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Intensive chemotherapy with autologous bone marrow transplantation for small-cell lung cancer*

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Summary. Since 1980, 75 patients with small-cell lung cancer (SCLC) have been entered into four consecutive studies of high-dose chemotherapy using autologous bone marrow transplantation (ABMT) to assist haematological recovery. In the first study, 25 patients were treated with cyclophosphamide (160–200 mg/kg) as the sole chemotherapy; in the second (26 patients), the cycle of high-dose cyclophosphamide (with or without 800–1,200 mg/m^2 etoposide) was repeated as induction treatment. In the first study, response was high [14 complete responses (CR), 7 partial responses (PR)] but was not increased by repeating the cycle (15 CR, 8 PR), and survival was slightly worse in the second trial. In the third study, 15 patients were treated with doxorubicin, vincristine and etoposide for two cycles and then with 200 mg/kg cyclophosphamide. Although high-dose cyclophosphamide increased the complete response rate, the additional responses were short-lived. In the final study, an attempt was made to increase the initial CR rate by combination chemotherapy using carboplatin (400–600 mg/m^2), etoposide (120 mg/m^2 × 4) and either high-dose cyclophosphamide (40 mg/kg × 4) or melphalan (140 mg/m^2). Although all nine patients responded, none underwent a CR. The long-term survival (up to 7 years) does not appear to be different from that in comparably selected cases treated with conventional chemotherapy.

Introduction

Small-cell lung cancer (SCLC) is among the most chemoresponsive of adult cancers, yet survival with modern combination chemotherapy regimens is disappointing and has shown little sign of improving in recent years. In 1979 we started a programme of very intensive chemotherapy as initial treatment, using autologous bone marrow transplantation (ABMT) to lessen haematological toxicity. The initial studies used very high-dose cyclophosphamide first in one cycle and then, encouraged by the high response rate, in two cycles of treatment. These studies have previously been reported [9, 10, 12]. Since the second study demonstrated a rapid development of resistance to the alkylating agent, which made the second high-dose treatment ineffective, we began the third and fourth studies. In the third we used a brief initial treatment with two cycles of conventional chemotherapy without an alkylating agent, followed by high-dose cyclophosphamide, and in the fourth we used a single treatment with very intensive multiple agent therapy using the most active agents in the treatment of SCLC.

In planning the third study we were aware that Smith et al. [7] had shown that after four cycles of chemotherapy, durable responses to high-dose cyclophosphamide had not occurred, and that other studies [4, 13] had not been especially encouraging for the benefit of "late intensification". We wished to determine if a high proportion of durable responses could be achieved after a very brief period of initial treatment that might be expected not to confer drug resistance. The aim of the fourth study was to try to achieve a complete response (CR) rate close to 100% with initial high-dose therapy since, if responses of this order could be achieved, this might justify a randomised trial against conventional treatment.

This report gives the results of all four studies, with a follow-up time of up to 7 years, and compares the results with those of cases selected for comparable prognostic factors [11] from a randomised trial in which most of our patients were entered over the same time.

Patients and methods

A total of 75 patients were entered into the studies. This represents a very highly selected group, since during this period the collaborating hospitals treated over 1,100 patients in randomised trials. All of the patients had histologically proven SCLC. Staging procedures included chest X-ray, bronchoscopy, full blood count, tests of liver and kidney function, bone marrow aspiration and biopsy, isotope bone scan, liver ultrasonographic scan, computerised axial tomographic (CAT) scan of the thorax and abdomen to the pelvic brim. The intention was to treat only patients with negative bone marrow examinations and diesease confined to one hemithorax that could be included in a radiation field. All patients had a performance status ECOG) of 0 or 1. On review of CAT scans and ultrasonographic examinations, we found that three patients in trial 1 had disease in the liver, as did one in trial 3. A subsequent review of the bone marrow examinations revealed cells compatible with SCLC in one patient in trial 1. The

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Table 1. Characteristics of the patients in each of the studies

	1	2	3	4
Patients (*n*)	25	26	15	9
Mean age (range)	52 years (32–69)	52 years (37–65)	58 years (35–60)	47 years (38–64)
Sex (men/women)	13/12	18/8	11/4	7/2
Limited/extensive disease	21/4	26/0	14/1	9/0

