Outpatient 5-Fluorouracil, Folinic Acid and Cisplatin in Patients with Advanced Esophageal Carcinoma

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In a multicenter phase II study, 30 patients with unresectable, locally advanced or metastatic squamous cell or adenocarcinoma of the esophagus were treated with folinic acid 200 mg/m^2/d, 5-FU 300 mg/m^2/d, and cisplatin 20 mg/m^2/d intravenously for 5 days every 4 weeks. Two of 13 patients with squamous cell carcinoma (SCC) had a complete response (CR), but one died of pneumonia after 9 months while still in CR, and the other still in CR after more than 5 years. Six other patients (3 SCC, 2 of 16 with adenocarcinoma, 1 mixed histology) had a partial response with a median duration of 9 months (range 5 to 57 + months) for an overall response rate of 27%. A further 6 patients (20%) had stable disease. Grade 4 neutropenia occurred in 6 patients (20%), with 5 requiring antibiotics for associated fever. Other grade 4 toxicities were nausea and vomiting (1), anemia (1), and thrombocytopenia (1); there were three early deaths (emphysema, cardiac arrest, pulmonary embolism). This combination appears to be an active, convenient regimen for advanced esophageal cancer, resulting in prolonged remission and survival in some patients.

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Although esophageal cancer is relatively uncommon in North America compared with other parts of the world, it is an important cause of cancer mortality because of its extremely high case fatality rate. Of the estimated 12 300 new cases diagnosed in the United States in 1996, 11 200 deaths are anticipated (1).

The most commonly used chemotherapy regimen for both squamous cell and adenocarcinoma of the esophagus is the combination of cisplatin 100 mg/m^2 on day 1, and 5-FU 1 000 mg/m^2/d by continuous infusion for 96 to 120 h (2, 3). In the preoperative setting, response rates as high as 72%, with complete response (CR) rates as high as 44% have been reported (4). For patients with metastatic, recurrent, or locally advanced disease, however, the response rate ranges from 25 to 35% with a low CR rate, short duration of response and severe toxicity (3, 5). This regimen also has the disadvantage of requiring hospital admission in many centers, or the use of a more complex and costly route of administration such as an ambulatory infusion pump.

The ability of pharmacologic doses of folinic acid, given prior to the administration of 5-FU, in order to significantly increase the response rate to 5-FU has been well documented for colorectal cancer (6). Encouraging results have also been seen with the use of this approach in combination with cisplatin for squamous cell carcinoma of the head and neck (7) as well as adenocarcinoma of the stomach (8). Accordingly, we undertook a phase II study to evaluate the efficacy and toxicity of the combination of 5-FU, folinic acid and cisplatin for patients with locally advanced, recurrent, or metastatic squamous cell or adenocarcinoma of the esophagus. A divided dose schedule for cisplatin of 20 mg/m^2 daily for 5 days was chosen, as this appears to be as effective as high-dose bolus cisplatin and less toxic (9–11). Combined with 5-day bolus injections of 5-FU and leucovorin, this facilitated out-patient therapy. Our hope was that this regimen might eventually prove not only to be more convenient than conventional 5-FU and cisplatin, but also more effective and/or less toxic.

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PATIENTS AND METHODS

Eligibility criteria

To be eligible for this study patients had to have histologically confirmed squamous cell carcinoma or adenocarcinoma of the esophagus which was either metastatic, locally advanced or recurrent, and unsuitable for surgery or radiation therapy; no prior chemotherapy; measurable or evaluable disease that had not been previously irradiated; age > 18 years; life expectancy of at least 12 weeks and ECOG performance status ≤ 2; adequate marrow function (absolute neutrophil count $> 2.0 \times 10^9$/L and platelet count $> 100 \times 10^9$/L) and adequate renal function (creatinine < 150 μmol/L unless creatinine clearance > 1.5 ml/sec). Patients were excluded if they had a history of previous malignancy other than localized basal or squamous cell carcinoma of the skin or non-invasive carcinoma of the cervix; an active infectious process; brain metastases; or had received radiotherapy to more than 25% of their bone marrow. Informed signed consent was obtained from all patients prior to study entry.

