

Multiple Courses of High-Dose Ifosfamide, Carboplatin, and Etoposide With Peripheral-Blood Progenitor Cells and Filgrastim for Small-Cell Lung Cancer: A Feasibility Study by the European Group for Blood and Marrow Transplantation

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Purpose: To determine the feasibility and safety of multiple sequential courses of high-dose chemotherapy and peripheral-blood progenitor cells (PBPCs) administered in a multicenter setting to patients with small-cell lung cancer.

Patients and Methods: Sixty-nine patients (limited disease, $n = 30$; extensive disease, $n = 39$) treated at 15 European centers were scheduled to receive three courses of high-dose chemotherapy with ifosfamide 10 g/m², carboplatin 1200 mg/m², and etoposide 1200 mg/m² (ICE) divided over 4 days at 28-day intervals. PBPCs were harvested before treatment and mobilized with epirubicin 150 mg/m² administered via an intravenous bolus divided over 2 days and filgrastim 5 μg/kg/d administered subcutaneously.

Results: The performed leukaphereses (one to five per patient) yielded a median of 16.6×10^6 /kg (range, 1.0 to 96.6×10^6 /kg) CD34⁺ cells, which was sufficient for three reinfusions. Fifty patients (72%) completed the treatment according to schedule. Nine patients completed two courses, and six patients completed one course of treatment. The increase in dose-intensity was 290% that of a standard ICE regimen. The median duration of myelosuppression was similar between

courses, namely 4 days (range, 1 to 12 days) for leukocytes less than 0.5×10^9 /L and 4 days (range, 0 to 22 days) for thrombocytes less than 20×10^9 /L. Febrile neutropenia developed in 66% of courses, severe diarrhea in 14%, mucositis in 10%, and nausea and vomiting in 21% of courses. There were six cases of toxic death (9%), most of which occurred in the first year of accrual and thus were attributable to the learning curve. The antitumor effect of the regimen was reflected in an 86% remission rate (95% confidence interval [CI], 74% to 93%), with 51% of patients achieving a complete response (95% CI, 38% to 63%). Median overall survival was 18 months for patients with limited disease and 11 months for patients with extensive disease.

Conclusion: This multiple sequential high-dose ICE regimen could be safely administered on a multicenter basis to patients with small-cell lung cancer. The dose-intensity could be increased to 290% that of standard ICE regimen. The benefit of this approach is currently being tested in a randomized trial that aims to double the long-term rate of survival for patients with small-cell lung cancer.

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MORE THAN 25 YEARS ago, it was suggested that small-cell lung carcinoma (SCLC) would be the next on a list of curable cancers, following choriocarcinoma, lymphoma, testicular cancer, and some forms of acute leukemia. It was regarded as a distinct histopathologic entity¹ with a high labeling index, a high growth fraction, and a short doubling time, similar to Burkitt's lymphoma.² These characteristics and the discovery of SCLC's high metastatic potential³ provided the basis for testing chemotherapeutic agents. Researchers found that intermittent high-dose cyclophosphamide (40 mg/kg/mo) led to significant improvements.⁴ The efficacy of cyclophosphamide was enhanced by applying maximum-tolerated doses instead of low daily doses.⁵ The next series of improvements came with the introduction of combination regimens, which not only afforded better response rates and higher complete remission rates but also prolonged the median survival even more.⁶ Multiple agents had to be administered at doses high enough to induce some myelotoxicity.⁷⁻⁹ Combination

therapy comprising cyclophosphamide, doxorubicin, and vincristine (CAV) was the first regimen to become an established standard,¹⁰ at least until the synergistic association of cisplatin and etoposide (PE) was discovered.¹¹ Response rates in extensive disease were in the 51% to 78% range, including a 7% to 13% complete remission rate and a median survival of 8 to 9 months. The corresponding data for patients with limited disease were 16% to 18% or 11.7 to 12.4 months, respectively.¹²⁻¹⁴

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Early clinical results also suggested some impact of dose on the outcome of SCLC.^{5,15} However, a relatively recent meta-analysis of combination regimens including CAV and PE failed to confirm any such systematic correlation between dose-intensity and complete response or survival.¹⁶ The range of intensity variation was narrow, rarely exceeding 30% to 50% of the standard dose. Randomized studies designed to clarify this issue actually added to the confusion; some studies yielded negative results,¹⁷⁻¹⁹ whereas the more recent studies have tended to yield positive results.²⁰⁻²³ These discrepancies may, of course, be due to differences in patient selection, size of the patient sample, and rate of intensification. Moreover, the study designs also differed in terms of end points, depending on whether their focus was response rates, median survival, or long-term survival.

