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Cisplatin and Intravenous Continuous Infusion of Bleomycin in Advanced and Metastatic Esophageal Cancer

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Abstract—*Thirty-four patients with locally advanced or metastatic esophageal cancer were treated with cisplatin* 35 mg/m^2/*day* × 3 *days in bolus, plus bleomycin* 15 mg/*day* × 3 *days, as an* 18 h *infusion, every* 21–28 *days. Twenty-nine are evaluable for response. Objective response was seen in* 15 (52%, 95% *confidence limits* 35–69%) *patients. Toxicity was mild. Twelve patients with locoregional disease were treated with this combination followed by radiotherapy and three of them are alive without disease at* 18, 22 *and* 36 *months. This combination warrants further study in the setting of combined treatment.*

INTRODUCTION

COMBINATION chemotherapy for advanced or metastatic esophageal cancer has shown limited effectiveness, with response rates ranging from 15 to 50% in the largest series [1]. Cisplatin (CDDP) and bleomycin alone [2, 3] or in combination [4–6] are reported as effective treatments by several investigators especially in the setting of combined treatment. This paper reports our experience with CDDP plus bleoemycin in 18 h i.v. infusion ± radiotherapy in esophageal cancer.

MATERIALS AND METHODS

Thirty-four patients with advanced, recurrent or metastatic esophageal cancer were studied. All the patients had histologic proof of squamous esophageal carcinoma. Eligibility criteria included: age <70 years, stage T_3 and/or N_{1-2} and/or M_1, grade 0–3 in the ECOG performance status scale, no esophagopulmonary fistula, good bone marrow reserve and renal function and no prior chemotherapy. Patient characteristics are shown in Table 1. Pretreatment study comprised: anamnesis and physical examination, complete blood and platelet counts, renal and liver function tests, proteinogram, chest roentgenogram, barium esophagram and bronchoscopy. The 12 patients with locally advanced tumors who were treated with chemotherapy and radiotherapy underwent pulmonary function tests before and after chemotherapy, and after radiotherapy. Anamnesis, physical examination, complete blood and platelet counts and renal function tests were repeated prior to each course of chemotherapy. Evaluation of response was performed every one or two courses of treatment.

The therapy schedule consisted of CDDP 35 mg/m^2/day × 3 days in bolus with forced diuresis followed by bleomycin 15 mg/day in 18 h i.v. infusion × 3 days, repeated every 3–4 weeks. Treatment response and toxicity were evaluated using the standard WHO criteria for solid tumors [7] and response criteria described by Kelsen *et al.* [8] when locoregional disease was the only evaluable parameter for response: complete remission is defined as a total normalization in the barium esophagram and no disease at repeat endoscopy (including biopsies and negative cytology); partial remission includes those patients with 50% tumor reduction in the barium esophagram and also those who have a normal barium swallow, but who are found to have macroscopic or microscopic disease at endoscopy. The other patients were considered as not responding.

In the evaluable group, 14 patients with recurrent or metastatic disease and three patients with locoregional disease received therapy for as long as response was maintained. In 12 patients with only advanced locoregional disease (T_3 or N_{1-2}), three courses of chemotherapy were given, followed by radiotherapy over mediastinum with radical pur-

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Table 1. Evaluable patients characteristics

Characteristics	No. of patients
Total	29
Sex	
Male	28
Female	1
Disease sites	
Locoregional disease only	15
Metastatic ± locoregional disease*	14
Lung	6
Lymph nodes	6
Esophagus	5
Liver	1
Previous treatment	
Radical surgery	1
Radical radiotherapy	5
Radical surgery + radiotherapy	4
No treatment	19
Performance status (ECOG scale)	
0–1	18
2	7
3	4
4	0

*Evaluable site.

Table 2. Response to treatment

	CR	PR	NR	Total
Locoregional disease	0	8	7	15
Metastastic disease	2	5	7	14
Total	2	13	14	29

CR = Complete response; PR = partial response; NR = no response.

poses. Radiotherapy was delivered with a ^{60}Co source; 40–45 Gy in two opposed-fields over esophagus and mediastinum and then to 50–65 Gy with pendular technique over the tumor bed. The median dose was of 55 Gy (range 6–64 Gy). Three patients received less than 40 Gy because of progression during the radiotherapy treatment.