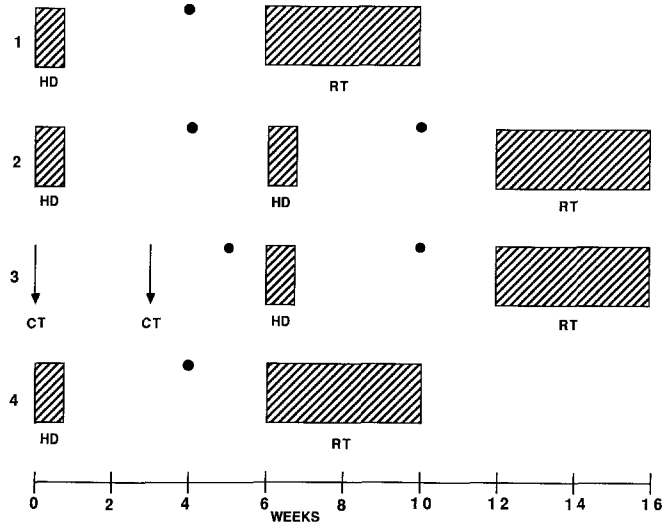


Fig. 1. Plan of studies. *HD*, high-dose chemotherapy; *RT*, thoracic radiotherapy; *arrows* in study 3 indicate induction chemotherapy; ●, time of response assessment

characteristics of the patients are outlined in Table 1. Informed consent was obtained after a very careful discussion with each patient of the risks and potential benefits of the procedure.

Methods

The plan of the studies is shown in Fig. 1. Bone marrow was harvested from multiple iliac crest and sternal marrow sites and was cryopreserved, and treatment was started 2 days later. The chemotherapy regimens were as outlined in Table 2. For studies 1 and 2, the treatment has previously been described [12]. In all studies where high-dose cyclophosphamide was used, mesna (2-mercaptoethane sulphonate) was given concurrently at 66% of the cyclophosphamide dose. In study 3, patients received two cycles of 50 mg/m^2 i.v. doxorubicin on day 1, 2 mg i.v. vincristine on day 1, 120 mg/m^2 i.v. etoposide on days 1–3, with a 3-week interval. Patients were reassessed for response after these two courses and were treated 3 weeks later with 50 mg/kg cyclophosphamide on days 1–4. Marrow was harvested 2 days before the high-dose treatment and reinfused 2 days after. In study 4 the aim was to achieve a CR rate approaching 100%. The first five patients received 400–600 mg/m^2 carboplatin on day 1, 120 mg/m^2 i.v. etoposide on days 2–5, and 140 mg/m^2 i.v. melphalan on day 5. Since all patients obtained only a partial response (PR), we treated the next four patients with 40 mg/kg i.v. cyclophosphamide on days 2–5 substituted for the melphalan. These patients also obtained only a good PR and the study was stopped.

Table 2. Details of chemotherapy

	Drug	Dose	Patients (*n*)	Cycles (*n*)
Study 1	Cyclophosphamide	40 mg/kg i.v. × 4	9	1
		50 mg/kg i.v. × 4	16	
Study 2	Cyclophosphamide	50 mg/kg i.v. × 4	18	2
	Cyclophosphamide and etoposide	40 mg/kg i.v. × 4 400–600 mg/m^2 over 2 days	8	2
Study 3	Doxorubicin	50 mg/m^2 × 1	15	2
	Etoposide	120 mg/m^2 × 3		
	Vincristine	2 mg × 1		
	followed by			
	Cyclophosphamide	50 mg/kg × 4	15	1
Study 4	Carboplatin	400–600 mg/m^2 day^1	9	1
	Etoposide	120 mg/m^2 days 2–5		
	either melphalan or	140 mg/m^2 day 5		
	Cyclophosphamide	40 mg/kg days 2–5		

In each study a period of neutropenia followed the high-dose procedure, during which the patient was barrier-nursed in a single room without laminar-flow air purification. After return to a normal blood count, the patient was discharged from hospital and returned 2 weeks later for response assessment. The patient then received thoracic irradiation and prophylactic cranial irradiation (PCI). In studies 1 and 2, the thoracic dose was 40 Gy in 20 fractions over 4 weeks. Since many tumours recurred locally in those studies, in the next two studies the dose was increased to 54 Gy in 27 daily fractions. The PCI dose was 20 Gy in 5 fractions over 8 days.

