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High-Dose Cyclophosphamide with Autologous Marrow Transplantation for Small Cell Carcinoma of the Bronchus

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Summary. *Twenty-five patients with previously untreated small cell carcinoma of the bronchus have been treated with cyclophosphamide 160–200 mg/kg and subsequent radiotherapy to the primary site. Eighty-four percent of patients responded to the single cycle of chemotherapy, with 56% attaining a complete response. Median duration of remission was 43 weeks and median survival 69 weeks. 2-Mercaptoethane sulphonate was given to prevent urothelial toxicity. Autologous bone marrow transplantation was used to mitigate bone marrow depression but sequential delay in reinfusing cryopreserved bone marrow did not alter the period of cytopenia. Other toxicities were mild. The procedure proved safe and manageable. High-dose chemotherapy may prove to be useful in the initial management of this tumour.*

Introduction

In a previous report [9] we presented the early results of the use of cyclophosphamide in a very high dose as the initial treatment of small cell carcinoma of the bronchus (SCCB). The present paper describes the results in a larger group of patients and with longer follow-up.

Patients

Twenty-five previously untreated patients with histologically proven SCCB were entered into the study. The patients gave informed consent after full discussion of the procedure. Patients selected were fit, with a performance status of 0–2 using the criteria of the Eastern Co-operative Oncology Group. There were 13 women and 12 men, with a mean age of 52 years (range 32–69 years). Staging procedures used included chest X-ray, bronchoscopy, full blood count, biochemical tests of liver and renal function, isotope scans of bone and liver, bone marrow aspirate and trephine biopsy, and CT scan of thorax and abdomen to the pelvic brim. According to these methods, 21 patients had disease limited to one hemithorax and ipsilateral supra-clavicular nodes (limited disease) and four patients had disease outside these limits (extensive disease). The sites of spread were liver (3) and bone (1).

Methods

Marrow was harvested under a general anaesthetic from multiple iliac crest and sternal aspirations. The technique of harvesting and cryopreservation has been described previously [5]. One or 2 days later, treatment was began with cyclophosphamide 40 mg/kg (9 patients) or 50 mg/kg (16 patients) by IV injection over 30 min on each of 4 successive days (total dose 160–200 mg/kg). The lower dose was given to the first nine patients while experience with the technique was being gained. The urine output was maintained at 3 l/day. Mesna (mercaptoethane sulphonate) was given each day as three IV doses at 4-h intervals, starting at the time of the cyclophosphamide administration. The total dose each day was 60% of the cyclophosphamide dose. The stored bone marrow was thawed and immediately reinfused 2 days after the last cyclophosphamide dose in 17 patients, after 4 days in 5, and after 6 days in 3. A variable period of severe neutropenia then developed and prophylactic oral co-trimoxazole and amphotericin were given. In 14 patients fever developed, usually after 7 days of agranulocytosis, and parenteral antibiotics were given. After haematological recovery, the patients were discharged from hospital. Two weeks later the response was assessed by chest X-ray and a second bronchoscopy and CT scan. Radiotherapy to the site of primary disease was then started, 40 Gy being given as a mid-plane dose in 20 daily fractions over 26–29 days. Following this, no further treatment was given until relapse, when additional chemotherapy with either *cis*-platinum 100 mg/m^2 on day 1 and VP16 150 mg/m^2 on days 1, 3, and 5 (11 patients) or vincristine 2 mg IV on day 1 and adriamycin 60 mg/m^2 (3 patients) on day 1. Cycles of chemotherapy were given 3-weekly provided the blood count was normal.

Results

Response and Survival

The response to chemotherapy assessed at 35 days by chest X-ray and bronchoscopy is shown in Table 1. The criteria for response were as previously described [9]. Fourteen patients (56%) had a complete response; in three of these slight external bronchial compression was seen or mucosal pallor was present. Seven patients had a partial response (28%) and four patients (16%) did not respond. The overall response rate was thus 84% as judged by conventional criteria but the second CT scan (before radiotherapy) showed residual tumour in all patients.

The median follow-up is now 17 months (range 6–28 months). Fourteen patients have relapsed, and of these 12 have died of disease. A further patient died of an opportunistic fungal pneumonia and hyperosmolar non-ketotic diabetic

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Table 1. Bronchoscopic and radiological response to cyclophosphamide

Complete response		
No tumour on X-ray or bronchoscopy	11	56%
No tumour on X-ray, bronchial narrowing but negative biopsy and cytology	3	
Partial response		
No tumour on X-ray but bronchoscopy + ve	3	28%
Tumour on X-ray (partial response) bronchoscopy + ve	4	
No response		
Tumour on X-ray (no response) bronchoscopy + ve	4	16%

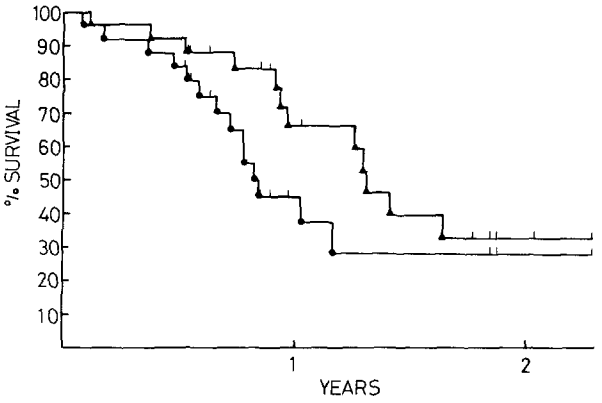

Fig. 1. Median disease-free survival, (●) (= 43 weeks) and median survival (▲) (= 69 weeks)

coma at 58 weeks. At post mortem no sign of residual disease was found. The median duration of response is 43 weeks and median survival is 69 weeks (Fig. 1). One patient has developed pulmonary tuberculosis but remains well without relapse at 96 weeks. On relapse 11 patients have been treated with *cis*-platinum and VP16/213. Seven (63%) had substantial regressions lasting a mean of 28 weeks (range 2–56 weeks). The sites of first relapse were the primary site, 11; liver, two porta hepatitis two; and brain one. More recently patients have been treated with adriamycin and vincristine on relapse, but the numbers are too small for an assessment of response rate.