To further increase the dose-intensity, autologous bone marrow cells (ABMT) or peripheral-blood progenitor cells (PBPCs) were used to control the hematologic toxicity of high-dose chemotherapy. Unfortunately, most of these trials were uncontrolled and comprised small patient numbers with heterogeneous prognostic factors. Those studies mainly tested late intensification strategies, in which a single course of intensive chemotherapy is administered in an attempt to consolidate the response to standard treatment. A combined analysis did not reveal an apparent improvement in survival, even though the percentage of complete responders almost doubled.²⁴ At the same time, it was proposed that late intensification might improve the long-term survival in a significant proportion of complete responders with limited disease.²⁵ A randomized trial suggested an improvement in median survival among limited-disease patients from 14 to 19 months.²⁶ These results were not statistically significant, however, presumably because of the small sample size and the high toxic death rate (18%) in the intensified group.

High-dose chemotherapy with ABMT was also administered up front as first-line treatment. The rationale of this was to intensify therapy for all patients while avoiding drug resistance induced by previous chemotherapy. Although this approach resulted in impressive rates of complete remission (56% to 67%) among limited-disease patients,²⁷⁻²⁹ the impact on median or long-term survival could not be reliably assessed because of insufficient sample sizes and the absence of control groups.

This prompted us to prepare a randomized trial comparing standard chemotherapy regimens with high-dose combination regimens to elucidate the role of dose-intensity in chemotherapy for SCLC. The main objective of the present study was to test the feasibility of the high-dose regimen across various European centers in preparation for a multicenter randomized trial. The requirements defined for the high-dose regimen were that it had to be (1) three times more

dose-intensive than the standard regimen,³⁰ (2) safe and simple enough to be administered to patients up to 65 years old, and (3) suitable to be carried out on a multicenter basis. It consisted of a sequential combination regimen supported by PBPCs and granulocyte colony-stimulating factor (G-CSF).

PATIENTS AND METHODS

Patients

Patients were eligible for the study if they had newly diagnosed and untreated SCLC. Inclusion criteria included age of 18 to 65 years, performance status of less than 2, blood count within the normal range, and normal cardiac, hepatic, and renal function. All patients were required to give informed consent. Cerebral metastasis was not an exclusion criterion.

Before study entry, all patients underwent staging investigations, including physical examination, chest x-ray, computerized tomography (CT) of chest and abdomen, bone scintigraphy, full blood count, electrolyte measurements, liver and renal function tests, fiberoptic bronchoscopy with biopsy, and bone marrow biopsy. Brain CT scans and serum neuron-specific enolase (NSE) levels were obtained optionally. Limited disease was defined as tumor confined to one hemithorax with or without ipsilateral supraclavicular lymphadenopathy or pleural effusion. All other patients were defined as having extensive disease.

During the follow-up, patients underwent weekly clinical examinations, including a full blood count. Patients who developed fever during granulopenia were admitted to the hospital for parenteral antibiotics. A biochemical profile, renal function tests, and chest x-ray were obtained before each treatment cycle. After the end of treatment, patients underwent clinical examinations every month and radiodiagnostic assessment every 3 months.

Mobilization and Collection of PBPCs

PBPCs were mobilized with epirubicin 75 mg/m²/d administered intravenously (IV) on days 1 and 2, followed by G-CSF 5 µg/kg/d administered subcutaneously from day 3 until the last leukapheresis. The blood separators used for harvesting depended on the equipment and experience available at the various centers. The collection was finished when enough cells were obtained to support three high-dose treatments. According to the European Group for Blood and Marrow Transplantation (EBMT) recommendations for PBPC reinfusion, 6 × 10⁸/kg mononuclear cells or 6 × 10⁶/kg CD34⁺ cells was defined as the minimum requirement.³¹

Quantitation of CD34⁺ cells was subjected to quality assurance at the beginning of the study. The exact equipment and technique was selected by the various centers to best suit their experience. The 13 centers participating in the standardization scheme were supplied with the same sample for CD34⁺ cell quantitation. The same antibody (HPCA-2, Becton Dickinson, Rutherford, NJ) was used in 11 centers, but the measurements were performed with different flow cytometers. Quantitation was performed on the day of collection (n = 3 centers), on day 2 (n = 4), on day 3 (n = 5), or on day 4 (n = 1). Figure 1 shows that 12 laboratories (92%) were within two SDs, so that the results could be pooled for direct comparison. Colony assays such as granulocyte-macrophage colony-forming units (GM-CFU) were performed in only a few centers and were not standardized.