Response was assessed after the high-dose treatment before radiotherapy (see Fig. 1). A CR indicated the disappearance of all signs of tumour on chest X-ray and bronchoscopy. A PR was defined as a shrinkage of the tumour on chest X-ray such that the sum of the two maximal perpendicular diameters was reduced by at least 50%. All responses had to be maintained for at least 4 weeks. The progression-free interval was the time from the start of treatment to the appearance of unequivocal signs of tumour recurrence. In the first two studies, treatment on progression involved 50 mg/m^2 cisplatin on day 1 and 120 mg/m^2 etoposide on days 1–3. These drugs were also used in studies 3 and 4, but haematological toxicity often necessitated dose reduction.

Results

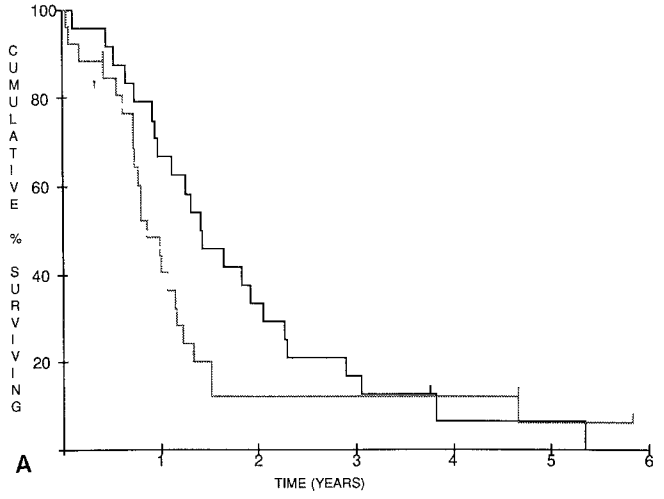
Response to chemotherapy

Table 3 shows the chemotherapy response in each of the studies. The results for studies 1 and 2 have previously been reported [12] and show an overall response rate of 84% and 88%, respectively. In study 2, although some patients with a PR after the first high-dose treatment became complete responders, the overall response rate was unchanged by the second dose. In study 3, 10 of 15 patients showed a response to the first two cycles of conventional chemotherapy (2 CR, 8 PR), and 4 of the 8 patients obtaining a PR were complete responders after the high-dose

Table 3. Response rates in each of the studies

Study no.	1	2		3		4
		1st HD	2nd HD	Post-IND	Post-HD	
Patients (n)	25	26	23	15	15	9
CR	14	8	15	2	6	0
PR	7	15	8	8	4	9
NR	4	1	1	5	3	0
Death	0	2	1	0	2	0
Response:						
(CR + PR)	21/25 (84%)	23/26 (88%)	23/26 (88%)	10/15 (67%)	10/15 (67%)	9/9 (100%)

HD, high dose; IND, induction therapy



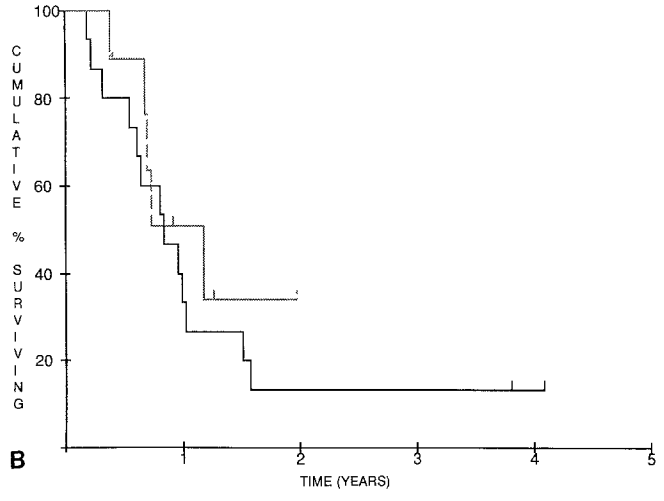


Fig. 2. A. Survival in studies 1 (*continuous line*) and 2 (*dashed line*). **B.** Survival in studies 3 (*continuous line*) and 4 (*dashed line*)

procedure, the overall response rate remaining unchanged (67% of the entire group, including 2 patients with treatment-related deaths who were unassessable for response). In study 4, none of the patients had a CR with either the melphalan- or the cyclophosphamide-containing regimen. All patients responded, usually with considerable reduction of the tumours on chest X-ray.

