ARTICLE

A Threefold Dose Intensity Treatment With Ifosfamide, Carboplatin, and Etoposide for Patients With Small Cell Lung Cancer: A Randomized Trial

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Background The dose intensity of chemotherapy can be increased to the highest possible level by early administration of multiple and sequential high-dose cycles supported by transfusion with peripheral blood progenitor cells (PBPCs). A randomized trial was performed to test the impact of such dose intensification on the long-term survival of patients with small cell lung cancer (SCLC).

Methods Patients who had limited or extensive SCLC with no more than two metastatic sites were randomly assigned to high-dose (High, n = 69) or standard-dose (Std, n = 71) chemotherapy with ifosfamide, carboplatin, and etoposide (ICE). High-ICE cycles were supported by transfusion with PBPCs that were collected after two cycles of treatment with epidoxorubicin at 150 mg/m^2, paclitaxel at 175 mg/m^2, and filgrastim. The primary outcome was 3-year survival. Comparisons between response rates and toxic effects within subgroups (limited or extensive disease, liver metastases or no liver metastases, Eastern Cooperative Oncology Group performance status of 0 or 1, normal or abnormal lactate dehydrogenase levels) were also performed.

Results Median relative dose intensity in the High-ICE arm was 293% (range = 174%–392%) of that in the Std-ICE arm. The 3-year survival rates were 18% (95% confidence interval [CI] = 10% to 29%) and 19% (95% CI = 11% to 30%) in the High-ICE and Std-ICE arms, respectively. No differences were observed between the High-ICE and Std-ICE arms in overall response (n = 54 [78%, 95% CI = 67% to 87%] and n = 48 [68%, 95% CI = 55% to 78%], respectively) or complete response (n = 27 [39%, 95% CI = 28% to 52%] and n = 24 [34%, 95% CI = 23% to 46%], respectively). Subgroup analyses showed no benefit for any outcome from High-ICE treatment. Hematologic toxicity was substantial in the Std-ICE arm (grade $\geq$ 3 neutropenia, n = 49 [70%]; anemia, n = 17 [25%]; thrombopenia, n = 17 [25%]), and three patients (4%) died from toxicity. High-ICE treatment was predictably associated with severe myelosuppression, and five patients (8%) died from toxicity.

Conclusions The long-term outcome of SCLC was not improved by raising the dose intensity of ICE chemotherapy by threefold.

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Lung cancer is a leading cause of death in industrialized countries and accounts for 20% of all cancer deaths. Modifications in smoking habits and in the tar and nicotine composition of cigarettes have led to changes in the distribution of histologic subtypes. Adenocarcinoma is now the most common type of lung cancer; squamous cell carcinoma and small cell lung cancer (SCLC) have decreased during the past 20 years (1–3). SCLC accounted for 25% of all lung cancers in the United States in the 1990s but only 12.9% in 2002 (2,4). The number of patients who are diagnosed with lung cancer has also decreased in some European countries but has continued to increase in others (2) and remains at 25 000–50 000 people per year in Europe (5,6).

Chemotherapy has dramatically improved the prognosis of SCLC patients, but the recurrence rate after chemotherapy is still

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CONTEXT AND CAVEATS

Prior knowledge

Most small cell lung cancers (SCLCs) recur and become resistant to chemotherapy.

Study design

Randomized trial to compare high-dose (High) with standard-dose (Std) ifosfamide, carboplatin, and etoposide (ICE) in SCLC patients with limited or extensive disease.

Contributions

The treatment intensity in the High-ICE arm was almost three times that in the Std-ICE arm. No differences between the two groups in 3-year survival or in overall or complete response were observed. Both treatments induced severe toxicities.

Implications

Long-term outcome of SCLC was not improved by increasing ICE treatment intensity nearly threefold, and toxicities were severe. Thus, intense ICE therapy for SCLC should not be used in the future.

Limitations

The study had low accrual, and the initial trial design had to be altered to include interim analyses.

high. Indeed, patients with limited disease can expect to live for a median of only 12–20 months after diagnosis and those with extensive disease only 8–10 months. Only 10% of patients with limited disease survive for 5 years (4,7–8). Despite initial response to chemotherapy, tumors recur in the majority of patients in less than a year and are then highly resistant to further therapy.