Pretreatment evaluation included a chest radiograph, bone scan and ultrasound or CT scan of the abdomen. Other investigations such as endoscopy and barium swallow were carried out if necessary to evaluate disease.

Treatment schedule

Most of the patients received dexamethasone, prochlorperazine and lorazepam as antiemetics prior to chemotherapy. Folinic acid 200 mg/m^2 was administered intravenously in 50 cc normal saline over 15 min, immediately followed by 5-FU 300 mg/m^2 intravenous push, followed by cisplatin 20 mg/m^2 in 500 cc normal saline infused for over 1 h. A minimum of 500 cc normal saline over at least 1 h was given prior to and following chemotherapy for hydration. This treatment was given daily for 5 consecutive days and repeated every 4 weeks until tumor progression. Treatment was discontinued after 6 courses if patients had still not progressed, provided they had received at least 2 courses after maximum tumor response.

Toxicity evaluation

Toxicity was assessed using ECOG criteria. White blood cell count with differential, platelet count, and serum creatinine were obtained weekly during the first cycle of treatment. Just prior to each treatment, complete blood count and biochemistry including serum magnesium were obtained. Patients were questioned specifically about nausea and vomiting, mucositis, diarrhea, malaise, anorexia and ototoxicity. Audiograms were performed if clinically indicated. Daily cisplatin dose was decreased to 15 mg/m^2 if day 1 serum creatinine was above 170 μmol/L. and cisplatin was withheld if serum creatinine was above 200 μmol/L. The daily dose of 5-FU was reduced by 15% if on the preceding cycle $\geq$ grade 2 mucositis or diarrhea, or grade 4 myelotoxicity occurred. If necessary, treatment was delayed at weekly intervals until the granulocyte count rose above 1.5×10^9/L or platelet count above 100×10^9/L. If during any 5-day-treatment grade 2 or higher mucositis or diarrhea, or grade 4 toxicity of any kind developed, the remainder of the chemotherapy was held for that course and the dose of 5-FU reduced for the next course.

Assessment of response

Response was evaluated clinically every 4 weeks and radiologically every 8 weeks. Bone scan was performed every 12 weeks if initially abnormal. Endoscopy was only repeated if there was no other site of evaluable disease or if necessary to confirm response. Objective response was defined according to WHO criteria (12). A complete response (CR) was defined as the disappearance of all evidence of disease for at least 6 weeks. A partial response (PR) required a 50% or greater decrease of the sum of the products of the two longest perpendicular diameters of all measurable lesions, maintained for at least 6 weeks, and no progression of evaluable lesions or new lesions. Stable disease (SD) was defined as less than 50% regression and less than 25% progression of measurable disease for at least 6 weeks, with no new lesions. Progressive disease was defined as a greater than 25% increase in the sum of the products of two diameters of one or more measurable tumors or the appearance of new lesions. The overall duration of response was calculated from the start of treatment to disease progression and the survival time was calculated from the start of treatment to death or last follow-up.

RESULTS

Between January 1991 and September 1994, 30 patients with a median age of 60 years (range 41 to 81) were enrolled in this study. Enrolment was arbitrarily halted after 30 patients for reasons unrelated to the study results. Complete follow-up information is available through September, 1998. Sixteen patients had adenocarcinoma, 13 squamous cell carcinoma, and one had a mixed adenocarcinoma and squamous histology. Twenty-four patients had distant metastases and 16 had liver metastases. Their characteristics are summarized in Table 1.

Sixteen of the 30 patients received only one cycle of treatment. The reasons were: disease progression in 7, protocol violation (1 patient), patient refusal (1 case), toxicity in 4 cases (only one was clearly treatment related), and death in 3 cases. Reasons for treatment discontinuation in patients who received 2 or more cycles were: disease progression in 6 patients, treatment-related toxicity in 6 patients, patient request in one case, and completion of protocol requirements after 7 cycles in one case.