Table 4. Survival (weeks) in each of the studies

	1	2	3	4
Median survival	74	45	43	55
Relapse-free survival	34	41	30	31
Survival after relapse	30	10	11	18
2-year survival	8/25	3/26	2/15	–[a]

[a] Insufficient follow-up

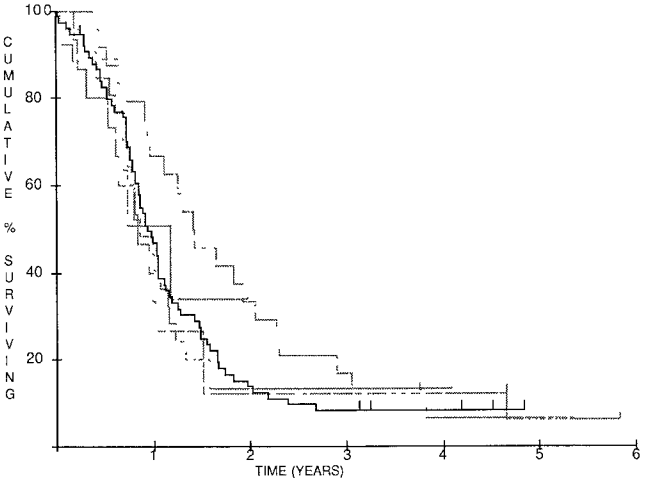


Fig. 3. Survival in all four studies (*dashed lines*) compared with all patients from a concurrent randomised trial showing the same prognostic factors at diagnosis (*solid line*)

Survival

Follow-up was complete for all patients after 6 years in the first study, after 5 years for study 2, and after 4 and 1 years for studies 3 and 4, respectively. Overall survival is shown in Fig. 2 and the results for median survival, 2-year survival and progression-free survival, taken from the start of treatment, are given in Table 4. We have recently described factors that are strongly predictive for prognosis in SCLC and give more information than the categorisation into limited and extensive disease [11]. We compared the results of these high-dose studies with those in a consecutive group of patients who were matched for these factors and disease extent but who were treated in a large randomised collaborative trial using conventional chemotherapy (1 g/m^2 cyclophosphamide, 2 mg i.v. vincristine, 120 mg/m^2 i.v. etoposide on day 1, 100 mg tds on days 2 and 3, given as four or eight 3-weekly cycles). The survival curves are shown in Fig. 3, from which no evidence can be seen that the survival of the patients receiving high-dose treatment was greatly different from this matched group. Median survival was longest in study 1. Although this might be a chance effect, it was noticeable that in this study re-treatment after relapse was much easier than in the other studies, where patients had received more chemotherapy. This is perhaps reflected in the better duration of survival after relapse, and relapse-free survival was broadly comparable in all studies. Taking all of the studies together, 8 patients have survived for more than 2 years (10.7%).

Table 5. Sites of first relapse or progression

	1	2	3	4
Local	11	9	8	4
Liver	6	9	2	2
Bone	1	1	0	1
Brain	1	0	0	0
Other	2	1	0	1
Not assessable[a]	4	5	3	0
Not relapsed	0	2	2	0

[a] No response or died in therapy

Table 6. Duration of neutropenia and thrombocytopenia with each high-dose treatment

	1	2		3	4
		1st	2nd		
Mean duration (days) of mean WBC < 500	10.6	10.5	14.8	14	12
Mean duration (days) of platelets $< 50\,000$	6.3	6.3	14.5	7.1	14

Site of relapse

The primary tumour was the most common site of relapse in all four studies, in spite of the increase in radiation dose in studies 3 and 4 (Table 5). The liver was the most frequent site of distant metastases. These relapse sites were very similar to those occurring with conventional chemotherapy, and there was no evidence that marrow infusion had altered the pattern of metastasis.

Toxicity

There were five treatment-related deaths (6%) in the entire series (Table 3); these were due to infection during the period of neutropenia. The duration of myelosuppression for each of the high-dose treatment protocols is given in Table 6. On average, patients were hospitalised for 7 days before the WBC and platelets fell below the indicated levels; they were discharged 3–5 days after the recovery of blood counts above these levels. The contribution of ABMT to recovery is the subject of a separate analysis. Alopecia always occurred and almost all patients had a transient erythematous skin rash that occurred within a few days of the high-dose chemotherapy. Nausea and vomiting were mild for most patients, and haematuria did not occur in any patient. During the period of aplasia, mild to moderate mucositis developed in all patients. Following radiotherapy, all patients developed radiation fibrosis in the treated area, which we thought was greater that that seen following conventional chemotherapy. There was no clinical or electrocardiographic evidence of cardiac toxicity.