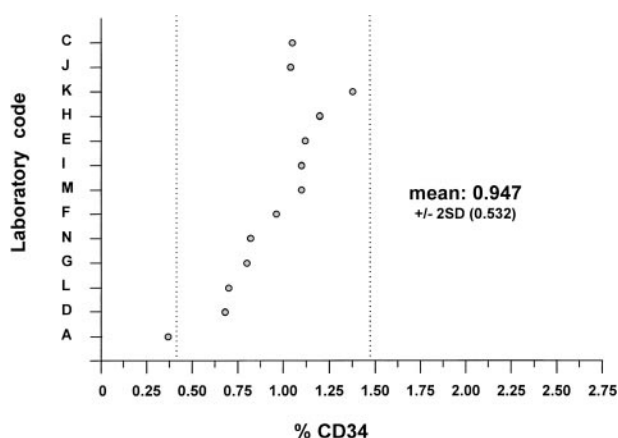


Fig 1. Quality control of CD34⁺ quantitation across 13 centers.

High-Dose Treatment Regimen

The treatment program was started within 21 days of day 1 of mobilization and consisted of a high-dose ifosfamide, carboplatin, and etoposide (ICE) regimen. Ifosfamide was given at 2.5 g/m²/d as a 17-hour IV infusion in 1,000 mL of 5% dextrose for 4 days. Carboplatin was given at 300 mg/m²/d as a 3-hour IV infusion in 250 mL of physiologic saline over 4 days. Etoposide was given at 300 mg/m²/d as a 3-hour infusion in 1,000 mL of physiologic saline over 4 days. Mesna 1,000 mg/m² was given 1 hour before ifosfamide as a 1-hour IV infusion, followed by 4,000 mg/m²/d as a continuous IV infusion over 5 days. Hydration consisted of 2,500 mL of 5% dextrose and 0.33% NaCl per day supplemented with 50 mEq of KCl. Chemotherapeutic cycles were repeated three times in intervals of 4 weeks. Subsequent radiotherapy was left to the discretion of the various centers, but it was recommended that responders be subjected to thoracic and/or prophylactic cranial irradiation.

Forty-eight hours after the end of chemotherapy, PBPCs were reinfused and G-CSF was introduced at 5 µg/kg/d administered subcutaneously until the leukocytes rose to $\geq 0.5 \times 10^9$ /L. After the first cases of septic death had occurred, the recommendation was issued to prophylactically administer oral antibiotics (methylpenicillin and ciprofloxacin).

Subsequent cycles were delayed by 1 or 2 weeks until recovery of leukocytes to $\geq 3.5 \times 10^9$ /L, granulocytes to $\geq 1 \times 10^9$ /L, platelets to $\geq 100 \times 10^9$ /L, and serum creatinine to ≤ 120 µmol/L or creatinine clearance to ≥ 60 mL/min, in addition to normal hepatic function tests. Patients in whom these values could not be reached within 2 weeks were withdrawn from the study. Etoposide was reduced by 30% in cases of World Health Organization (WHO) grade 3 esophagitis or drug-related diarrhea. Carboplatin was omitted in case of \geq WHO grade 3 peripheral neuropathy, as was ifosfamide for \geq grade 3 CNS toxicity according to the M.D. Anderson Cancer Center toxicity criteria.

Assessment of Toxicity, Response, and Survival

General toxicity was classified according to the WHO grading system,³² and neurotoxicity was classified according to the M.D. Anderson scale.³³ Response was determined by clinical examination and chest x-ray. Posttherapeutic CT scans of the chest, abdomen, and brain were performed in cases of assessable disease on the entry scan or if clinically indicated. Bronchoscopy with biopsy and bone marrow biopsy were obtained if they were abnormal before treatment. Response was defined as (1) complete response (CR) if there were no more signs

of tumor; (2) near complete response (nCR) if there was a greater than 90% reduction in lesions with persistent radiographic abnormalities (residual parenchymal scarring without nodular characteristics, pericardial thickening, and residual mediastinal adenopathy < 1.5 cm in maximum diameter); and (3) partial response if the reduction was 50% to 90% of the product of perpendicular diameter of all measurable disease. Response had to be present for 4 weeks with no recurrence of lesions. Stable disease was defined as a less than 50% reduction or a less than 25% increase of lesions for 8 weeks or longer.²⁵

Progression-free survival and overall survival were calculated from the first day of chemotherapy to first progression or death, whichever occurred first. The study was approved by the ethics committees in charge of the various centers.

