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Small cell carcinoma: combined approach to treatment

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ABSTRACT Fifty-six patients with untreated small cell carcinoma of the bronchus were treated with three courses of chemotherapy (cyclophosphamide, vincristine, and procarbazine and methotrexate) and assessed for response. Thirty-one patients (55·4%) were classified as responders; they were given a course of radiotherapy and were then randomly allocated to continued cyclical chemotherapy or no further chemotherapy until relapse. Non-responders to chemotherapy were treated with radiotherapy or palliatively. The median survival was 10·5 months in responders and 6 months in non-responders ($P<0·01$). The one-year survival in responders was 42%. There was no statistical difference in survival between patients treated with continued chemotherapy and those treated at relapse. Sixty-nine per cent of patients experienced no side effects from chemotherapy.

Three indicators of non-response to chemotherapy were identified – exercise tolerance at diagnosis, macroscopic liver metastases, and inappropriate ADH secretion.

Small cell carcinoma of the bronchus is a disseminated disease in most patients at presentation (Selawry, 1974). After reports of response and improved survival using radiotherapy (Miller *et al*, 1969), and chemotherapy (Selawry *et al*, 1974) we have tested whether a combination of chemotherapy and radiotherapy could be used to prolong useful life and whether prognostic factors could be identified.

Methods

Previously untreated patients with histologically confirmed small cell bronchial carcinoma and adequate renal function were included. From October 1975 to October 1977 56 patients (42 male, 14 female) were treated. Their ages ranged from 44 to 74 (mean 61·2). The diagnosis was obtained in 48 cases (85·7%) by fibreoptic bronchoscopy, in five (8·9%) by rigid bronchoscopy, in two (3·6%) at operation, and in one (1·8%) by sputum cytology. At entry into the trial patients' exercise tolerance was assessed, and histology was reviewed by a consultant histopathologist. The proposed treatment, including possible side effects, was discussed with the patient before giving treatment. Investigations after history and full clinical examination included:

(1) Chest radiograph, PA and lateral: mediastinal tomography.
(2) Erythrocyte sedimentation rate and full blood count.
(3) Urea and electrolytes, serum calcium, phosphate, and creatinine estimations.
(4) Standard liver function tests (alkaline phosphatase, gamma glutamyltranspeptidase, aspartate transaminase, lactic dehydrogenase, creatinine phosphokinase, and bilirubin).
(5) Cortisol levels (morning and midnight), paired plasma and urinary osmolalities.
(6) Liver and bone scintiscans, using ^{99m}technecium sulphur colloid.
(7) Bone marrow aspiration and trephine biopsy.

The patients' exercise tolerance was assessed on a scale of 0–4 (0=normal, 1=breathless after two flights of stairs, 2=breathless after one flight of stairs, 3=breathless on the flat, 4=breathless at rest), and level of activity on a modification of the Karnofsky scale (Karnofsky, 1956 (0=normal, 1=ambulant, 2=housebound, 3=bedbound). Information was recorded on proforma sheets for each patient.

Cyclical chemotherapy consisted of courses of cyclophosphamide, 1 g, and vincristine, 1 mg, both intravenously, methotrexate 200 mg (as a 24-hour infusion), and procarbazine 500 mg in two daily doses. Folinic acid was given at the end of the methotrexate infusion. The patients were given antiemetics. All patients received three courses of chemotherapy at three-weekly intervals and were then assessed for response, objectively and subjectively. Toxicity was carefully recorded. Chest radiographs, full blood count, and full biochemical profile were repeated before each course. Levels of $3{\cdot}0\times10^9$/l white cells and 100×10^9/l platelets were taken as adequate for chemotherapy. Radioisotope scans were repeated when indicated.

Patients remained under the care of the referring physician but their management was supervised by the oncologist co-ordinating the study (AG).

Criteria of response were at least a 50% reduction in measurable tumour diameter in two planes, as judged by two observers, with no evidence of differential progression and no evidence of emergence of previously undetected metastases. Responders and non-responders with intrathoracic disease only then received irradiation to the primary tumour, mediastinum, and supraclavicular fossae. A tumour dose of 3500 rads was delivered over four weeks (five times a week fractionation), through two parallel opposed treatment portals using megavoltage apparatus.

Responders were randomly allocated to a group whose chemotherapy continued for six months from diagnosis or until relapse (17 patients, 54·8%) or a group who had no further chemotherapy after irradiation until relapse (14 patients, 45·2%). Non-responders with extensive disease were treated palliatively, including irradiation as indicated.

Patients receiving regular chemotherapy were admitted for two days every three weeks; patients not receiving regular cycles of chemotherapy were assessed on an outpatient basis. Patients included in the trial were followed up until January 1978.

