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Therapy for Small Cell Lung Cancer Using Carboplatin, Ifosfamide, Etoposide (Without Dose Reduction), Mid-cycle Vincristine with Thoracic and Cranial Irradiation

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The aim of this study was to assess the efficacy and toxicity of intensive chemotherapy, administered without dose reduction, with cranial and thoracic radiotherapy given when possible as a single fraction in small cell lung cancer. 87 patients were eligible on the basis of good performance status, normal or near normal biochemistry and clinical staging, 73 limited and 14 extensive stage, computed tomography scanning was not mandatory. Six cycles of carboplatin, ifosfamide and etoposide with vincristine on day 15 at 4 weekly intervals were planned. Dosages were not reduced in response to myelosuppression. Prophylactic cranial irradiation (PCI) as a single fraction after the first cycle and thoracic irradiation (when possible as a single fraction) following the third cycle were delivered. Seventy-two per cent of patients completed the protocol. Complete response rate was 55% and 26% of patients had a partial response. The median nadirs of neutropenia were 0.5 × 10^9/l and thrombocytopenia 14 × 10^9/l, with 6% probable treatment-related deaths. Performance status and dyspnoea improved markedly to normal or near normal levels following the second course. Brain metastases occurred in 13% of patients. The median survival was 16.2 months with a 2-year survival of 31% (95% confidence interval, 24–41%) for a minimum follow-up of 26 months. These results compare favourably with other combined modality studies, using multiple radiotherapy fractions with cisplatin-based combinations and dosage reduction for patients staged in more anatomical detail. The toxicity spectrum and efficacy data could lead to the use of this chemotherapy regimen with haematopoietic growth factors and, in the future, peripheral blood progenitor cell rescue.

Key words: small cell lung cancer, VICE chemotherapy, dose intensity, single fraction radiotherapy
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INTRODUCTION

CARBOPLATIN, IFOSFAMIDE and etoposide are known to be among the most active agents available for small cell lung cancer (SCLC), and the combination of carboplatin, ifosfamide and etoposide with mid-cycle vincristine (to prevent relapse between cycles of treatment) with thoracic radiotherapy has been reported [1]. Six cycles of treatment at monthly intervals were planned and thoracic radiotherapy, usually as a single fraction, was given 4 weeks after the last cycle of chemotherapy. Furthermore, in this and the subsequent platinum combination study, protocol doses were administered without dose reduction, although dose delay was allowed for recovery [1, 2]. The response rate for limited stage (LS) disease patients, although not all patients were intensively staged with computed tomography (CT) scans etc., was 79%, median survival was 14 months with a 2-year survival of 33% for a minimum follow-up of 24 months on an updated analysis. Myelosuppression was severe, however, with a median nadir of neutropenia of 0.2 × 10^9/l [1]. A similar study with ifosfamide, carboplatin and etoposide was conducted at the Royal Marsden Hospital (London, U.K.) [3]. The carboplatin dose was higher, 400 mg/m^2, with hyperfractionated concurrent thoracic radiotherapy. The initial response rate for 18 LS patients was an impressive 94% (complete response, CR, 72%) and median survival was 19 months, but the predicted 2-year survival was disappointingly only 24%. Haematological toxicity was again severe, and the lower 2-year survival could have been related to the institute's policy of reducing doses (72% of patients) during treatment due to myelosuppression [3].

In an attempt to diminish myelosuppression, our group conducted a further study using a similar regimen, but alternating cisplatin with carboplatin on successive cycles [2]. In addition, a single fraction of prophylactic cranial irradiation

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(PCI) after the first cycle of chemotherapy, and a single fraction of thoracic radiotherapy after the third cycle of chemotherapy were given in the majority of patients [2]. Response rates and survival were comparable to the earlier study [1, 2]. Surprisingly, myelosuppression was not markedly reduced. Indeed, neutropenic-related deaths were higher (10%) in the cisplatin regimen than in the more myelosuppressive (7%) carboplatin combination [1, 2]. However, PCI did reduce the incidence of brain metastases compared with the first study when it was not included [1, 2].