Response to treatment

Of the 13 patients with squamous cell carcinoma, 2 had a CR, 3 a PR, and 2 had SD, while of the 16 patients with adenocarcinoma, 2 had a PR and 4 had SD. The patient with mixed histology had a PR. The overall response rate was thus 27% (95% CI 11% to 43%) for all 30 patients, with an additional 20% achieving stable disease. Seven of the 11 evaluable patients with liver disease had disease response or stabilization (1 CR, 2 PR, 2 SD).

Neither of the two patients who achieved a CR showed evidence of progression. One patient, who had a biopsy-proven local recurrence 3 years after previous resection, received 3 cycles of chemotherapy and refused further treatment. He is still alive five years after study entry with no disease progression. The other, who had metastatic disease in the stomach and liver, received 6 cycles of treatment and then developed dysphagia. Ultrasound of the liver showed a complete tumor response. Endoscopy revealed the disappearance of all tumor and a dislodged esophageal stent, which was repositioned. Biopsies of the stomach and esophagus confirmed complete response. The patient died 3 months later of sudden dysphagia and bilateral aspiration pneumonia, presumably caused by recurrent dislodging of the esophageal stent. An autopsy was not performed. Another patient, who presented with an adenosquamous carcinoma of the lower esophagus and biopsy-proven liver metastases, had a PR and was taken off the study after 5 cycles because of peripheral neuropathy. Fifteen months later he required cranial irradiation for brain metastases. He is still alive almost 5 years after study entry, with no clinical evidence of systemic progression. His liver was last imaged 3 years ago and he has declined radiologic reassessment.

Table 1

Patient pretreatment characteristics (n = 30)

Median age (range)	60 (41–81) yrs
Male/Female	27/3
Histology	
Adenocarcinoma	16
Squamous cell	13
Adenosquamous	1
Extent of disease (at study entry)	
Locally advanced	6
Metastatic	24
Previous therapy	
None	17
Surgery	8
Radiation therapy	3
Surgery and radiation therapy	2
Performance status	
1	22
2	8
Sites of disease	
Esophagus	18
Lymph nodes	11
Liver	16
Lung	6
Bone	1
Other	3

Table 2

Toxic events observed in 83 cycles administered to 30 patients

Toxicity	Worst grade (ECOG) on any cycle			
	1	2	3	4
Neutropenia (or leukopenia)	0	1	4	6[1]
Thrombocytopenia	4	3	0	1
Anemia	4	4	2	1
Nausea/vomiting	6	7	10	1
Stomatitis	3	2	0	0
Diarrhea	5	7	5	0
Increased creatinine	2	0	0	0
Hypomagnesemia	2	3	3	0
Neurotoxicity	5	4	2	0
Fatigue and weakness	6	9	4	0

[1] Five associated with fever and/or sepsis.

The median time to disease progression for the patients with PR was 9 months (range 5–57 + months) and for the patients with SD was 5 months (range 2–15 months). Median survival from study entry for all patients was 6 months. There was no difference in median survival between patients with squamous cell carcinoma and those with adenocarcinoma.

Toxicity

Toxicity data are available for all 30 patients and are outlined in Table 2. Most patients did not receive 5HT3 antagonists as antiemetics. The major toxicity was hematologic. Treatment delays were necessary in 15 of the 55 cycles administered beyond cycle one, and dose reductions were necessary for 14 cycles. Seven patients came off the study at their own request or at the request of the investigator because of severe toxicity clearly related to treatment: sepsis (1 patient), prolonged thrombocytopenia (2 patients), peripheral neuropathy (2 patients), depression (1 patient), dehydration secondary to nausea and vomiting (1 patient). One patient, who was removed from the study after four cycles because of prolonged grade 4 thrombocytopenia, had not had the dose reductions stipulated in the protocol after the previous three cycles. In addition, after the first cycle, two patients were taken off the study because of myocardial infarctions and one patient because of congestive heart failure. In two of these cases a relationship to the treatment could not be excluded.

