Eur J Cancer Clin Oncol, Vol. 20, No. 6, pp. 743–747, 1984.
Printed in Great Britain.

0277-5379/84$3.00+0.00

Cisplatin, Bleomycin and Methotrexate in the Treatment of Advanced Oesophageal Cancer

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Abstract—*From February 1981 to September 1982, 34 patients with metastatic or locally advanced (inoperable) epidermoid carcinoma of the oesophagus were treated with a combination of cisplatin, bleomycin and methotrexate. Thirty-one patients are now evaluable for response: 16 of 31 (52%) experienced some improvement, but only eight (26%) obtained major responses (one complete and seven partial). Responses were obtained rapidly within the first two courses. The median duration of responses was 5 months. The median survival from start of therapy was 8 months for responsive and 5 months for non-responsive patients. Gastrointestinal toxicity (cisplatin-related) and mild myelosuppression were the most prominent side-effects. This combination chemotherapy proved to be only of small efficacy in the long-term control of advanced oesophageal cancer. However, because the responses were obtained rapidly, it is conceivable that a similar regimen (with increased dosage of cisplatin) applied before surgery to patients with limited disease could obtain a reduction of the bulky tumour, with a possible increase of the resectability rate and destruction of micrometastases.*

INTRODUCTION

PROGNOSIS for oesophageal cancer is very poor: the median 5-yr survival is between 5 and 20% for operable cases and under 5% for advanced disease [1, 2]. Neither aggressive surgery nor radiation therapy alone seem to have significantly improved the long-term survival [3, 4]. Even when these two modalities have been combined together the results are still disappointing, with only a small number of patients surviving for more than 2 yr [5, 6]. Many studies have been performed to test the efficacy of single-agent chemotherapy; the best-studied single agent is bleomycin, which induced complete plus partial responses in only 10–25% of patients and of short duration [7–10]. Cisplatin alone in two trials proved to be of modest activity; the overall response rate was 18%, with remissions of short duration [11, 12]. Other active chemotherapeutic agents are 5-fluorouracil, methotrexate, vindesine, methyl-GAG and adriamycin, but their activity does not seem superior to that of bleomycin [13–15].

A three-drug combination (cisplatin, bleomycin and methotrexate) has obtained encouraging results in head and neck tumours of squamous cell type [16] according to a preliminary report in a small series of oesophageal cancers [17]. This study was undertaken to test this promising combination in a larger series of patients.

The original 'MBD' regimen was modified, increasing the dosage of bleomycin from 10 mg per person to 10 mg/m^2.

MATERIALS AND METHODS

From February 1981 to September 1982, 34 patients with histologically proven metastatic or inoperable epidermoid carcinoma of the oesophagus entered into this study. Thirty-one patients are now evaluable. Six of the 31 patients had previously undergone surgical operation, but they had recurrent or metastatic disease when admitted. Twenty-five other patients were not considered as candidates for surgery. The causes of inoperability were: locally advanced tumour (for extension >15 cm invasion of trachea or bronchi, localization in the upper third with or without lymph node invasion) in 15 cases, metastatic disease in 10 cases.

Accepted 29 November 1983.
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The main characteristics of the patients are presented in Table 1.

Pretreatment evaluation included physical examination, 21-channel screening profile, blood and platelet count, chest X-ray, barium oesophagram, oesophagoscopy, bronchoscopy and, when indicated, laparoscopy. In addition, pulmonary function tests were performed in 24 patients.

To evaluate response to treatment, the barium oesophagram and endoscopy were repeated at least every two courses of therapy, while bronchoscopy and laparoscopy were repeated only in cases with bronchial or liver invasion. CT scan and echotomography were also applied to response evaluation when initially positive.

The treatment schedule consisted of three drugs (MBD regimen), as shown in Table 2. Bleomycin was given i.m. on days 1, 8 and 15 at the dosage of 10 mg/m^2; methotrexate was given i.m. on days 1 and 15 at the dosage of 40 mg/m^2; and cisplatin was given at the dosage of 50 mg/m^2 on day 4 and administered according to Vogl's 2-hr infusion programme [18]. The cycle restarted from day 22. In order to avoid cisplatin-induced nausea and vomiting, all patients received 1 mg/kg of metoclopramide 30 min before and 2 mg/kg 60 min after cisplatin infusion [19].

With leukocyte counts between 3000 and 3500/μl and platelet counts between 80,000 and 100,000/μl the doses were reduced to 50%; with lower values the course was delayed to permit haematological recovery.

Complete remission (CR) was defined as the disappearance of all clinical evidence of disease for a minimum of 1 month. Partial remission (PR) was defined a >50% decrease in the sum of the product of the two largest perpendicular diameters of any measurable mass and/or a >50% shrinkage of the tumour lesions as seen in a barium oesophagram and in oesophagoscopy. Minimal response (MR) was defined as a 25–50% regression. Duration of response was calculated from the moment of its evaluation.

The survival curves were calculated by the Kaplan–Meier product limit method [19, 20].

Table 1. Main characteristics of the patients

	No. of patients
Males	30
Females	4
Median age (yr)	56 (range: 42–71)
Median performance status (Karnovsky)	60 (range: 40–90)
Median time to diagnosis (months)	4 (range: 1–20)
Extent of disease	
Locally advanced tumour	18
Primary tumour and distant disease	10
Distant spread (primary removed)	6
Sites of metastatic disease	
Lung	5
Lymph nodes	1
Trachea plus residual oesophagus	2
Liver	2
Liver plus lymph nodes	3
Mediastinum plus lymph nodes	1
Skin	1
Skin plus bones	1

RESULTS

Of the 34 patients entered into the study, three are not evaluable: one died at home from cardiac failure within 10 days from the start of therapy and two other patients refused the treatment before the completion of the first course. The patients received a median of four courses (range: 2–6).