Therefore, in the present investigation, carboplatin was used throughout the protocol with etoposide, ifosfamide, mid-cycle vincristine and concurrent radiotherapy in an attempt to improve response rates and survival, with a more favourable side-effect profile. In keeping with previous studies, no dose reductions were undertaken, but treatments were deferred if myelosuppression so demanded. The PCI was given directly after the first cycle of chemotherapy as a single fraction, when the tumour burden was likely to be smallest and before toxicity from intensive chemotherapy developed. The use of single fraction thoracic irradiation and PCI has been described previously [1, 2, 4]. Patients who have received a single PCI fraction, as described in the present study, appear to have less long-term cognitive impairment than patients receiving multiple fractions [5]. Thoracic radiotherapy was given directly after the third cycle of chemotherapy, when the large majority of patients should have responded [1].

PATIENTS AND METHODS

A total of 87 previously untreated patients entered the prospective study between June 1988 and January 1991. There were 33 females and 54 males. Median age for the group was 56 years. Clinical details are summarized in Table 1.

All the patients had histologically proven small cell lung cancer. Tumour material was obtained by bronchoscopic biopsy in 65 patients (75%) and at thoracotomy in 13 patients (15%). 73 patients had LS disease, defined by clinical evaluation, radiology and diagnostic intervention as tumour confined to one hemithorax, the mediastinum and ipsilateral supraclavicular lymph nodes or ipsilateral pleural effusion. The remaining 14 patients, all with extensive stage (ES) disease, were considered to have a good prognosis as defined by the Manchester prognostic score, i.e. Karnofsky performance ≥60 and normal biochemistry [6]. 13 of the 14 patients with ES disease had one site of metastatic disease and 1 patient had two sites (Table 1).

Table 1. Pretreatment clinical features of the 87 patients

	LS (n=73)	ES (n=14)
Interval from symptoms to diagnosis		
<1–3 months	48	9
3–6 months	20	3
>6 months	5	1
NK	—	1
Interval from diagnosis to treatment		
<1 month	51	10
1–2 months	21	4
>2 months	1	—
Weight loss (>5%)	33	8
Superior vena caval obstruction	9	3
Stridor	3	3
Lymphadenopathy		
Hilar	49	9
Mediastinal	35	7
Ipsilateral SCF	5	4
Contralateral/SCF*	—	1
Axillary*	—	3
Retroperitoneal*	—	1
Para aortic*	—	1
Ipsilateral pleural effusion	11	5
Contralateral lung tumour/effusion*		1
Liver*		3
Bone*		4
Bone marrow*		1
Elevated enzymes		
Alkaline phosphatase	13	—
Lactate dehydrogenase	20	—
ALT/GGT	18	—
Karnofsky performance		
Median	80	80
Range	(70–100)	(60–90)

NK, not known; LS, limited stage; ES, extensive stage; SCF, supraclavicular fossa; ALT, alanine transaminase; GGT, gamma glutamyl transaminase. * Sites of metastatic disease which define the 14 ES patients (1 patient had two sites of metastatic disease).

Investigations before and during treatment

Before treatment, patients with clinical and or haematological and biochemical abnormalities suggestive of metastatic disease, e.g. leucopenia, thrombocytopenia, elevated liver transaminases, alkaline phosphatase, lactate dehydrogenase, were investigated further with a bone marrow examination and appropriate radionuclide, ultrasound and CT scans. However, CT and other scans were not performed on patients, if there were no clinical or biochemical indications, a policy consistent with the unit's other studies [1, 2]. The extra information derived from radiological scans, above those of the other important prognostic factors, e.g. performance status, biochemical parameters, simple anatomical staging, has not been shown to have a major advantage in separating patients into different prognostic groups [6–8].

Patients with metastatic disease were entered into the study provided no other adverse prognostic factors, i.e. low sodium, Karnofsky performance <60, elevated alkaline phosphatase or lactate dehydrogenase, were present [6]. Before each cycle of treatment, patients had a complete clinical examination with chest radiology, full blood count, routine serum biochemistry including hepatic enzymes and creatine clearance. Karnofsky performance status and respiratory scores were evaluated as in previous studies [1, 2]. Repeat bronchoscopy also was requested 4–6 weeks after completion of therapy.