Various approaches to improve the efficacy of chemotherapy and to overcome chemoresistance of SCLC have been explored by testing novel agents, new combination regimens, and different schedules. Regimens that contain cisplatin are used most commonly and have been demonstrated by meta-analysis to yield a survival benefit over regimens that lack cisplatin (9). The etoposide/cisplatin (PE) regimen is a widely accepted standard (10). Indications of better outcomes with irinotecan instead of etoposide (11) have not been confirmed by recent evidence (12). The addition of paclitaxel to PE increases toxicity but does not improve response rates or median survival (13,14). Other investigators have incorporated ifosfamide in regimens known as ICE (ifosfamide, carboplatin, and etoposide) and VIP (cisplatin, ifosfamide, and etoposide). Randomized studies with these regimens have suggested statistically significant benefits in progression-free and overall survival compared with standard PE or cyclophosphamide, doxorubicin, and vincristine (CAV) regimens (15,16). The ICE regimen, which avoids the nephrotoxicity, ototoxicity, and neurotoxicity of cisplatin, has been tested extensively for the treatment of SCLC, mainly in European institutions (17–19). However, it has not been widely accepted because ICE is more toxic than PE and cannot be given concurrently with radiotherapy.

Given its high chemosensitivity but early appearance of chemoresistance, we deemed SCLC suitable for attempting to maximize the chemotherapy dose level per cycle, the total dose, or the dose intensity. This strategy was supported by experimental data obtained in vitro, suggesting that drug concentrations had to be increased threefold to fivefold to obtain a similar level of cell lysis in resistant SCLC cell lines as in sensitive ones (20). The high-dose ICE combination (High-ICE) has been tested in different tumor types (21,22) and has a known toxicity profile (myelosuppression) that can be controlled by support with peripheral blood progenitor cells (PBPCs). Furthermore, the European Group for Blood and Marrow Transplantation (EBMT) has previously tested administration of High-ICE in multiple and sequential cycles in patients with SCLC supported by the transfusion of PBPCs (23). We carried out a trial to compare standard-dose ICE (Std-ICE) with repeated High-ICE treatment administered to SCLC patients with a relatively good prognosis who might benefit from such a very intensive strategy. The main objectives were to double the 3-year survival rate, to compare response rates and toxicity, and to define the impact on different patient subgroups.

Subjects and Methods

Patient Selection

Eligible patients had previously untreated, histologically confirmed SCLC. Participating centers had to be members of the EBMT. Disease staging was determined by clinical examination; chest, abdominal, and brain computed tomography (CT) scan; bone scan; and bone marrow biopsy and aspiration. Patients were included if they had limited disease (no metastases outside the thorax) or extensive disease with two or fewer metastatic sites, excluding brain; were 65 years old or younger; had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; had no previous treatment; had normal hematologic, renal, and cardiac function; and had liver function tests within 2.5 times the normal range (the standard for patients with potential liver metastases to have adequate liver function to tolerate chemotherapy).

Study Design

The trial was a phase III two-arm open-label trial, with centralized randomization by the minimization method (stratification factors: limited disease extent, extensive without liver metastases, and extensive with liver metastases; ECOG performance status of 0 or 1; and normal or elevated levels of lactate dehydrogenase [according to the laboratory upper normal values of each center]). Random allocation was with center override to avoid imbalances of more than three patients between the two arms. All patients provided written informed consent, and the trial was approved by each institution's Institutional Review Board. Trial registration: EU-98001, NCI-V-1645, NCT00011921.

High-Dose Chemotherapy with Ifosfamide, Carboplatin, and Etoposide Arm

Every 28 days, patients were intravenously administered three cycles of ifosfamide at 2.5 g/m^2 per day × 4 days (10 g/m^2), carboplatin at area under the curve (AUC) = 5.0 per day × 4 days (AUC = 20), etoposide at 300 mg/m^2 per day × 4 days (1200 mg/m^2), and uromitexan at 5.0 g/m^2 per day on days 1–5 (23). PBPCs (≥2 × 10^6 CD34+ cells per kg) that had been collected before ICE treatment began (see below) were reinfused 48 hours after chemotherapy, and filgrastim at 5 μg/kg per day was administered subcutaneously for 14 days.