Statistics

The trial was designed as a two-stage phase II study,³⁴ with response rate (CR and nCR) as the main end point. For the purpose of sample size calculations (significance level and power defined as 5% and 90%, respectively) it was necessary to recruit 25 patients for the first phase. If there had been fewer than 11 responders, then the study would have been terminated (true response rate < 40%). The score of 17 of 25 responders in the interim analysis enabled us to proceed to the second phase, for which another 41 patients needed to be accrued. With 33 or more responders between both phases, the study would support a percentage of antitumor activity (CR plus nCR) of at least 60%. This criterion was achieved with the 66 patients, but for administrative reasons, accrual was stopped at 69 patients.

Differences in distribution of continuous and categorical variable were assessed using the Kruskal-Wallis and χ^2 tests, respectively.³⁵ Survival probabilities were estimated according to Kaplan-Meier³⁶ and the corresponding standard deviations according to Greenwood.³⁷ Differences between survival curves were analyzed based on the log-rank test.³⁸ Logistic regression was used to study the simultaneous effect of selected factors on the probability of response. Results were quantified in terms of odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Progression-free survival was analyzed according to Cox and the results similarly presented in terms of hazard ratios (HRs) and corresponding 95% CIs.³⁵ In both cases, the following variables were used and coded into binary indicators: sex, performance status (0 v 1), disease extent and liver involvement (limited v extensive without liver involvement v extensive with liver involvement), NSE (below or above local normal values), and lactate dehydrogenase (LDH; below and above normal values). All reported *P* values are based on two-sided tests. Statistical analysis was performed using Stata software (STATA Corp, College Station, TX).

RESULTS

Patient Characteristics

Sixty-nine patients were enrolled at 15 European centers between March 1994 and October 1997. Six centers included the majority of patients and nine centers enrolled one or two patients. Pertinent patient data are listed in Table 1. Of these 69 patients, 43% showed limited disease and 57% showed extensive disease. Of the patients with extensive disease, 69% had two or more metastatic sites and 59% had liver metastases. Three patients presented with brain metastases. LDH levels were elevated in more than one half of all patients. Only 16% of patients were female.

Table 1. Patient characteristics

Characteristic	No. of Patients
Total	69
Sex	
Male	58
Female	11
Age, years	
Median	53
Range	35-65
Performance status	
0	35
1	34
Stage	
Limited	30
Extensive	39
Tumor-stage*	
T1	2
T2	15
T3	23
T4	24
Unknown	5
Nodal-stage*	
N1	5
N2	30
N3	30
Unknown	4
Location of metastases	
Liver	23
Bone	14
Distant nodes	13
Bone marrow	12
Adrenal gland	10
Lung	7
Pleura	6
Brain	3
Other†	5
Number of metastatic sites	
1	12
2	10
3	9
4	6
5	2
LDH level	
Normal	30
Elevated	36
Unknown	3

*According to the tumor-node-metastasis staging system.

†Pericardium, skin, soft tissue, parathyroid, and prostate account for one metastatic site each.

Mobilization and Collection of PBPCs

After administration of epirubicin 150 mg/m² IV over 2 days, filgrastim was administered at 5 µg/kg/d for a median of 11 days (range, 5 to 16 days). The interval from day 1 of mobilization to the start of leukaphereses was 11 days (range, 8 to 14 days). The median number of leukaphereses performed per patient was three (range, one to five). Four patients did not undergo leukapheresis because of inadequate CD34⁺ cell counts (n = 1) or toxicity (n = 3).

Collection of mononuclear cells yielded 6.3×10^8 /kg (range, 2.2 to 21.3×10^8 /kg), which corresponded to a median of 16.6×10^6 /kg CD34⁺ cells (range, 1.0 to 96.6×10^8 /kg). The quality control allowed comparison between CD34⁺ counts obtained across centers. GM-CFU assays were performed in 47 patients, but the results were highly variable because of the absence of any standardization and hence were unsuitable for direct comparison (data not shown).

Hematologic toxicity was minimal, with median nadirs for leukocytes at 3.8×10^9 /L (range, 0.1 to 11.9×10^9 /L), platelets at 120×10^9 /L (range, 14 to 323×10^9 /L), and hemoglobin at 105 g/L (range, 8.8 to 142 g/L). Fever occurred in 12 patients (17%), eight of whom had proven infection, including catheter infection (n = 1), lung abscess (n = 1), pararectal abscess (n = 1), sepsis (n = 4), and unknown cause of infection (n = 1). Mucositis occurred in six patients but did not reach WHO grade 3 except in one case. Due to antiemetic premedication, nausea and vomiting was not a major toxicity and was grade 3 in five patients. Nine patients had diarrhea, of whom one had grade 3 diarrhea. One patient died of acute heart failure, and one patient with sepsis died of septic shock.