Treatment regimens

The planned full course of treatment comprised a single fraction of prophylactic cranial irradiation and thoracic irradiation, when possible as one fraction, with a maximum of six cycles of combination chemotherapy.

Carboplatin 300 mg/m^2 in 500 ml of normal saline (N/S) was given intravenously (i.v.) over 1 h on day 1. Etoposide 120 mg/m^2 was given i.v. on days 1 and 2, and 240 mg/m^2 orally on day 3. Ifosfamide 5 mg/m^2 with the same dose of mesna mixed in 2 l of N/S was administered as a 24-h i.v. infusion, beginning on day 1. Additional mesna 3 g/m^2 in 1 l of N/S was given i.v. over the subsequent 12 h. Treatment cycles were repeated when possible at 4-weekly intervals. Vincristine 1.0 mg i.v. was given on day 15 of each cycle. Metroclopramide i.v. boluses (maximum

of six) over the first 36 h and then orally for the next 2–3 days were the main anti-emetic, but when necessary, additional cyclizine was given as required during i.v. chemotherapy. A policy of no dose reduction was followed, but if necessary, treatment was deferred on a weekly basis until the WBC count was $\geq 3 \times 10^9$/l and the platelet count was $\geq 100 \times 10^9$/l. Prophylactic co-trimoxazole (960 mg) was given twice daily by mouth for the duration of treatment. Patients were seen at the hospital on a weekly basis to check the blood count and for assessment of toxicity according to World Health Organization (WHO) criteria.

On day 5 of the first cycle of chemotherapy, prophylactic cranial irradiation was given by opposing lateral fields in one fraction of 8 Gy. Following the third cycle of chemotherapy, again on day 5, thoracic radiotherapy was given. The post-chemotherapy volume was irradiated with a margin of 2 cm around any residual disease. The mediastinum and supraclavicular fossa were always included if bulk disease was present initially. The supraclavicular fossa received a single fraction of 12.5 Gy using a single field matched to the thoracic field when appropriate. In brief, two methods were used: (1) 33 patients received a single fraction when technically feasible of 12.5 Gy using a 360° rotation technique to exclude the spinal cord from the high-dose volume. (2) 50 patients received 27.5 Gy midline dose in eight fractions over 10 days using a parallel opposed pair. 4 patients did not receive thoracic radiotherapy because of early death or withdrawal from the study due to progressive disease.

Follow-up

Final assessment for response including plain radiography, biochemistry, bronchoscopy and appropriate scans (repeating initially abnormal scans or performing scans if indicated by clinical or laboratory parameters) was undertaken at first follow-up (4–6 weeks) after the end of treatment and determined by standard WHO criteria. Thereafter, patients were seen at monthly intervals for 4 months, at 3-month intervals for a year and then at 6-month intervals. At each attendance, patients had a full clinical examination, a chest radiograph, routine haematology and serum biochemistry. Brain and other scans were only performed in the follow-up period on clinical suspicion of metastatic disease.

RESULTS

Response and survival

A total of 85 previously untreated patients with SCLC were assessed for response and toxicity. An additional 2 patients, who had a pneumonectomy before chemotherapy, were not evaluable for response but had lymphatic infiltration and were assessed for survival and toxicity. 48 patients (55%; 95% confidence interval, CI, 44–66%) of assessable patients were identified as in complete response (CR) 1 month after the end of treatment (Table 2). 23 patients (26%; CI 18–37%) had a partial response (PR). A further 14 patients (16%) had no response to treatment. Forty-five per cent of all complete responses occurred with the first cycle of chemotherapy, 43% with the second cycle and 6% with the third. 40 of the 48 patients in clinical and radiological CR agreed to be rebronchoscoped, and, in all cases, there was no evidence of tumour. The median duration of CR was 16.0 months (range 5–52.5+) and was not significantly different ($P>0.05$ log rank χ^2 analysis) for patients with limited stage disease (16.5 months) when compared to those with extensive stage disease (12.8 months). The median duration of PR was 9.4 months (range 1.6–28.8), and again was not significantly different for patients with limited stage disease (9.4 months) or extensive stage disease (10.0 months).

