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High-Dose Cyclophosphamide with Autologous Marrow Transplantation as Initial Treatment of Small Cell Carcinoma of the Bronchus

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Summary. *Sixteen patients with untreated small cell carcinoma of the bronchus received cyclophosphamide in a total dose of 160–200 mg/kg. Autologous marrow transplantation was used to minimise the period of hypoplasia and 2-mercaptoethane sulphonate to prevent urothelial toxicity. The procedure was well tolerated, with predictable and manageable toxicity. Complete radiological and bronchoscopic response was achieved in seven patients and partial response in a further seven. High-dose cyclophosphamide may be a useful initial treatment for this disease.*

Introduction

The development of autologous bone marrow transplantation has allowed very high-dose chemotherapy to be given to patients with cancer without the development of irreversible or protracted marrow aplasia. In solid tumours this technique has usually been used in patients who have relapsed while receiving previous chemotherapy [8], and the high-dose chemotherapy has included several drugs in combination [3]. However, the rational development of this approach depends on its use in previously untreated tumours and on an understanding of the response rates of single agents in high doses. Cyclophosphamide is usually reported to produce responses in 30%–40% of patients with small cell carcinoma of the bronchus when the drug is used in conventional doses, but complete responses are very uncommon [1]. The urothelial toxicity of the drug can now be mitigated by the use of 2-mercaptoethane sulphonate [7]. We have therefore treated patients with previously untreated small cell carcinoma of the bronchus with cyclophosphamide in a very high dose, using autologous bone marrow to minimise haematological toxicity and 2-mercaptoethane sulphonate for protection of the urinary tract.

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Patients and Methods

Patients. The 16 patients all had histologically confirmed small cell carcinoma of the bronchus. Patients were selected who were fit, with a mean age of 52 years, and had no other unrelated disease. The characteristics of the group are shown in Table 1. All patients gave informed consent after full discussion of the procedure. The disease extent was assessed clinically, bronchoscopically, by chest x-ray, liver function tests, isotope scans of bone and liver, CT scans of thorax and abdomen, by bone marrow aspirate, and by trephine biopsy. 'Limited disease' means disease confined to one hemithorax and ipsilateral supraclavicular lymph nodes and 'extensive disease' means disease more extensive than this, including metastatic disease outside the thorax.

Procedure. The plan of the procedure is shown in Table 2. Marrow was harvested under a general anaesthetic from multiple iliac crest and sternal aspirations. The technique of harvesting and cryopreservation will be described elsewhere (D. C. Linch et al. 1981, unpublished work). One or two days later treatment with cyclophosphamide was begun, 40 mg/kg being given by IV infusion over 30 min on each of 4 successive days in 13 patients, and 50 mg/kg according to the same schedule in 3 patients. Three litres of normal saline was given daily. 2-Mercaptoethane sulphonate was given each day as three IV doses at 4-h intervals, starting at the time of cyclophosphamide administration. The total dose each day was 60% of the cyclophosphamide dose. Two days after the last cyclophosphamide injection the marrow was thawed and immediately reinfused. A variable period of severe neutropenia then developed and the patient was isolated with reverse barrier nursing. After haematological recovery the patient went home and came back 2 weeks later for chest x-ray, repeat CT scan, and bronchoscopy. Radiotherapy to the thoracic tumour was then started, 4,000 rads being given in daily fractions over 4 weeks. Following this, there was no further treatment unless relapse occurred, when additional chemotherapy (with *cis*-platinum and VP16) was given.