In 49 patients, the antitumor effect could be assessed by standard chest x-ray. None of these x-rays showed tumor progression. Twenty-one patients (43%) responded to a single cycle of high-dose epirubicin, including one complete responder. All other patients showed stable disease (three with minor response).

Sequential High-Dose Chemotherapy

At the time of this analysis, 50 patients (72%) have completed the entire program of three sequential high-dose courses according to schedule. Nine patients have completed two cycles, and six patients have completed one cycle. Reasons for early discontinuation included toxic death (n = 3), unacceptable toxicity (n = 5), noncompliance (n = 3), deep vein thrombosis (n = 2), hepatitis (n = 1), and pulmonary aspergillosis (n = 1).

The treatment plan was to accomplish an increase in average dose-intensity based on dose per time unit or single dose-intensity to 310% of the standard ICE regimen.²² Ifosfamide was planned to be increased by a factor of 2, carboplatin by a factor of 4, and etoposide by a factor of 3.3. Treatment could be given as planned every 4 weeks and was delayed in only 39 cycles (23%). The reasons were asthenia or patient refusal (n = 7), toxicity (n = 11), and lack of available beds in some centers (n = 21). Owing to treatment delays and missing cycles, the actual delivered median dosages were reduced to ifosfamide 2,380 mg/m²/wk (range, 1,560 to 2,780 mg/m²/wk), carboplatin 282 mg/m²/wk (range, 185 to 335 mg/m²/wk), and etoposide 282 mg/m²/wk

Table 2. Hematologic Toxicity of Sequential High-Dose ICE According to Treatment Courses

	Treatment Course		
	1	2	3
Leucocytes \leq 1.0 g/L, days			
Median	9	9	9
Range	4-12	6-11	8-12
Thrombocytes \leq 20 g/L, days			
Median	9	9	9
Range	5-18	5-18	6-27
IV antibiotics use, days			
Median	9	8	6
Range	0-30	0-62	0-27
Hospital length of stay, days			
Median	20	20	19
Range	11-42	5-75	5-28
Cycles with febrile neutropenia, %	74	63	60
Transfusion of erythrocytes, rate/patient	2.02	2.00	1.78
Transfusion of thrombocytes, rate/patient	2.22	2.17	2.11

(range, 205 to 335 mg/m²/wk).³⁹ Based on all three drugs, the implemented dose-intensity was 94% of the planned dose-intensity.

Toxicity

A total of 172 cycles of high-dose ICE chemotherapy were analyzed for toxicity (Tables 2 and 3). Durations of leukopenia and thrombocytopenia were estimated from the day of PBPC reinfusion until recovery. The median interval to reach a leukocyte count of $\geq 1.0 \times 10^9/L$ was 9 days (range, 4 to 12 days), with similar findings between cycles 1, 2, and 3 ($P = .719$). Similarly, thrombocyte counts required a median of 9 days (range, 5 to 27 days) to recover to $\geq 20 \times 10^9/L$, again with no differences between cycles ($P = .525$).

The median interval in terms of severe leukopenia (leukocytes $< 0.5 \times 10^9/L$) was 4 days (range, 1 to 12 days), with no differences between cycles ($P = .290$). Severe thrombocytopenia (thrombocytes $< 20 \times 10^9/L$) also lasted for a median of 4 days (range, 0 to 22 days). Repeated treatment cycles involved no cumulative thrombocytopenia, as confirmed by similar rates of platelet transfusion per patient per cycle ($P > .3$). Febrile neutropenia developed in 74%, 63%,

Table 3. Number of Cycles With Nonhematologic Toxicity in Association With Sequential High-Dose ICE (n = 172)

	WHO Grade				
	0	1	2	3	4
Mucositis	94	33	27	16	2
Diarrhea	80	37	30	21	4
Nausea/vomiting	38	47	51	34	2
Neurologic	150	14	3	4	1
Otologic	162	4	5	—	1
Cardiac	162	4	2	4	—
Infection	119	7	24	17	5

and 60% ($P = .254$) and proven infection developed in 43%, 36%, and 37% ($P = .674$) of cycles 1, 2, and 3, respectively. Major infection (\geq WHO grade 3) occurred in 21 cycles (12%), including sepsis in 17 cycles, pneumonia in two cycles, and enteritis and urinary tract infection in one cycle each. Septic shock occurred in five patients, three of whom died. One patient died as a result of a multiorgan failure after the third cycle with concomitant progressive metastases in the cerebellum.