Table 2. Response, relapse, progression status and stage

	NE		NR		PR		CR	
	LS	ES	LS	ES	LS	ES	LS	ES
Patient numbers	1	1	11	3	17	6	44	4
Alive								
No relapse/ progression	—	—	—	—	—	—	13	1
Relapse/ progression	—	—	—	—	—	—	1	—
Dead								
Not of lung carcinoma	—	—	1	—	3	1	4	—
Of lung carcinoma	1	1	6	2	14	5	26	3
Treatment-related death	—	—	4	1	—	—	—	—

LS, limited stage; ES, extensive stage; NR, no response or progression; PR, partial response; CR, complete response; NE, non evaluable (2 patients who had a pneumonectomy prior to treatment and no evaluable disease).

The median survival of all 87 patients was 16.2 months (range 1.6–52.5+; Figure 1), with an actual 2-year survival of 31% (95% CI, 24–41%). The median follow-up of those still alive is 44 months. The median survival of the 73 LS patients was 16.6 months (range 1.6–52.5+), and the actual 2-year survival was 31.5% (95% CI, 22–42%). The median survival of the 14 ES patients was 13.4 months (range 2.4–39.6+), and the actual 2-year survival was 21.4% (95% CI, 4–42%). Median survival for the 48 CR was 23.8 months (range 10–52.5+), and the 2-year

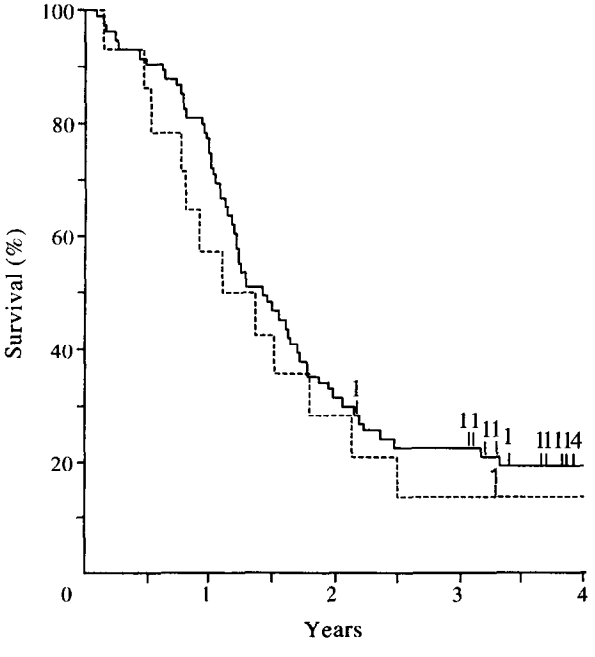

Figure 1. Survival of limited stage patients (——, $n=73$) and extensive stage patients (----, $n=14$).

survival was 48% (95% CI, 39–59%). The median survival of the 23 PR was 13.2 months (range 1.6–26.2). Of the 26 patients alive at 2 years, 23 were originally LS and 3 ES. 9 patients died of causes other than SCLC or treatment-related toxicity (Table 2). One patient with a history of three previously myocardial infarctions (MI) died at home with a suspected further MI after the third cycle of chemotherapy. 2 of the 4 CR patients died from other malignancies which were not evident at the start of chemotherapy for SCLC: 1 with breast carcinoma and 1 with renal carcinoma, at 12 and 14 months, respectively. 2 other patients died of a cerebrovascular accident and from a myelodysplastic syndrome. The 4 PR patients died suddenly at home, 2 probably with cerebrovascular accidents and the other 2 from suspected myocardial infarcts.