Discussion

For such a chemoresponsive tumour, the cure rate for SCLC remains stubbornly and disappointingly low. In the view of the high response rate, it is reasonable to suppose that an increase in the intensity of drug treatment might be one way to improve results. The difficulty with this approach lies in planning studies which might indicate the way forward. In 1979, at the start of the present studies, we chose to avoid the use of intensive treatment after conventional chemotherapy. Since at that time there was little evidence that an increase in dose to the point of prolonged myelosuppression improved the response rate in SCLC, there was more to be learned from using drugs at high doses as the initial and sole treatment. We did not anticipate that all of the intrathoracic tumour would be killed by this means but thought that clinically undetectable metastases might be eliminated and, with radiotherapy to control the primary disease, this might lead to a long disease-free interval. Pilot studies of this kind might provide evidence that the proportion of long-term survivors was high enough to justify a randomised trial against conventional therapy.

The first study therefore asked the question as to whether there was a marked increase in response with a major increase in dose of a single agent. Cyclophosphamide was used because there had been considerable experience in its use in allogeneic bone marrow transplantation and since it is one of the most effective agents in the treatment of SCLC. With this drug the choice of dose and schedule is not straightforward, since cyclophosphamide has much greater alkylating activity when given in divided daily doses [6]. The study showed a very high response rate and an encouraging progression-free interval, leading to a good quality of life for the patients. The second study attempted to determine whether repeating the dose would prevent the relapses that were nevertheless occurring. As previously reported [12], this proved not to be the case. Although some PRs were converted to CRs, the overall response rate was unchanged, implying that there was relative resistance to the second cycle of alkylating agent, which we have attempted to quantify [2].

In study 3 the intention was to determine whether a high CR rate could be attained with high-dose cyclophosphamide in patients whose tumour had been reduced in size by previous treatment using drugs of an entirely different class. In many previous "late intensification" studies, the same drug has often been used in both initial and intensification treatment [5, 13]. In this situation, response seemed likely to be limited by drug resistance, and for this reason only two cycles of induction treatment were given before the high-dose cycle. A similar approach has been adopted by Smith et al. [7] with the same agents, but in their study the cyclophosphamide was given as a single 12-h infusion and 12 weeks of treatment had preceded its use. Nevertheless, the present results, using the 4-day schedule of administration of cyclophosphamide after only two cycles of treatment, are similar to theirs. There was an increase in the number of complete responders, although these were not durable or useful. This finding is probably explained by the existence of a degree of cross-resistance between cyclophosphamide and these drugs of different class.

These three studies showed the limitations of using a high dose of a single alkylating agent, and the fourth study was designed to determine whether superior results could be obtained by using all of the most effective agents whose dose-limiting toxicity was likely to be myelosuppression. Carboplatin has been shown by Smith et al. [8] to be associated with a high response rate, with marrow suppression as its major toxicity; the same has been reported for etopo-

side [14]. Increased response rates have been reported for high-dose melphalan in other types of drug-resistant tumours [1], and we made the change to that drug in the first instance. All drugs were given in doses well above the maximum usually delivered in combination. The aim was to continue only if there were CRs in the great majority of patients since in this group of carefully selected cases, conventional chemotherapy might be expected to produce a 40%–50% CR rate. This did not occur, even when cyclophosphamide was substituted for melphalan in the combination; for this reason, the study was stopped at an early stage.

These results indicate that although it is relatively easy to kill the sensitive component of SCLC, the disease is associated with a considerable capacity to regenerate in a drug-resistant form. An initial treatment with an alkylating agent or a triple-drug combination at high doses does not circumvent this. The limitations of the approach in terms of toxicity, case selection and expense suggest that initial high-dose treatment of this type does not have any place in routine treatment. However, the procedure remains essential as a means of determining which drugs and drug combinations are associated with a substantial increase in response when given at high doses.