Treatment with IV antibiotics lasted for a median of 8 days (range, 0 to 62 days) with no difference between cycles. The median number of 20 days (range, 5 to 75 days) of hospitalization was also similar across cycles ($P = .213$).

Based on severe (\geq grade 3) forms of toxicity, mucositis occurred in 10% of cycles, diarrhea in 14%, vomiting in 21%, neurotoxicity in 3%, and cardiac and renal toxicity in 2%. One patient developed grade 4 ototoxicity.

Response and Survival

Analysis was performed on all 69 patients. Complete remission (CR + nCR) was achieved in 35 patients (51%; 95% CI, 38% to 63%) and partial remission was achieved in 24 patients (35%; 95% CI, 24% to 47%). Hence the overall response rate was 86% (95% CI, 75% to 93%). One patient had stable disease, and two patients experienced disease progression during treatment. One of these two patients developed brain metastases during the third cycle. The other patient, who showed a partial response for liver disease, experienced disease progression with brain and lung metastases, also during the third cycle. Four patients never received treatment either because of toxicity ($n = 3$) or insufficient numbers of collected PBPCs ($n = 1$). Three additional patients were not assessable for response because of toxicity requiring discontinuation of treatment. Whereas the rate of complete responders correlated with tumor stage (ie, 70% in limited and 36% in extensive disease; $p = 0.05$), there was no such association with performance status, sex, NSE, or LDH levels or liver metastases. However, when all of these factors were simultaneously analyzed in a logistic regression with response as the dependent variable, an effect of disease extent was not confirmed (data not shown).

Bronchoscopy with or without biopsy was performed in 23 of the 33 complete responders and was invariably found to be normal. Based on the 24 partial responders, bronchoscopy was performed in 18 patients and found to be normal in 13.

The radiotherapy policies adopted in the various centers were not uniform. Radiation was administered to the primary site in 37 patients and in a prophylactic cranial approach in 24 patients. Five partial responders became complete responders after radiotherapy was administered to the chest.

All 69 patients were analyzed for progression-free survival and overall survival over a median follow-up of 45 months. Twelve deaths without tumor progression and 47 cases of disease progression resulted in a median progression-free survival time of 9.2 months. The median progression-free survival was higher in patients with limited disease than in patients with extensive disease (11 v 7 months; $P = .001$) and in patients with normal LDH levels than in patients with abnormal LDH levels (9.5 v 7.6 months; $P = .0011$). The main first site of tumor progression was the brain in 21 patients (30%), one of whom had carcinomatous meningitis. Locoregional progression was diagnosed in 17 patients (25%). Other sites of progression were liver ($n = 9$), distant lymph nodes ($n = 7$), bone ($n = 4$), pleura ($n = 2$), adrenal ($n = 2$), bone marrow ($n = 2$), skin ($n = 1$), chest wall ($n = 1$), and breast ($n = 1$).

The overall survival extended to a median of 13.5 months. As is apparent in Fig 2, which shows survival curves according to disease extent, the overall survival was 18 months in patients with limited disease and 11 months in patients with extensive disease ($P = .0001$). Based on LDH levels, overall survival was 16 months in patients with normal LDH levels versus 12 months in patients with abnormal LDH levels ($P = .011$). A Cox regression analysis using sex, performance status, disease extent, liver involvement, NSE, and LDH levels as parameters showed that the only significant prognostic factor was disease extent (HR = 4.67; 95% CI, 1.59 to 11.13; $P < .001$), irrespective of whether liver involvement was present or absent. As soon as disease extent was included in the calculus, the significance of LDH levels and performance status disappeared.

DISCUSSION

SCLC is a potentially curable disease, even though the 5-year survival rate after current strategies of standard combination chemotherapy and radiotherapy does not ex-

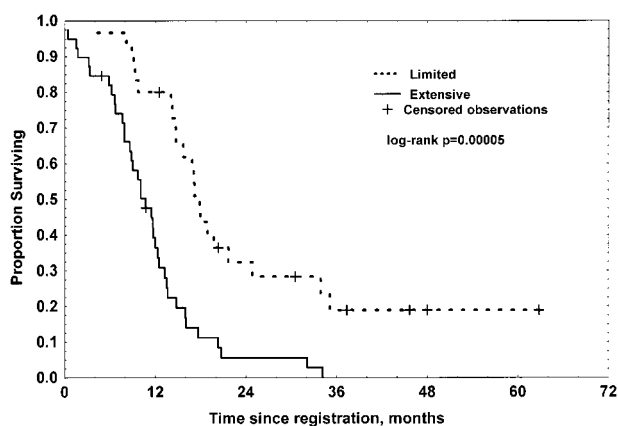


Fig 2. Overall survival according to disease extent.