Relapse

49 of the 71 patients who responded to treatment subsequently progressed or relapsed (Table 2). Of the 48 patients who had a CR, 4 relapsed locally only, 7 had a combination of local and distant relapse, and 19 relapsed at distant sites only. Of the latter two groups, 17 patients relapsed at one distant site only, 8 patients relapsed at two sites and 1 at three sites. Of the 23 patients who had a PR, 6 patients progressed locally, 11 progressed both locally and distantly and 2 patients relapsed at distant sites only. There was no significant difference ($P=0.34$) for thoracic relapse between patients treated with a single or multiple fractions. For those complete responders who relapsed locally, the minimum time to relapse was 5.5 months, and the maximum 54 months, with a median of 49.6 months. For those patients who developed brain relapse after CR, the minimum time to relapse was 10.8 months, and the maximum 53.5 months. Of the 6 patients in complete remission who subsequently relapsed at a single distant site only with no local relapse, 3 relapsed in the brain, 2 in the liver and 1 in soft tissue.

Toxicity

The marked neutropenia, with a median of 0.5×10^9/l, occurred usually 2 weeks after chemotherapy (Table 3). Maximum WBC toxicity occurred in 83% of patients and 76% of patients required hospitalisation and intravenous antibiotics for the management of neutropenic associated infections. There was also marked thrombocytopenia, with a median of 14×10^9/l, again occurring usually 2 weeks after chemotherapy, with maximum platelet toxicity occurring in 77% of patients who required platelet transfusion. Maximum haemaglobin toxicity occurred in only 12 patients, however, 82 patients were given a total of 778 units of blood on 244 occasions. 5 patients (6%) had treatment-related deaths, 3 due to neutropenic associated infection and 2 due to thrombocytopenic associated bleeding. 4 of these patients had LS with a Karnofsky performance ≥70 and were aged between 53 and 65 years. 54 patients developed mild renal toxicity, 47 patients had moderate toxicity and a further 7 patients had severe toxicity. Mild to moderate nausea and vomiting complicated the treatment of 59 patients (366 cycles of treatment) and was severe in a further 23 patients on 44 cycles, but $5HT_3$ antagonists were not routinely available. Oesophagitis occurred in 14 patients after radiotherapy. One patient had transient pneumonitis after radiotherapy, and 30 patients (34%) had radiographic evidence of lung fibrosis when assessed at the end of treatment.

Table 3. Maximum haematological toxicity

Haematological toxicity (WHO grade)	Haemoglobin		WBC		Platelets	
	n	%	*n*	%	*n*	%
0	2	2	—	—	1	1
1	1	1	—	—	—	—
2	20	23	—	—	2	2
3	52	60	12	14	15	17
4	12	14	72	83	67	77
Treatment deaths	—	—	3	3	2	2

n and % indicate number and percentage, respectively, of total patient groups.

Despite the toxicity of the treatment regimens, there was a clear overall improvement in Karnofsky performance with treatment, 57 patients (66%) had values of 80–100 pretreatment compared with 70 patients (80%) post-treatment. Only 32 patients (37%) had a respiratory score of 1 or 2 pretreatment, i.e. no or minimal dyspnoea, compared with 67 patients (77%) post-treatment.

Treatment delays and extra hospitalisation

All chemotherapy treatments were given at full dose. A total of 461 (88%) of the planned maximum 522 cycles of chemotherapy were administered. 63 patients (72%) received all six cycles of chemotherapy, 4 patients had five cycles, and 8 patients had four cycles. The remaining 12 patients (14%) received either one, two or three cycles of treatment. Three hundred and forty-six cycles of chemotherapy (75%) were administered on time according to protocol. Seventy cycles (15%) were delayed by 1 week, 31 cycles (7%) by 2 weeks and the remaining 14 cycles were delayed by 3 weeks or more.

The extra days in hospital required for support with i.v. antibiotics and transfusions was a median of 14 days for those patients who survived less than 2 years, and a median of 10 days for those who survived more than 2 years. The extra hospitalisation as a percentage of the total survival was a median of 3.3% for those surviving less than 2 years and 1% for those surviving more than 2 years.