Toxicity

Haematological toxicity always followed a similar pattern. On day 6 or 7 the white cell count fell below 0.5×10^9 with no detectable granulocytes. Agranulocytosis of this degree lasted 7–18 days (mean 12). Full haematological recovery took 12–21 days. All patients developed platelet counts below 60×10^9/l, and severe thrombocytopenia ($< 30 \times 10^9$/l) requiring platelet transfusion developed in 13. The degree of thrombocytopenia was dose-related. Of nine patients treated with cyclophosphamide 160 mg/kg, three required platelet support, whereas 10 of 16 treated with 200 mg/kg required support. Blood transfusion was required in 17 patients, an average of 4 U being given (range 3–10).

Non-haematological toxicity presented surprisingly few problems. Of 25 patients, 22 had a transient, erythematous, pruritic skin rash which we attributed to the cyclophosphamide. Nausea and vomiting during cyclophosphamide treatment was mild in 17, moderate in six, and severe in two. Seven patients experienced transient mild diarrhoea. The urine was examined each day; only four samples showed red cells and gross haematuria never occurred. Serial ECG and echocardiograms showed no abnormality in the first 13 patients and were not performed thereafter. One patient had a transient pericardial effusion which was thought to be malignant but was not aspirated. Fever which was low grade (1 and 2 on the WHO scale) developed in 11 and more severe fever in three (WHO grade 3). Only these latter three patients were given granulocyte infusions, having appeared unresponsive to antibiotics in the short term. Following radiotherapy, 17 patients have developed radiation pneumonitis, which was greater in degree than that seen in patients treated with the same radiotherapy protocol during lower-dose combination chemotherapy.

Table 2. Duration of granulocytopenia ($< 0.5 \times 10^9$/U) related to the number of days after the last dose of cyclophosphamide before marrow infusion

Interval (days) between chemotherapy and (marrow infusion)	No.	Total dose of cyclophosphamide (mg/kg)	Days of granulocytopenia (± SD)
2	9	160	10.7 ± 2.1
	8	200	12.1 ± 2.5
4	5	200	12.4 ± 3.3
6	3	200	13.7 ± 1.3

Marrow Transplantation and Haematological Recovery

The duration of granulocytopenia was slightly longer in patients treated with cyclophosphamide 200 mg/kg than in those who received 160 mg/kg. To find out whether autologous bone marrow was necessary for recovery of the blood count, we delayed return of the bone marrow to 4 days post chemotherapy in five patients and to 6 days in three patients (Table 2). The duration of granulocytopenia was not lengthened by this sequential delay. This suggests that the marrow infusion was not necessary for recovery of the blood count.

Discussion

The rationale for the use of very-high-dose chemotherapy in solid tumours is that a greater response might be obtained than if a drug is given as several smaller doses. Regression of melanoma [7] and drug-resistant Ewing's sarcoma [2] has been produced by melphalan in high doses. In previous studies of very-high-dose chemotherapy in SCCB [4, 10] multiple drugs have been used, often in patients who have relapsed while receiving other chemotherapy, and the contribution of each drug cannot then be assessed.

This larger study, with longer follow-up, confirms and extends our previous report [9], which also explained the rationale for the study design. The major toxicities of cyclophosphamide are bone marrow depression and haemorrhagic cystitis. The use of autologous bone marrow has been shown to lessen the period of aplasia induced by melphalan [6]. The use of autologous marrow carries the risk of reinfusing malignant cells. We did not feel justified in dispensing with autologous marrow, because of the age of our patients and the

need for as short a period of hypoplasia as possible. Instead we sequentially delayed the return of the marrow by small increments. This approach showed that even when the marrow was delayed by 6 days the period of hypoplasia was not lengthened. We conclude that for this dose and schedule of cyclophosphamide the marrow is probably not required.

Urothelial toxicity was almost entirely avoided due to the use of Mesna. No cardiac toxicity occurred, although this may limit further dose escalation, and radiotherapy to the mediastinum did not produce any immediate cardiac or pulmonary complicatioins. In the longer term, 17 patients developed marked radiation fibrosis and it appears that the drug may cause radiation sensitisation in this dose. Other toxicities of the drug were mild and transient.

The response rate, as judged by chest X-ray and bronchoscopy, is high (84%), with 56% complete responses. This is far higher than the response to conventional doses of the drug [1] and has been achieved after only a single cycle of treatment. Relapse did occur in most patients, although a median relapse-free interval of 43 weeks meant that many patients were free of treatment for several months. On relapse the response rate to treatment with *cis*-platinum and VP16/213 was approximately the same as in untreated patients. The median survival of 69 weeks compares favourably with most studies of combination chemotherapy in limited disease. At present, about 30% of our patients are alive 20 months after treatment.

Although we have shown that very-high-dose cyclophosphamide produces a high response rate, the contribution of the drug treatment to remission duration and survival is not certain. The patients mostly had limited disease and were also treated with radiotherapy. However, in the first MRC trial [3] the mean survival of patients treated with radiotherapy alone was 43 weeks, and in the second trial [8] the median survival was 25 weeks. Although our cases are selected differently it seems probable that the cyclophosphamide has contributed to the overall survival in our patients.

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