Results

At entry into the trial 33 (58·9%) patients had only intrathoracic disease detected (Eagan *et al*, 1973) while 23 (41·1%) had evidence of extrathoracic involvement. Liver metastases shown by a positive liver scan were seen in eight (14·3%) patients, four (7·1%) had positive bone scans, five (8·9%) had positive bone marrow aspiration, one (1·8%) had skin deposits, and six (10·7%) had evidence of inappropriate antidiuretic hormone secretion as shown by hyponatraemia ($Na^+ < 125$ mmol/l) in the presence of urinary to plasma osmolality ratio of 3 : 1 or greater. No patients had detectable inappropriate corticotrophin secretion, and no patients presented with intracranial tumour at the time of diagnosis.

Thirty-one patients showed objective response to chemotherapy, giving an overall objective response rate of 55·4%. Patients' sex had no influence on response to chemotherapy with 22 (71%) men and nine (29%) women among responders, and 20 (80%) men and five (20%) women among non-responders. Ages ranged from 44 to 73 (mean 60) among responders and 40 to 74 (mean 62·2) for non-responders. The extent of disease and sites affected at the time of diagnosis and their relation to response to chemotherapy are summarised in table 1. The patient's exercise tolerance at the time of diagnosis and its influence between responders and non-responders who performed normally is significant; the difference becomes progressively less with increased grade of disability.

Table 1 *Extent of disease at diagnosis*

	Total		*Responders*		*Non-responders*		P
	No	*%*	*No*	*%*	*No*	*%*	
Limited	33	58·9	21	67·7	12	48·0	NS
Extensive	23	41·9	10	32·3	13	52·0	
Liver	8	14·3	2	6·5	6	24·0	<0·05
Bone	4	7·1	2	6·5	2	8 0	
Bone marrow	6	10·7	3	9·7	3	12·0	NS
Paraneoplastic	6	10·7	1	3·2	5	20·0	<0·05

Table 2 *Exercise performance at diagnosis*

Performance	*Total*		*Responders*		*Non-responders*		P
	No	*%*	*No*	*%*	*No*	*%*	
Normal	37	66·1	25	80 6	12	48·0	<0·01
Ambulant	6	10·7	2	6·5	4	16·0	<0·05
House bound	10	17 9	2	6 5	8	32 0	NS
Bed bound	3	5 4	2	6 5	1	4 0	NS

The survival rates as an actuarial survival, calculated by the life table method, of the total group, responders and non-responders, are shown (fig 1). Median survival of the whole group was eight months compared to six months in non-responders treated with radiotherapy and 10·5 months in the group of 31 responders. One-year survival was 42% for responders as compared to 4% for non-responders ($P<0{\cdot}05$). Of the 31 responders, 21 died during the time of our follow-up, six have survived for less, and four for more, than one year. Of the non-responders, only two are

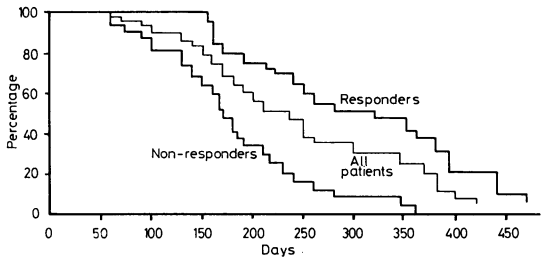

Fig 1 *Survival by actuarial analysis.*

alive at 60 and 170 days respectively. The mean ±SE and median survivals of subgroups of responders and non-responders are summarised (fig 2). There was a significant difference in survival between responders and non-responders with localised disease ($P<0.05$) and with extrathoracic disease ($P<0.01$). No statistical difference was observed in survival rates of responders who continued chemotherapy compared to those treated only on relapse. Of the 31 patients who responded, 18 patients (58·19%) relapsed, 50% of these at two or more sites (table 3). Seven patients relapsed in the site of original disease, two in the liver, and five in the lung. The favoured site for metastases was the brain (seven) and liver (six). The mean time interval between the development of metastases and the end of treatment was 95 days for brain and 102 days for liver. Of the 13 responders who did not relapse, 11 are alive at the time of writing and two died from conditions unrelated to their bronchial carcinoma. Once relapse occurred, prognosis was poor despite further treatment. Sixteen patients (89%) died within 70 days of relapse; two patients survived 180 days and 251 days.