DISCUSSION

Only a few studies have reported 2-year or more survival after the commonly used cisplatin/etoposide (PE) combination. Survival rates have varied from 16 to 28% in patients with limited stage disease, who had been routinely scanned [9–11]. When PE was reviewed as first-line therapy, the objective response rate was 88% in a total of 208 patients, but some degree of renal dysfunction was reported in half of the patients [12]. It was also observed that thrombocytopenia occurred in 40% of patients, although none needed platelet transfusions. Furthermore, 19% of patients required dosage reduction because of myelosuppression, and in 23%, a delay in treatment occurred because of low neutrophil counts [12]. Attempts at increasing the effectiveness of the PE combination with high-dose cyclophosphamide did not improve results. Indeed, cyclophosphamide intensification was not possible in 63% of the patients due to toxicity of the cisplatin induction regimen, and the 2-year survival rate was only 20% [13, 14]. Against this backdrop, it is difficult to see how the efficacy of the cisplatin and etoposide combination can be substantially enhanced.

Combination chemotherapy employing carboplatin, ifosfamide and etoposide with mid-course vincristine, given the high single-agent activities of the constituent agents, was therefore attractive. The current large study explored the possibility of

giving early radiotherapy, both prophylactic cranial irradiation and thoracic radiotherapy, with the carboplatin combination regimen extending over six courses. In the first two studies, CT and isotope scans were not routinely requested, unlike other studies with cisplatin, in which 2-year survival rates in fully staged LS patients of up 28% have been quoted [9–11]. It is, therefore, unlikely that the results are better than other studies because of stage shifting. Indeed, detailed anatomical staging with scanning, etc. has been shown in multivariate analyses not to be important in separating patients into different prognostic groups providing other prognostic factors, such as performance status and biochemical abnormalities, are taken into account. This pragmatic approach commends itself to general oncological practice, and the results described in the current paper are likely to reflect such general practice more closely than the results described in phase II studies with a strict anatomical staging and other entry criteria. Patients, despite extensive stage disease, could benefit from additional radiotherapy providing there were no other adverse factors [15]. As the eligibility and entry criteria of the consecutive Manchester studies have been identical, the 31% 2-year survival rate can be tentatively compared with a similar group of patients, balanced for the same prognostic factors and given ifosfamide, etoposide only, in which the 2-year survival rate, with the same follow-up, was 22% [16, 17]. Two-year survival figures have been quoted to aid comparison with previous studies. The current study had an extended minimum follow-up of 44 months in patients and survival curves can also be inspected in Figure 1 to assess actuarial comparison with other studies with shorter follow-up.

Other than the relaxed staging criteria, another difference from many other studies is the policy of no dose reduction, but dose delay to allow recovery from toxicity. In comparison with the ifosfamide, carboplatin and etoposide combination reported by the Royal Marsden Hospital [3], the relative dose intensities have been considerably higher with the policy of no dose reduction in the current study. The median value was 1 (range 0.71–1) over the first three courses of treatment compared with 0.92 (range 0.45–1.03) at the Royal Marsden Hospital [3]. For the latter three courses, the median value was 0.86 (range of 0.57–1.0) compared with 0.66 (range 0.28–1.03) [3]. The policy of no dose reduction in the current study does enable the dose intensity to be increased compared to a protocol where both dose reduction and dose delay are followed.

Despite the fact that dose reduction was not undertaken, treatment-related death rate, due to neutropenia, was 3.5% compared with the previous two platinum studies of 10 and 7% in similar patient populations, and 6% in the London study [1–3]. Thrombocytopenia again was a significant problem with two deaths from this complication. However, the total treatment-related death rate of 6% was still considerably lower than that of the previous regimen (15%) with the same radiotherapy, but in which cisplatin was alternated with carboplatin [2]. The 6% death rate also reflects the careful monitoring of this group of patients, with more accurate and detailed data being available than perhaps in some other studies. In conventional platinum–etoposide combination studies, treatment-related deaths have been reported to be of the order of 4% [11, 18]. In studies which could be considered as exploring intensive regimens, like the current study, death from toxicity has varied between 6 and 10%, [14, 19, 20], although substantial toxicity occurred in the British trial of alternating chemotherapy and radiotherapy, in which 4/24 patients died of probable treatment-related deaths [21]. In all these studies, good performance status patients with carefully defined limited stage disease were treated. One reason for the relatively low treatment-related death rate in our study was the very close monitoring on a weekly basis, and the worst blood count was taken for reporting. This monitoring, of course, not only highlighted the myelosuppression, but also contributed to an increased use of "prophylactic" transfusions and i.v. antibiotics dictated by the pancytopenia. The requirement for intravenous antibiotics and blood products for support was considerable, although this did not have a major impact on the total hospitalisation time of the patients. Indeed, for the total patient group, this represented only 2.1% of the overall number of extra days in hospital because of three factors: the good median, 2-year survival, intravenous antibiotics and transfusions were often given during the same hospital admission, and rapid recovery occurred in the blood counts. The previous alternating cisplatin, carboplatin study and other cisplatin studies have been associated with considerably more renal toxicity [2, 12]. Furthermore, in the current study, more patients received all six cycles, and fewer cycles were delayed than with the previous cisplatin, carboplatin alternating study [2]. It is noteworthy that despite the haematological toxicity, substantial early increases in performance status and reduction in dyspnoea still occurred in the majority of patients, and improvement was maintained throughout and after treatment.