ceed 3% to 5%.⁴⁰⁻⁴² Among the various possible approaches to improving outcome for patients with SCLC, intensification of chemotherapy is a particularly promising option. Unfortunately, the experience with this strategy has never transcended the level of uncontrolled trials focusing on early or late intensification programs. Whereas these numerous small studies have tended to reveal increased rates of complete remission, the long-term outcome was simply beyond their scope. The only randomized study on late intensification did suggest but could not demonstrate an improvement in survival, because the patient sample was too small and the death rate in the intensified group was too high.²⁶ In recent years, more randomized trials were performed to study early intensification regimens involving increases in dose-intensity of 7% to 33%.²⁰⁻²³ These studies did reveal encouraging improvements in 2-year survival, even though both CR and median survival remained unchanged in some studies. These trials thus far have a short follow-up period, but genuine data on long-term survival can be expected in the foreseeable future.

Experimental data have shown that drug concentrations must be increased to 300% to 500% *in vitro* to effect cell kill in resistant cell lines on a similar scale as in sensitive ones.⁴³ As hematopoietic growth factors and peripheral stem cells became available for clinical use, increases in dose-intensity by at least a factor of 3 became realistic.³⁰ Patients with lung cancer, however, tend to suffer from cardiovascular and pulmonary comorbidities that might be limiting to high-dose regimens,⁴⁴ which made it necessary before embarking on a randomized trial to test the feasibility of the high-dose approach in a multicenter setting.

The present study demonstrates that intensive sequential chemotherapy under the cover of PBPCs, filgrastim, and prophylactic antibiotics is indeed feasible. The actual implemented dose-intensity of ICE was 94% of the planned dose-intensity. Moreover, 72% of all patients completed the treatment program according to schedule. This compares very favorably with results obtained in a series of younger breast cancer patients, only 40% to 67% of whom completed all cycles of sequential chemotherapy as planned,^{45,46} or with a 56% rate of completion of six treatment cycles administered to another group of SCLC patients.²⁹ The 9% rate of toxic deaths was high in our series but was within the range of other intensification regimens.^{22,25,29,47} The high rate of toxic deaths might be due to the frequently associated comorbidities observed in these patients and also to the limited experience of some centers in administering sequential intensive therapy. Indeed, among the 15 centers, nine treated only \leq two patients. Five of the six toxic deaths in our study occurred among the first 25 patients treated within the first year of accrual and, therefore, might be ascribed to

the learning curve. There was only one toxic death over the entire remainder of the trial (44 patients) once the requisite experience with the adopted strategy was present in all centers and the need for prophylactic antibiotics during the myelosuppressive period recognized, allowing us to safely consider the launching of a large multicenter randomized trial. Other types of toxicity unrelated to the expected myelosuppression were rare and could be managed in our multicenter setting. Severe diarrhea occurred in 14% and mucositis in 10% of treatment cycles. Long-term toxicity, such as veno-occlusive disease or lung fibrosis of the type reported for repeated cycles of alkylating agents,⁴⁷ was completely absent from our study.

The ICE combination of chemotherapeutic agents has a favorable therapeutic index. A steep dose response combined with the potential of synergistic antitumor activity and a favorable spectrum of nonhematopoietic toxicity makes this combination a natural candidate for high-dose therapy.⁴⁸ Intensification of ICE in SCLC has been tested under the cover of hematopoietic growth factors with a cumulative dose-intensity during the first three cycles that was increased to 134%.²¹ The dose-intensity could be doubled by adding hematopoietic progenitor cells.²⁹ Our study demonstrates that further intensification of up to 290% of standard ICE can be achieved at an acceptable toxicity profile that compares favorably with less intensive regimens.^{21,22,29} If in this study the dose of carboplatin was administered on a mg/m² basis in order to have a simple comparison with the standard ICE regimen, then in the ongoing randomized EBMT trial, it is based on the area under the curve to avoid individual variation in dose and toxicity.