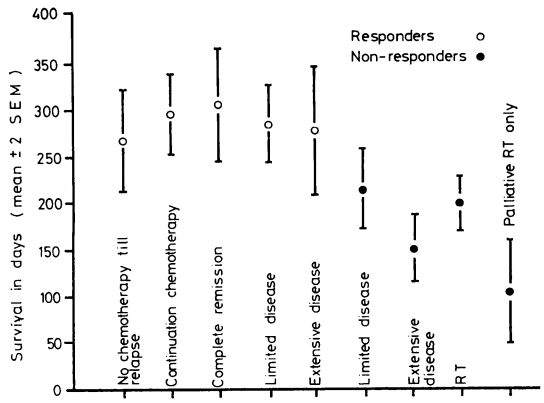

Fig 2 *Survivals of subgroups of responders and non-responders.*

Table 3 *Relapses*

Major site of disease	*Relapse site*	*No*	*% Patients*	*Mean time end of treatment to relapse (days)*	*Mean time relapse to death (days)*
Responders	Lung	7	22·6		
	Non-irradiated site	(2)	(6·4)	On treatment	72
	Irradiated site	(5)	(16·1)	47	76
	Brain	7	22·6	95	26
	Liver	6	19·3	102	25
	Bone	4	10·9	128	17
	Skin	1	3·2	4	70
	Lymph node	1	3·2	98	18
	None	13	41·9	—	—
Non-responders	Brain	4	16		
	Liver	8	32		
	Bone	3	12		
	Skin	1	4		
	Lymph node	4	16		
	None	3	12		

The side effects of chemotherapy are summarised in table 4. The early side effects are those observed during the initial trial of chemotherapy; 69% had no side effects while 12·5% had nausea and vomiting, the commonest side effect. On long-term chemotherapy the most troublesome side effects were nausea and vomiting that in three patients necessitated discontinuation of treatment. Two patients developed depression and refused further chemotherapy. One patient developed paraesthesiae after a total dose of 6 mg vincristine.

Table 4 *Side effects during the study*

Nature	*Total*		*Responders*		*Non-responders*	
	No	(%)	*No*	(%)	*No*	(%)
Early						
Nausea, vomiting, weight loss	7	(12·5)	3	(9·7)	4	(16·0)
Depression, malaise	3	(5·4)	2	(6·5)	1	(4·0)
Chemical conjunctivitis	5	(8·9)	4	(12·9)	1	(4·0)
Marrow toxicity	1	(1·8)	0	(0·0)	1	(4·0)
None	39	(69·6)	21	(67·7)	18	(72·0)
Late						
Nausea, vomiting, weight loss	7	(22·6)	7	(22·6)		
Depression, malaise	—	(0·0)	—	(0·0)		
Chemical conjunctivitis	2	(6·5)	2	(6·5)		
Marrow toxicity	5	(16·1)	5	(16·1)		
Infections	1	(3·2)	1	(3·2)		
Neurotoxicity	1	(3·2)	1	(3·2)		
None	11	(35·5)	11	(35·5)		

Of the patients who were on long-term chemotherapy, 47% had no complications. Partial alopecia was well accepted, and wigs were provided routinely.

Discussion

We have confirmed that responders to chemotherapy in terms of reduction in tumour size also survive significantly longer than non-responders (Eagan *et al*, 1973). COMP was used as our chemotherapy combination for the following reasons. Cyclophosphamide and methotrexate have reported activity when used singly (Selawry *et al*, 1974). Procarbazine has not been adequately tested on bronchial carcinoma (Selawry, 1974), and vincristine has been chosen for its reported synchronising action in combinations (DeVita and Schein, 1973). The drugs were given over 24 hours every three weeks to minimise haematological toxicity (Hill and Baserga, 1975). While addition of 1-chloroethyl-3-cyclohexyl-1-nitrosurea (CCNU) or adriamycin might have given a higher response rate (Livingstone *et al*, 1976), the much higher toxicity associated with their administration was in our view not acceptable for this type of study.

We chose to give three courses of chemotherapy initially to allow us to assess individual response early, as we felt that even relatively non-toxic chemotherapy should not be given when it has no demonstrable activity. Moreover, reduction of tumour mass may make subsequent radiotherapy more effective (Fletcher and Shukovsky, 1975). From a previous study the postponement of radiotherapy had no deleterious effect on survival (Gilby *et al*, 1977).

Two prognostic indicators of future non-response to chemotherapy were the presence of hepatic involvement and inappropriate ADH secretion. Of the eight patients who had positive liver scan at diagnosis, six (75%) were among the non-responders ($P<0.05$). Five out of six patients with demonstrably inappropriate ADH secretion failed to respond to chemotherapy ($P<0.05$). Bone marrow involvement at diagnosis carried no adverse prognostic significance and was not associated with increased haematological toxicity.