In a recent review of consecutive South West Oncology Group (SWOG) studies, the 2-year or more actuarial survival rate in limited disease, defined by careful staging criteria, increased from 21% with non-platinum-containing regimens to 43% with platinum/etoposide [13, 18]. The SWOG study, reported by McCracken and associates, used multiple conventional fractions of radiotherapy in patients intensively investigated with CT scans, etc. [18]. For this group, the complete response rate was 56%, which is very similar to our own. The authors considered this to be possibly under-representative because of radiation changes seen on chest X-ray. In this study, it would appear that dose reduction was not routinely practiced and the radiotherapy was given concurrently and early [18]. The present study describes the use of single large fractions of radiotherapy both for PCI and for thoracic irradiation. To date, we have seen no obvious neurological deficit from the PCI and formal psychometric testing has been undertaken in all 2-year survivors from this and other centres' studies [5]. Certainly, single-fraction PCI reduced the incidence of cerebral metastases and appears to be associated with fewer long-term sequelae [5]. With PCI, the cerebral relapse rate for all CR patients was 13% in the present study, the updated value without PCI being 45% for the same risk period in a study when no PCI was given [1]. In the second study, using alternating cisplatin and carboplatin, in which PCI was given, the brain relapse rate was 20% in CR patients [2]. However, there is relatively poor control of intrathoracic disease, with local recurrence still occurring in 42% of the complete responder group. In the recent study from SWOG with impressive but actuarial survival figures, the recurrence rate in the ipsilateral hemithorax as the initial site of failure was 14% in all responding patients. However, the overall recurrence rate in complete responders was probably similar to the current study, although the rate was not clearly quoted [18].

The 2-year survival figures of 31.5% in apparently LS patients, who had not been submitted to intensive staging procedures, compares with more modern approaches of alternating modality therapy and hyperfractionated radiotherapy with chemotherapy. The latter studies have been performed in very carefully staged patients of normal or near normal performance status [19–22].

Despite these patient characteristics, alternating radiotherapy and chemotherapy at full protocol could not be given in a recent British MRC Working Party Lung Study because of toxicity [21]. By altering the fractionation of thoracic radiotherapy, the local control rates may be improved, and the use of haemopoietic growth factors could reduce the toxicity and possibly allow more dose intensive regimens [19, 20, 22, 23]. However, the use of granulocyte (G) or granulocyte–macrophage colony-stimulating factor (GM-CSF) alone is unlikely to produce major advantages in this context due to thrombocytopenia, anaemia and other non-myelosuppressive toxicities [23]. The ICE type regimen reported in this present study is particularly attractive for investigating haemopoietic growth factor support and chemotherapy intensification, given that the major dose-limiting toxicity to the exclusion of any other side effects is predominantly myelosuppression. Harvesting circulating progenitor cells following ICE combination chemotherapy may well enable considerable reduction in the interval between treatments, thereby achieving dose intensification with reduction in toxicity. The avenue is being actively pursued, based on the data presented in this report, with peripheral blood stem cell rescue and ICE chemotherapy given on a 2-weekly basis.

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