Among the 31 evaluable patients there were one complete, seven partial and eight minimal responses. The CR was observed in a patient who developed skin deposits 5 months after oesophageal resection; another patient with lung metastasis (the primary tumour had been removed) experienced a complete disappearance of the lesion for 5 months as seen on standard X-ray but, because stratigraphy had not been performed, this response was classified as PR. In two other patients there was a mixed response: in spite of an evident regression (>50%) of the oesophageal tumour, the metastatic lesions (lung and lymph nodes) did not respond, so they were classified among the non-responders.

Table 2. 'MBD' regimen (modified)

	Days														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Bleomycin (mg 10/m^2 i.m.)	!							!							!
Methotrexate (mg 40/m^2 i.m.)	!														!
Cisplatin (mg 50/m^2 2-hr infusion)				!											
	Recycle on day 22														

Table 3. Characteristics and survival of patients obtaining major responses

Responsive patients	Prior therapy	P.S.	Site of disease	Response	Duration (months)	Survival (months)
1°	surgery	90	lung	PR	5	7
2°	—	80	oesophagus	PR	3	5
3°	—	70	oesophagus	PR	4	17
4°	—	80	oesophagus trachea	PR	7	10
5°	—	80	liver	PR	5	7
6°	—	70	lymph nodes	PR	5	8
7°	surgery	70	lymph nodes liver	PR	7	12
8°	surgery	70	skin	CR	5	7

Overall, 16 of 31 patients (52%) improved during the MBD regimen, but major responses (CR + PR) were seen in only eight cases (26%) (Table 3). The maximum degree of response was observed within the first two courses of treatment; the median duration of major responses was 5 months. Of the 16 responding patients, six had primary advanced tumour and ten had metastatic disease.

There was no difference in the response rate of the different metastatic sites. To date all patients have died (30 from progression of disease and one from renal failure). The median survival for all the patients is 5 months from the start of therapy and 9 months from diagnosis. Patients responsive to the MBD regimen lived longer than the non-responsive ones, but not significantly so (Fig. 1).

Toxicity

The treatment was generally administered on an outpatient basis. Gastrointestinal toxicity, pulmonary toxicity and myelosuppression were the most prominent side-effects in a total of 140 courses. Stomatitis occurred 20 times; nausea and vomiting (occurring approximately in 60% of courses) were generally associated with cisplatin infusion but rarely severe. Myelosuppression was moderate: treatment was delayed in 14 of 140 (10%) courses for leukopenia or thrombocytopenia, while the dose was reduced in another 17 courses (12%). There was one case of severe leukopenia (450 granulocytes/μl) associated with bronchopneumonia. Infections (microbial or viral) were seen 11 times and four patients had to stop the treatment for recurrent pneumonia infections; in one patient it was due to a bronchooesophageal fistula. In five patients there was an impairment of the respiratory function tests (>30% decrease of vital capacity). Nephrotoxicity was observed in three cases: one non-responding patient died of renal failure following cisplatin infusion; two other patients had an increase in serum creatinine of 2.5 mg/dl, but of short duration.

DISCUSSION

The present study indicates that the MBD regimen has only partial efficacy in the control of advanced oesophageal cancer. While over 50% of patients showed an improvement during chemotherapy, only 26% obtained a complete or partial remission. The median duration of response was 5 months. Possible explanations of the low response rate and its brief duration may be the extension of the disease and the poor nutritional status of the patients: none of our patients received a complete parenteral nutrition during the intensive chemotherapy that has been administered on an outpatient basis. A study of the same chemotherapy regimen associated with intensive parenteral or enteral nutrition may seem advisable.

Kelsen, using a combination of three drugs (cisplatin, vindesine and bleomycin), obtained major objective regression in 55% of cases [21]. However, most of his patients received chemotherapy as first treatment and in fact 75% of them underwent surgical operation soon after.

Probably patients with very advanced disease (as many of ours were) should be excluded from multiple-agent chemotherapy because they could

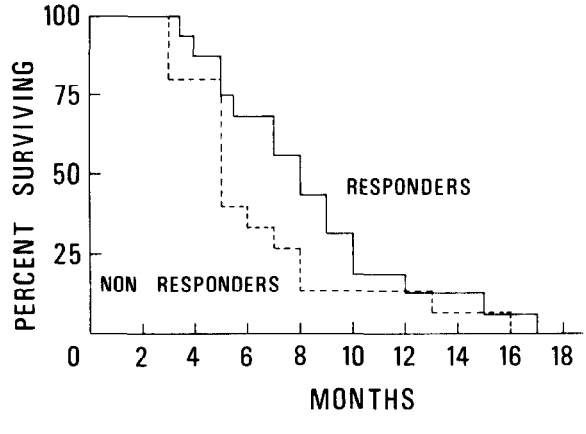

Fig. 1. Actuarial survival of responsive and non-responsive patients.

obtain a similar palliation even if treated with a single active cytotoxic agent such as bleomycin.

Although the haematological toxicity does not seem prohibitive, the frequent association of lung toxicity by bleomycin with pneumonia infections and the possible toxic synergism of the three-drug combination advised us not to increase the doses of the drugs further.

Nevertheless this MBD combination could be employed in an early pre-surgical phase because it has induced in some patients early responses both in the primary oesophageal tumour and in metastatic disease. It is conceivable that this approach could increase the number of surgical resections and permit a longer post-surgical survival. Furthermore, this or a similar regimen could also be used in the post-surgical phase of operated patients to prevent or delay relapses. Both these hypotheses need confirmation in a large series of patients.

Acknowledgement—The authors are grateful to Rossana Rigoni for secretarial assistance.

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