RESULTS

Thirty-four patients received 117 courses of chemotherapy (median 3 courses; range 1–11). Five patients were evaluable only for toxicity (four patients with osseous metastases as single evaluable parameter and another with locoregional disease who required an esophageal tube because of severe dysphagia). Twenty-nine from the 34 patients entered in the study were eligible for assessment. Objective responses were seen in 15 patients (52%, 95% confidence limits 35–69%) (Table 2). Two patients (one with lymph node and the other with lung metastases) achieved a complete response lasting for 10 and 11 months. The mean duration of response (excluding 12 patients with further radiotherapy over esophagus) was 5.8 months. The median duration of survival, from the start of treatment, was 7 months.

Twelve patients with advanced locoregional disease were treated with radiotherapy (^{60}Co), nine > 50 Gy/t over esophagus and mediastinum after three courses of cisplatin plus bleomycin. After combined treatment, three patients (25%) achieved complete response, remaining disease-free 18, 22 and 36 months after beginning of treatment, and the other six patients (50%) achieved partial response, with an overall response rate of 9/12 patients (75%). The median duration of survival in this group was 8 months.

Toxicity was generally mild. Nausea and vomiting were the more frequent toxic effects and were observed in 27 (79%) patients. Eighteen patients (53%) had fever. Anemia (Hb < 11 g/dl) was seen in eight (23%) patients and leukopenia in 9 (26%) patients. All patients with anemia or leukopenia fell into grade I–II in the WHO classification. Thrombocytopenia was less frequent, and only five patients (15%) showed a fall to between 50,000 and 100,000/mm^3. Nephrotoxicity was observed in two (6%) patients and it was the cause of the only treatment-related death. Ototoxicity was seen in two (6%) patients. Five of the 12 patients treated with chemotherapy and radiotherapy were found to have a 20% decrease in the pretreatment DLCO (diffusing capacity for carbon monoxide) in the pulmonary function tests performed, but only one patient developed mild respiratory symptoms (dyspnea on exertion) (Table 3).

Table 3. Toxicity

Nausea and vomiting	27/34 (79%)
Myelotoxicity*	
Anemia (Hb < 11 g/dl)	8/34 (23%)
Leucopenia (< 4000/mm³)	9/34 (26%)
Thrombocytopenia (< 100,000/mm³)	5/34 (15%)
Nephrotoxicity	2/34 (6%)
Ototoxicity	2/34 (6%)
Dyspnea	1/34 (3%)
DLCO reduction > 20%†	5/12 (42%)
Fever	18/34 (53%)

*All patients with WHO grade II.

†Diffusing capacity for carbon monoxide in the pulmonary function tests which were only performed in patients with locally advanced esophageal cancer treated with chemotherapy and radiotherapy.

DISCUSSION

Combined CDDP and bleomycin, as used in this study, has proved effective in the treatment of locally advanced or metastatic esophageal carcinoma, with a response rate of 52% (95% confidence limits, 35–69%) and mild toxicity. These results seem better than those reported by Coonley *et al.* [5] with the same combination therapy. Since both series have used identical drugs and response criteria, the different results could possibly be attributed to a different schedule in terms of CDDP fractioning, number of cycles in locoregional disease and interval between cycles. In spite of the high response rate, the median survival and mean duration of response are still low (7 and 5.8 months), which agrees with the natural history of recurrent or metastatic esophageal cancer. Nevertheless, the high response rate (nine out of 12 patients) obtained with chemotherapy followed by radiotherapy in the group of patients with locally advanced tumors without prior treatment, and the fact that three patients are alive and disease-free 18, 22 and 36 months after beginning treatment is encouraging. These results seem to corroborate that induction chemotherapy followed by radiotherapy could be less toxic than chemotherapy followed by surgery ± radiotherapy, while maintaining the efficacy. In the series of Memorial Hospital [9] and Wayne Univerity [10], the number of patients without evidence of disease after treatment with chemotherapy followed by surgery ± radiotherapy is similar to the patients of our study treated with chemotherapy followed by radiotherapy.

Overall toxicity was acceptable, myelosuppression in all cases was less than grade II on the WHO scale, and only one patient presented with dyspnea (the longest survival in the group treated with chemotherapy and radiotherapy). This low incidence of clinical pulmonary toxicity can be explained in part by the short survival of the patients and in part by the moderate dose of bleomycin administered. A single death was observed by nephrotoxicity.

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