and a reversal in the degree of dysplasia in patients with oral leukoplakia treated with 13-cis-retinoic acid (CRA).[6] A second study by Hong et al. showed a decreased incidence of second primary tumors in patients treated with CRA after curative treatment of locoregional head and neck carcinoma.[7,8]

Preclinical studies have demonstrated synergy between retinoids and cytokines in a variety of cell lines.[9–12] The mechanism of synergy is not understood completely. Ultimately, retinoic acid appears to increase expression of a transcription factor that regulates IFN gene expression and thereby may modulate IFN-induced cell death and apoptosis.[13]

Based on preclinical data, Lippman et al. reported a 68% overall response rate to CRA (1 mg/kg/day) and IFN (3 million U/day) in heavily pretreated patients with advanced squamous cell carcinoma (SCC) of the skin.[14] This group then used a similar regimen for patients with previously untreated, locally advanced SCC of the cervix. Of 26 patients, 13 had a major response including 4 patients with a clinical complete response.[15,16]

Analogous to nonsmall cell lung carcinoma, both SCC and adenocarcinoma (AC) of the esophagus have a similar natural history with the early development of disseminated disease. Response proportions for the two histologies overlap in chemotherapy trials.[17–19] Based on the enhanced activity of 5-FU observed with IFN in patients with esophageal carcinoma and the antitumor activity of IFN plus CRA observed in patients with SCC of the skin and cervix, a trial of IFN plus CRA for SCC or AC of the esophagus was initiated.

PATIENTS AND METHODS

Study Design

This was a Phase II, single institution trial. After approval by the Internal Review Board at the Memorial Sloan-Kettering Cancer Center, this study was conducted from August 1993 until April 1995.

Eligibility

Patients with histologic confirmation of SCC or AC of the esophagus were required to have unresectable or metastatic disease. Lesions had to be bidimensionally measurable by chest X-ray or computed tomography scan or evaluable as measured by barium swallow. Patients were required to have a Karnofsky performance status ≥60%. Prior treatment with no more than one chemotherapy regimen was permitted. Patients could have no previous exposure to IFN or CRA. Radiation therapy had to be completed at least 4 weeks prior to the initiation of protocol therapy. Adequate bone marrow function (defined as a leukocyte count ≥ 3000 cells/mm^3 and platelet count ≥ 100,000/mm^3), liver function (defined as bilirubin < 1.5 mg/dL), and renal function (defined as serum creatinine ≤ 2 mg/dL or creatinine clearance of ≥ 50 mL/minute) was required. Signed informed consent was obtained from all patients prior to the initiation of therapy.

Treatment Plan

Pretreatment evaluation included complete history and physical examination, blood work, computed tomography of the chest and abdomen, and barium esophagram if clinically indicated.

Recombinant IFN (Roferon®-A; Hoffman-La-Roche, Nutley, NJ) and CRA were supplied by the Investigational Drug Branch of the National Cancer Institute. IFN was given at a dose of 3 million u daily by subcutaneous injection. CRA was given at a dose of 1 mg/kg/day orally in 2 divided doses, preferably with a fat-containing meal. Because gelatin capsules of CRA were available in 10 mg, 20 mg, and 40 mg dosages, doses were rounded to the nearest 10 mg. Patients were encouraged to premedicate with acetaminophen prior to IFN injection and to continue acetaminophen every 4 hours as needed for fever and myalgia. Therapy was administered in cycles of 4 weeks.

Standard response criteria were used.[20] Reassessment of tumor status by appropriate studies occurred at least every 8 weeks until maximum response and then every 2–3 months thereafter. Patients were taken off protocol if they developed disease progression, defined as a >25% increase in the sum of all measured lesions or size of an individual lesion or the appearance of new lesions.

Toxicity was graded according to National Cancer Institute Common Toxicity Criteria. Fatigue was assessed by Cancer and Acute Leukemia Group B toxicity criteria. Dose adjustment for anticipated IFN-associated toxicity (such as fatigue or granulocytopenia) was made for all Grade 2 or higher neurologic toxicity and for all other Grade 3/4 toxicities, except hematologic toxicity manifested by low hemoglobin. In all cases both IFN and CRA were withheld until toxicity was reduced to ≤Grade 1. CRA then was resumed and IFN attenuated to a dose of 1 daily injection 5 days per week. Further attenuation to the delivery of IFN to 3

TABLE 1
Demographics

Entered	19
Eligible	18
Evaluable for response	16
Evaluable for toxicity	16
Male/female	15:1
Median age (yrs) (range)	59 (30–73)
Median Karnofsky performance status (range)	80 (90–70)
Squamous cell carcinoma: adenocarcinoma	3:13
Prior chemotherapy only	4
Prior radiotherapy only	0
Prior chemotherapy and radiotherapy	8

days per week occurred if the significant toxicity recurred.

Dose adjustment for anticipated CRA-associated toxicity (such as dry skin, cheilitis, hypertriglyceridemia, conjunctivitis, or epistaxis) was made for Grade 4 skin toxicity and all other Grade 3/4 toxicity. CRA was withdrawn until toxicity declined to either Grade 2 skin toxicity or Grade 1 other toxicity and then readministered at a dose of 0.5 mg/kg/day. CRA was discontinued if significant toxicity recurred at the attenuated dose. For Grade 3/4 toxicity in which IFN and CRA overlapped, (such as nausea/emesis), both drugs were withheld and a dose attenuation of IFN was made first.