Our initial concern that administration of multiple sequential cycles might progressively and cumulatively exhaust hematopoiesis proved to be unfounded. There were no differences between treatment cycles regarding the duration or time until recovery of leukopenia and thrombocytopenia, nor were there any differences regarding the number of erythrocyte and platelet transfusions. This is in contrast to the patterns observed with whole blood²⁹ as the source of hematopoietic progenitors or even hematopoietic growth factors only.²¹ Those studies were characterized by a progressive decrease in platelet nadirs starting during the second cycle with an increase in the requirement for platelet transfusion.²⁹ One way of explaining this phenomenon would be that the hematopoietic progenitors collected after each high-dose chemotherapy course were declining in both quality and quantity.⁴⁹ In our own series, we did not have this problem, thanks to a large-scale collection of progenitors (median CD34⁺ cells, $16.6 \times 10^6/\text{kg}$) harvested after the administration of combined high-dose epirubicin and filgrastim before high-dose ICE therapy was started. In

accordance with EBMT recommendations for safe reinfusion, 93% of our patients received at least $2 \times 10^6/\text{kg}$ of CD34⁺ cells.³¹ Furthermore, our policy of harvesting hematopoietic progenitors before therapy also reduced the number of leukaphereses. Considering the different techniques used in the various centers, it is remarkable that a median of three leukaphereses were enough to obtain the targeted collection, with only 15 patients (30%) needing four or five leukaphereses. Previous dose-intensive multiple approaches have, by comparison, required at least six to eight leukaphereses,^{29,45,46} which is both more expensive and renders the procedure as a whole cumbersome. The constraints inherent in any multicenter randomized trial required us to develop a simpler and more economical design.

The main objective of this study was to ascertain whether the adopted strategy of sequential high-dose chemotherapy of SCLC was feasible, and, therefore, the criteria for patient selection remained broad. Certain adverse prognostic factors such as brain metastases or multiple metastatic sites were not considered to be exclusion criteria. Likewise, the use of radiotherapy was not standardized but left within the discretion of the various centers. Given these broad criteria, the achieved rates of complete remission of 51% in the absence and 58% in the presence of radiotherapy was in the range of other intensive approaches. This rate was significantly higher in patients with limited disease (70%) than in patients with extensive disease (36%), and all complete responders were tumor-free as determined by bronchoscopy and histopathology. These results are obviously better than those usually reported for standard treatment, where the rate of CR does not tend to exceed approximately 20% in limited disease and 10% in extensive disease.¹²⁻¹⁴ They are in the range, however, of what is obtained after other intensive treatment programs such as two cycles of high-dose cyclophosphamide, whether alone²⁷ or in combination.^{24,28}

Equally high rates of complete remission have been put forward in relatively recent randomized trials,²⁰⁻²² and interestingly not only for the intensified chemotherapy arms but also for the standard arms. Two explanations are possible for these puzzling data. First, the method of assessing response may not have been sensitive enough to discriminate between CR and good partial response, which would be consistent with the fact that these studies relied solely on standard chest x-ray. Second, there is evidence that the prognosis of patients with limited SCLC has improved in recent years.⁵⁰ Viewed in this way, the rate of complete remission would not be a surrogate for long-term survival, a notion that is accepted for most tumors. Despite similar rates of CR, the intensified arm of these studies showed an improvement at 2 years.²⁰⁻²² Furthermore, the figures on median survival were comparable but were not predictive of

long-term outcome.²¹ This suggests that improvement in long-term survival, rather than response rate or median survival, should be the main end point in designing a randomized trial for SCLC.

The present study resulted in a median survival of 18 months among patients with limited disease, and 32% of them were alive at 2 years. The corresponding results in extensive disease were 11 months for median survival, with 5% of patients alive at 2 years. In the published randomized trials, the 2-year survival rate in the intensive arm was 32% to 42% in limited disease^{19,20} and \leq 5% in extensive disease. Any comparison of treatment outcomes from different trials is hampered by the wide variety of prognostic factors resulting from broad inclusion criteria. Based on our comparable results, however, as well as on the fact that the majority of patients still died of tumor recurrence (although a possible plateau might appear after 3 years in patients with limited

disease), it would seem that any advantage in survival tends to be small and confined to patients with distinct clinicopathologic characteristics. These populations remain to be defined in large prospective trials. The EBMT has launched such a trial in which biologic specimens from the primary tumor, from the bone marrow, and from the leukaphereses will be studied for molecular markers. In this ongoing trial, standard and intensive ICE regimens are being compared with a view to doubling the rate of long-term survival at 3 years in patients with limited and extensive SCLC involving not more than two metastatic sites. Radiotherapy has been defined similarly in both arms to improve locoregional control and decrease the brain recurrence rate.

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APPENDIX

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