A recent randomised trial [3] has shown that an increase in drug dose given as "late intensification" produces a slight prolongation of survival compared with the same drugs given as conventional chemotherapy. This study is the only randomised trial to test the value of this approach. However, the difference was a matter of weeks and might not be regarded as clinically useful. What might make a difference in this form of study of high-dose treatment is the demonstration of a lack of cross-resistance between one drug or drug combination and another. Treatment schemes could then be devised where there was a reasonable expectation that a later high-dose treatment might be clinically worthwhile after induction with a different regimen.

References

1. Cornbleet MA, McElwain TJ, Kumar PJ, Filshie J, Selby P, Carter RL, Hedley DW, Clark ML, Millar JL (1983) Treatment of advanced malignant melanoma with high dose melphalan and autologous bone marrow transplantation. Br J Cancer 48: 329
2. Gregory MW, Birkhead BG, Souhami RL (1988) A mathematical model of drug resistance applied to treatment for small cell lung cancer. J Clin Oncol 6: 457
3. Humblet Y, Symann M, Bosly A, Delaunois L, Francis C, Machiels J, Beauduin M, Doyen C, Weynants P, Longueville J, Prignot J (1987) Late intensification chemotherapy with autologous bone marrow transplantation in selected small-cell carcinoma of the lung: a randomized study. J Clin Oncol 5: 1864
4. Ihde DC, Lichter AS, Deisseroth AB, Bunn PA, Carney DN, Cohen MH, Makuch RW, Johnston-Early A, Minna JD (1983) Late intensive combined modality therapy with autologous bone marrow infusion in extensive small cell lung cancer. Proc Am Soc Clin Oncol C774
5. Klastersky J, Nicaise C, Longeval E, Stryckmans P, for the EORTC Lung Cancer Working Party (1982) Cisplatin, Adriamycin and etoposide (CAV) for remission induction of small cell bronchogenic carcinoma. Evaluation of efficacy and toxicity and pilot study of a "late intensification" with autologous bone marrow rescue. Cancer 50: 652
6. Schuler U, Ehninger G, Wagner T (1987) Repeated high-dose cyclophosphamide administration in bone marrow tranplantation: exposure to activated metabolites. Cancer Chemother Pharmacol 20: 248
7. Smith IE, Evans BD, Harland SJ, Robinson BA, Yarnold JR, Glees JG, Ford HT (1985) High-dose cyclophosphamide with autologous bone marrow rescue after conventional chemotherapy in the treatment of small cell lung carcinoma. Cancer Chemother Pharmacol 14: 120
8. Smith IE, Harland SJ, Robinson BA, Evans BD, Goodhart LC, Calvert AH, Yarnold J, Glees JP, Baker J, Ford HT (1985) Carboplatin: a very active new cisplatin analog in the treatment of small cell lung cancer. Cancer Treat Rep 69: 43
9. Souhami RL, Harper PG, Linch DC, Trask C, Gladstone AH, Tobias J, Spiro SG, Geddes DM, Richards JDM (1982) High dose cyclophosphamide with autologous bone marrow transplantation as initial treatment of small cell carcinoma of the bronchus. Cancer Chemother Pharmacol 8: 31
10. Souhami RL, Harper PG, Linch DC, Trask C, Goldstone AH, Tobias JS, Spiro SG, Geddes DM, Richards JDM (1983) High dose cyclophosphamide for small cell carcinoma of the bronchus. Cancer Chemother Pharmacol 10: 205
11. Souhami RL, Bradbury I, Geddes DM, Spiro SG, Harper PG, Tobias JS (1985) The prognostic significance of laboratory parameters measured at diagnosis in small cell carcinoma of the lung. Cancer Res 45: 2878
12. Souhami RL, Finn G, Gregory W, Birkhead BG, Birkhead BG, Buckman R, Edwards D, Goldstone AH, Harper PG, Spiro SG, Tobias JS, Geddes D (1985) Very high dose cyclophosphamide as initial treatment for small cell carcinoma of the lung. J Clin Oncol 3: 958
13. Spitzer G, Farha P, Valdivieso M, Dicke K, Zander A, Vellekoop L, Murphy WK, Dhingra HM, Umsawasdi T, Chiuten D, Carr DT (1986) High-dose intensification therapy with autologous bone marrow support for limited small cell bronchogenic carcinoma. J Clin Oncol 4: 4
14. Wolff S (1983) High dose etoposide as single agent chemotherapy for small cell carcinoma of the lung. Cancer Treat Rep 67: 957

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