Three patients died before they could receive the second treatment cycle. One patient died of bullous emphysema, another of pulmonary embolism and in neither of these cases did the investigator feel the death was treatment related. One patient died of an unexplained cardiac arrest.

DISCUSSION

In North America the combination of infusional 5-FU and cisplatin is considered standard therapy for patients with metastatic, recurrent, or locally advanced cancer of the esophagus that is not amenable to surgery or radiation (2). A recent large European study of this regimen in patients with advanced squamous cell cancer, however, found it to be excessively toxic with a treatment related death rate of 16%. The authors concluded that no standard chemotherapy can be recommended for patients with advanced esophageal cancer (3).

The results of several recently published studies of out-patient regimens for esophageal cancer should be mentioned. Ajani et al. (13) achieved a 32% response rate in a mixture of adenocarcinoma and squamous cell carcinoma patients using the combination of high-dose paclitaxel and G-CSF. An unspecified number of patients, however, had locoregional rather than metastatic disease. Arthralgias, myalgias and bone pain occurred frequently and alopecia was universal. The cost of this regimen is also very high. Conroy et al. (14) reported a 20% response rate to single agent vinorelbine in patients with metastatic squamous cell carcinoma of the esophagus. The median duration of response was only 21 weeks. Spiridonidis (15) used a 5-day regimen of cisplatin 30 mg/m^2/d and etoposide 60 mg/m^2/d to treat 27 patients with esophageal adenocarcinoma. Although 7 of the 16 patients with metastatic disease responded (42%), this was associated with substantial treatment-related toxicity. Seventy percent of patients had grade 4 neutropenia with one septic death; alopecia was also universal.

In our study 30 patients with metastatic squamous cell or adenocarcinoma of the esophagus were treated with a 5-day out-patient regimen of 5-FU, cisplatin and folinic acid. When analyzed on an intent-to-treat basis, the response rate was 27% with another 20% of patients achieving stable disease. Although this is similar to what has been observed with the commonly used combination of high-dose cisplatin and infusional 5-FU (3, 5), the latter, in many centers, requires admission to hospital for up to five days. In addition, the activity of our regimen in the presence of liver metastases and the fact that two of our patients are still alive off treatment after five years with no evidence of systemic disease progression, is encouraging. Because of the relatively small number of patients, however, confirmation of these results is necessary.

The toxicity observed in our study appears quantitatively and qualitatively similar to that reported for infusional 5-FU and cisplatin. Since most of the patients were treated prior to the widespread use of 5HT3 antagonists as antiemetics, the degree of nausea and vomiting is higher than would be expected with today's antiemetic regimens. One somewhat disappointing finding in our study was the hematologic toxicity, with 5 of the 30 patients (17%) developing febrile neutropenia. Most patients who received more than two treatment cycles required a dose reduction. Although this degree of myelotoxicity is similar to that observed with infusional 5-FU and cisplatin (3), it is probably unacceptably high for patients with advanced disease. We would, therefore, recommend that one consider repeating this study initiating the treatment as a 4-day regimen with the same daily doses as in the current protocol (i.e. a 20% dose reduction). If there were no significant toxicity during the first cycle, dose escalation to a 5-day regimen could then be performed for subsequent cycles. We suspect efficacy would not be significantly compromised by such an approach, but this remains to be proven.

In summary, the combination of 5-FU, folinic acid and cisplatin, is a convenient out-patient regimen which appears to have significant activity and the ability to produce very prolonged remissions in a proportion of patients with metastatic or recurrent carcinoma of the esophagus. The ultimate test of this regimen's utility, however, would be to determine whether it can prolong survival when used in the adjuvant or neoadjuvant setting. Since both 5-FU and cisplatin are radiation sensitizers, this would be an ideal regimen to combine with neoadjuvant or adjuvant radiation therapy. Some very encouraging preliminary results of such an approach have been reported (16, 17). If the efficacy and tolerability of this regimen is confirmed, a randomized study comparing this regimen with the combination of cisplatin 100 mg/m^2 on day 1 with 5-FU 1 000 mg/m^2/d by continuous infusion over 5 days is warranted.

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