RESULTS

Demographic Characteristics

Nineteen patients were entered into the trial. Of these, one patient was found to be ineligible because he had received two prior chemotherapeutic regimens. Of the 18 eligible patients, 16 were evaluable for response and toxicity. One patient was unable to swallow the CRA and therefore was inevaluable for response and toxicity. Another developed Grade 4 nausea and emesis after 1 week of therapy and was not evaluable for response. One patient had rapid clinical progression after 4 days of treatment and was inevaluable for toxicity.

Of the 16 patients evaluable for response, all had Stage IV disease with 13 demonstrating AC histology. Eight patients previously had received chemotherapy and radiation therapy; four had received chemotherapy only and four had received no prior therapy. Chemotherapy included cisplatin and 5-FU (seven patients), paclitaxel (two patients), or cisplatin, paclitaxel, and 5-FU (two patients). Patient characteristics are outlined in Table 1.

Toxicities

IFN-related toxicity was predominant. Ten patients (63%) had Grade 2 or higher neurosensory toxicity and 5 patients (31%) had Grade III fatigue. Two patients were admitted for fatigue and dehydration. CRA-related toxicity was limited with little skin toxicity and no significant hypertriglyceridemia. Overlapping toxicity of IFN and CRA was notable for Grade 3/4 nausea in 4 patients (25%) and alkaline phosphatase elevated to Grade 3 levels in 3 patients (19%). One 73-year-old patient had a mild stroke after 2 days of therapy (adjudicated as nontreatment-related) and continued his regimen 1 week later for 8 more weeks of treatment. Toxicities are reported in Table 2.

TABLE 2
Toxicities

Toxicity grade (n = 16 patients)	1	2	3	4
Hematologic				
Anemia	8	4	2	0
Leukopenia	4	2	1	0
Granulocytopenia	1	2	0	0
Thrombocytopenia	5	1	0	0
Other				
Fatigue	2	8	5	0
Nausea	4	6	3	1
Emesis	4	4	0	1
Alkaline phosphatase	5	2	3	0
Neurosensory	2	8	2	0
Pulmonary	7	2	2	0
Stomatitis	5	0	1	0
Skin/cheilitis	10	3	0	0
Alopecia	1	0	0	0
Epistaxis	6	0	0	0
Diarrhea	9	1	0	0
Neuroconstipation	1	3	0	0
Fever	5	6	0	0
Chills	1	2	0	0
Pain	0	3	0	0

Response to Treatment

No major responses were observed. Eleven patients with AC and 3 patients with SCC developed disease progression. Only 1 patient with AC was found to have a minor response in skin nodules lasting 22 weeks and 1 patient with AC had stable disease lasting 45 weeks. Both patients were taken off protocol due to disease progression. The median time to progression was 5 weeks. The median survival was 22 weeks.

DISCUSSION

Despite the early reports of response to combination IFN and CRA in patients with SCC of the skin and cervix, a number of subsequent studies have failed to show benefit in patients with more advanced or heavily pretreated disease. For instance, in 13 refractory patients with SCC of the cervix treated with IFN and CRA, no complete or partial responses were ob-

served.[21] Combined IFN and CRA also were examined in patients with recurrent SCC of the head and neck. Of 21 evaluable patients only 1 had a partial response and 2 had minor responses.[22] Similarly, only 1 of 34 patients with advanced nonsmall cell lung carcinoma (17 of whom had squamous histology) treated with IFN and CRA had a brief partial response.[23]

A Phase I study by Toma et al. of SCC patients treated with combined IFN and CRA hinted that this regimen may have promising activity in patients with esophageal carcinoma.[24] Both patients who had previously undergone resection of an SCC of the esophagus had a complete response. However, Phase II trials have been disappointing. Slabber et al. examined this regimen in previously untreated patients with inoperable SCC of the esophagus. Of 15 evaluable patients, no objective responses were documented, with a median survival of 15 weeks.[25] A letter by Kok et al. confirms these findings.[26] In their study of 10 patients with previously untreated metastatic SCC of the esophagus, no objective responses were observed.[26] The poor results achieved in patients with advanced SCC of the esophagus, cervix, head and neck, and lung, may suggest that the benefit of this regimen is reserved primarily for chemoprevention and not for the treatment of advanced or treatment-refractory disease.

The toxicity in our study was higher than that in many previously reported trials of IFN and CRA. Slabber et al. administered the same dose of CRA and twice the dose of IFN used in this study to previously untreated esophageal carcinoma patients and found it to be well tolerated with only one patient developing a Grade 3 toxicity requiring dose modification.[25] Notably, no significant nausea, emesis, or fatigue were noted in patients who at baseline were divided evenly between Eastern Cooperative Oncology Group performance statuses 1 and 2. Similarly, Kok et al. reported little toxicity in their previously untreated esophageal carcinoma group.[26]

Toxicity varied greatly among other studies as well. For instance in two studies by the same authors, toxicity ranged from negligible in patients with previously untreated cervix carcinoma[16] to severe in patients with previously treated SCC of the skin.[15] Multiple studies have demonstrated that Grade 3 fatigue may range from a low of 3% to a high of 43%.[14,16,21–23] Generally, it appears that toxicity in these studies correlates well with the degree of pretreatment. This may account for the relatively high toxicity observed in our study.

Given the absence of response in a total of 28 patients in 3 Phase II studies of SCC of the esophagus and 13 patients with AC of the esophagus, further evaluation of this regimen in patients with advanced esophageal carcinoma is not warranted.

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