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Table 1. Details of patients

	No.
Number	16
Limited disease	13
Extensive disease	3
Male/female	9/7
Age range (mean)	39–69 (52)

Table 2. Plan of treatment

Day	
1	Marrow harvest
2–5	Cyclophosphamide 40–50 mg/kg
7	Marrow infusion
8–20	Hypoplasia
22	Patient goes home
36	Reassessment
38	Radiotherapy

Results

Toxicity

Haematological toxicity was predictable and uniform and is shown in Table 3. On day 6 or 7 the white cell count fell below 0.5×10^9/l, with no detectable neutrophils. Agranulocytosis of this degree lasted 7–16 days (mean 11.5 days). Full haematological recovery took 12–21 days. All patients had platelet counts below 60×10^9/l, and severe thrombocytopenia ($< 30 \times 10^9$/l) requiring platelet transfusion developed in 5/16. Only one patient had significant bleeding, from a previous peptic ulcer. Anaemia requiring blood transfusion developed in 15/16 patients. An average of three units was given.

Non-haematological toxicity presented surprisingly little problem. All patients had a transient erythematous skin rash, usually confined to the areas of skin covered by sticking plaster after the marrow harvest, which we attribute to cyclophosphamide. Nausea was mild, and only nine patients vomited, usually on two occasions only. Although the patients received antiemetics, it is possible that 2-mercaptoethane sulphonate may modify the drug-induced nausea. Five patients experienced transient mild diarrhoea. A morning urine sample was examined each day for all patients and only four samples had red cells microscopically. Serial ECGs and echocardiograms showed no abnormality in the first 13 patients and were not performed thereafter. One patient had a transient pericardial effusion, which was

Table 3. Haematological toxicity

	No.
Severe neutropenia (WBC $< 0.5 \times 10^9$/l)	
Mean duration 11.3 days (range 7–16)	16
Thrombocytopenia	
Mild ($30–60 \times 10^9$/l)	12
Severe ($< 30 \times 10^9$/l)	4
Transfusions (mean no. of units given, 22)	4
Anaemia	
Mild (> 9 g/dl)	13
Severe (< 9 g/dl)	3
Transfusions (mean, 3 units)	15

Table 4. Radiological and bronchoscopic response

	No.
No tumour on x-ray or bronchoscopy	7
No tumour on x-ray, bronchial narrowing but negative biopsies	3
No tumour on x-ray, bronchoscopy positive	1
Tumour on x-ray (partial response) bronchoscopy positive	2
Tumour on x-ray (no response) bronchoscopy positive	3

Table 5. Relapse-free interval and survival

Patients	Disease extent (limited or extensive)	Relapse-free survival (weeks)	Outcome
Relapsed			
1. E. W.	L	19	Died at 24 weeks
2. D. G.	E	39	Alive at 47 weeks
3. P. G.	L	16	Died at 48 weeks
4. E. W.	E	8	Died at 34 weeks
5. L. S.	E	4	Died at 6 weeks
6. S. W.	L	30	Alive at 52 weeks
7. J. S.-P.	L	27	Alive at 51 weeks
8. C. G.	L	17	Died at 32 weeks
9. B. H.	L	44	Alive at 46 weeks
Relapse-free			
10. W. F.	L	46+	
11. J. R.	L	50+	
12. J. F.	L	30+	
13. M. P.	L	56+	
14. T. O.	L	34+	
15. L. S.	L	70+	
16. G. M.	L	50+	

thought to be malignant but not aspirated. Fever, usually low-grade and lasting 4–5 days, occurred in 15/16 patients, usually towards the end of the agranulocytosis, but disappeared with recovery of the white count. Only one patient had proven bacterial infection.

Response

Responses were assessed 2 weeks after discharge, by chest x-ray bronchoscopy and repeat CT scan. The response rate according to chest x-ray and bronchoscopy is shown in Table 4. Eleven patients had a complete radiological response, two had a partial response (greater than 50% reduction), and three failed to respond. At bronchoscopy in seven patients there was no visible tumour with negative biopsies; in a further three patients there was an abnormal bronchoscopy but negative multiple biopsies. Complete radiological and bronchoscopic response was seen in 7/16, while a further three patients had normal chest x-rays and normal histology on multiple biopsies. Radiological and bronchoscopic response is the accepted criterion of efficacy of treatment, but in all our cases a repeated CT scan showed residual mediastinal abnormalities.