The correlation of exercise tolerance at diagnosis with survival is well known (Johnson *et al*, 1976). Its influence on objective response to chemotherapy is a new finding needing explanation. Of the responders, 80% were leading a normal life at the time of presentation as compared to 48% of non-responders ($P<0.01$). This cannot be explained by better tolerance of chemotherapy, as all patients received three courses and major toxicity was minimal and comparable in both groups. Patients' clinical state may reflect the true extent of the disease more accurately than available methods of detection.

Response to chemotherapy may be a marker selecting a group with better prognosis. This may be due to biological and behavioural differences of the tumours, so far unidentified in descriptive classifications based on tissue morphology. Support comes from the low response rate and poor survival in patients with demonstrably inappropriate ADH secretion. When designing new trials, these factors, unless taken into account, may influence the outcome of the study and invalidate results obtained.

The median survival of the whole group, eight months, compares favourably with other studies using radiotherapy and chemotherapy alone (Eagan *et al*, 1973; Hansen *et al*, 1971). The ability to assess individual response to chemotherapy made differential evaluation of survival results possible and confirms previous suspicions that benefit can be obtained only in patients showing definite response in measurable tumour mass. The median survival of responders was 10·5 months as compared to 5·8 months in non-responders treated with radiotherapy alone. This is also reflected in the one-year survival of 42% in responders, 4% in non-responders, and 36% in the group as a whole ($P<0.05$). We do not know whether effective chemotherapy prolongs survival or simply selects a group of patients with favourable prognosis, but the ability to identify prognostic factors justified, in our view, this type of study. Responders randomly allocated to continuation of chemotherapy survived longer than the group in which chemotherapy was withheld until relapse, although the difference did not reach statistical significance. Once relapse occurred, remission was not obtained despite the prompt administration of drugs to which the tumour had been sensitive at presentation. This is reflected in the shorter median survival (8·1 months) and in the short interval between relapse and death. We would recommend that once response to a particular chemotherapy combination is established in an individual patient, prolonged maintenance should be given, despite there being no clinical evidence of disease. The optimal length of treatment for this tumour is not known and will be the subject of a further study.

At the time of writing 58% of the responders had relapsed, but only two (6·4%) were receiving chemotherapy at the time of relapse. In both patients tumour recurred in the non-irradiated lung (CR) suggesting that in the presence of response to chemotherapy, local irradiation may increase effective control. Five (16·1%) tumours recurred in previously irradiated lung, all in

patients off chemotherapy at the time. Chemotherapy can help to control residual disease not sterilised by radiotherapy. Extent of disease at diagnosis and complete remission after three courses of chemotherapy did not influence survival in responders.

Non-responders with limited disease survived longer than those with extrathoracic involvement ($P<0.05$). This is due to the small survival gain achieved by radiotherapy in patients with thoracic disease only (Miller *et al*, 1969). (The median survival of 2·8 months in the four non-responders who received palliative treatment only would not have been improved by radiotherapy as they all had massive extrathoracic disease.)

Small cell carcinoma has a well-documented propensity (Johnson *et al*, 1976) to metastasise to the brain, and 22·6% of responders developed metastases in this protected site. Despite this, we would not advocate prophylactic whole brain irradiation routinely as resulting toxicity may jeopardise chemotherapy and irradiation necessary for control of the systemic disease (Johnson *et al*, 1976). In patients with good and prolonged response, however, its use may further increase disease-free survival by reducing the incidence of relapse at this site. This will be examined in a further study.

Complications of chemotherapy were rare; the first three courses, which tested tumour sensitivity, were tolerated without any complications in 70% of cases, irrespective of their tumour response. In the patients with side effects, nausea, vomiting, and anorexia were commonest (12·5%). This was slightly more common in non-responders (16%) than responders (9·7%). Chemical conjunctivitis associated with high dose methotrexate infusion occurred in 9% of cases. This was never severe and subsided spontaneously over 24 hours when folinic acid was given. Marrow toxicity as judged by failure of the peripheral blood count to return to levels of $3{\cdot}0\times10^9$ leucocytes and 100×10^9 platelets three weeks after a preceeding course occurred in one patient only in this trial period and in five patients receiving maintenance chemotherapy (16%). In no case was this life-threatening, and in only one case was the resulting neutropenia associated with respiratory infection. In the responder group receiving maintenance chemotherapy, the incidence of nausea and vomiting was 22·6%. Vincristine neurotoxicity with paraesthesiae occurred in one patient only, after a total dose of 6 mg. Possibly in this older population the small dose (1 mg) of vincristine chosen accounted for this low incidence.

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