The length of follow-up at present ranges from 16 months to 6 months. Nine patients have relapsed and of these five have died. The other seven patients are in remission, at times ranging from 30 to 70 weeks (Table 5). One patient (EW) died from a fungal pneumonia after having a complete response to chemotherapy. She did not receive radiotherapy for 9 weeks because of an acute paranoid psychosis. Seven of eight patients who experienced relapse have responded to further chemotherapy with *cis*-platinum and VP16-213. One patient (LS) with very widespread disease at diagnosis did not receive chemotherapy.

Discussion

The use of chemotherapy in a very high dose is based on the premise that the dose-response relationship of the tumour is steep, so that a large increase in dose (approximately ten-fold) will result in greatly increased tumour destruction. As yet there is little clinical evidence to support or refute this idea although responses to very high doses of melphalan have been seen in malignant melanoma, a tumour which is very resistant to this drug in conventional dosage [5]. Cyclophosphamide is a useful agent for studies of this kind, because it is a broadly effective alkylating agent with predictable toxicity. In ovarian cancer, response rates have been improved by increasing doses up to 120 mg/kg [2]. Since the introduction of 2-mercaptoethane sulphonate, dose-limiting urothelial toxicity can be avoided.

Small cell carcinoma of the bronchus is a rapidly fatal disease, which is nevertheless responsive to chemotherapy. Cyclophosphamide in conventional doses causes tumour regression in 30%–40% of patients although complete responses are seldom seen. There has recently been increasing interest in the use of high-dose chemotherapy with autologous support [8] because survival with combination chemotherapy has not been improving in the last 5 years, though a few patients do survive beyond 3 years [6]. The reported studies of high-dose chemotherapy have mostly concerned patients who have failed to achieve remission with other chemotherapy, and multiple drugs have been used in the treatment regimen. Responses have been seen but the full potential of the technique cannot be assessed in this way.

We have therefore used cyclophosphamide alone since the toxicity is predictable and controllable. All our patients were previously untreated and most had limited disease. We have given only one cycle of chemotherapy as treatment of the presumed distant metastases, with radiotherapy to provide additional treatment of the primary tumour. Maintenance chemotherapy was not given, since we wished to discover what long-term results could be achieved with a single cycle of high-dose chemotherapy. The morbidity of repeated cycles of combination chemotherapy is considerable, and one of the possible benefits of high-dose chemotherapy is that it might allow a long period in which the patient is well and receiving no treatment. Seven of nine patients who have relapsed and had subsequent treatment have responded to further chemotherapy. If a single agent is used on one occasion it is probable that good responses to further chemotherapy will be obtained should it prove necessary.

Small cell carcinoma frequently metastasises to bone marrow [4], and it is possible that malignant cells contaminate the infused marrow. The marrow from our patients has been examined very carefully for malignant cells and found in one case only. It is not known, moreover, whether tumour cells would survive after cryopreservation and reinfusion. It is also uncertain whether marrow transfusion is necessary with the dose and schedule of cyclophosphamide employed; because of the age of many of our patients we have not felt justified in dispensing with it at this stage.

This study shows that very high-dose cyclophosphamide can be safely given to patients, many of whom might be regarded as elderly for this form of therapy. The treatment is well tolerated and the complications manageable. It has proved to be compatible with subsequent radiotherapy to the mediastinum without evidence of carditis. Haemorrhagic cystitis has been prevented by the use of 2-mercaptoethane sulphonate.

The results of treatment with a single agent in a high dose have been most encouraging when compared with accepted combination chemotherapy regimens. The response rate is high (81%), and at least 44% of patients have had a complete response as assessed by chest x-ray and bronchoscopy. By comparison, in a parallel study in 268 patients who received cyclic combination chemotherapy a complete response rate of only 12% has been seen after 12 weeks' treatment. These early results therefore encourage us to believe that high-dose chemotherapy may be a valuable addition to the treatment of this disease.

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