Treatment cycles were delayed up to 2 weeks until leukocyte concentrations recovered to 3.5 × 10^9/L or greater, granulocyte

concentrations recovered to 1×10^9/L or greater, and platelet concentrations recovered to 100×10^9/L or greater. Etoposide dose was reduced by 30% in patients with World Health Organization (WHO) grade 3 or greater esophagitis, mucositis, or diarrhea. Carboplatin was omitted if grade 3 or greater neuropathy was present. Ifosfamide treatment was omitted in the presence of central nervous system toxicity (WHO grade ≥3) (24).

Collection of Peripheral Blood Progenitor Cells

Patients in the High-ICE arm only had PBPCs reinfused after each of the three ICE cycles to limit the magnitude of myelosuppression induced by the high treatment intensity. Six to eight weeks before patients were given ICE treatment, they were given two cycles of non–cross-resistant chemotherapy (ie, paclitaxel and epidoxorubicin) with the intent to purge circulating tumor cells in vivo (25). A 4-hour infusion of epidoxorubicin at 150 mg/m^2 was given on day 1, and a 3-hour infusion of paclitaxel at 175 mg/m^2 was given on day 2; both were repeated after 21 days. After the second cycle, filgrastim at 5 μg/kg was delivered until PBPC collection was completed. CD34+ cells [9×10^6 per kg, as measured by flow cytometry (26)] were collected to support the three cycles of ICE treatment, and low counts at leukapheresis ($<6 \times 10^6$ per kg) were regarded as treatment failure. Leukapheresis was repeated daily until adequate numbers of PBPCs were obtained.

Standard-Dose Chemotherapy with Ifosfamide, Carboplatin, and Etoposide Arm

Patients received six cycles (28 days per cycle) of ifosfamide at 5.0 g/m^2 and carboplatin at 300 mg/m^2 intravenously on day 1, etoposide at 180 mg/m^2 intravenously on days 1 and 2, and uromitexan at 5.0 g/m^2 on days 1 and 2 (27). No dose reduction was permitted. Chemotherapy was delayed up to 2 weeks in the presence of nonhematologic toxicity grade 3 or greater (except nausea, diarrhea, or alopecia) and if creatinine clearance was less than 50 mL/min, leukocyte concentrations were less than 3×10^9/L, and platelet concentrations were less than 30×10^9/L.

Ifosfamide, Carboplatin, and Etoposide Dose Intensity

Relative dose intensity (total dose received over actual treatment duration divided by total dose prescribed by the protocol over the theoretic treatment period) was calculated as described by Lorigan et al. (28) with the duration for the last treatment cycle set to 28 days. Median relative dose intensity was calculated for each treatment cycle for all patients. As a measure of relative dose intensification, relative dose intensity was also computed for patients in the High-ICE arm with reference to the Std-ICE protocol.

Radiotherapy

After the end of chemotherapy, when all toxicities had resolved, thoracic radiotherapy at a total dose of 60 Gy in 2-Gy fractions was proposed for patients who had responding limited disease and those who had extensive disease in complete remission. Patients in complete remission were also offered prophylactic cranial irradiation (PCI) at a dose of 30 Gy.

Assessment of Toxicity and Treatment Response

Examinations During Chemotherapy. Clinical examinations were performed weekly. Complete blood counts were obtained twice weekly using standard methods. Each treatment cycle was preceded by hepatic and renal function tests (transaminases, gammaglutamyltransphosphatase, alkaline phosphatase) using standard methods and chest radiography. Toxicity was graded according to WHO criteria (24).

Examinations After Chemotherapy/Radiotherapy. The following were performed after all cycles of chemotherapy were completed: physical examination; chest radiography; CT scan of the chest and abdomen; bronchoscopy, including biopsy; cardiac left ventricular ejection fraction (multiple-gated acquisition scan or echocardiography); bone scan if initially positive; bilateral bone marrow biopsy; complete blood count; biochemical profile; and renal function test. A CT scan of the chest was also performed in all patients at the end of thoracic radiotherapy.

Examinations During Follow-up. Comprehensive medical histories, clinical examinations, and complete blood counts were obtained every month. Biochemical profiles, renal function tests, and chest radiography were performed every 3 months. CT scans of the chest and abdomen were obtained at minimum intervals of 6 months.

Response Criteria. Each patient's total tumor load was established by summing bidimensional tumor measurements that were obtained from CT scan, in which the longest diameter of each lesion was multiplied by its perpendicular diameter. Response to treatment was classified in accordance with modified WHO criteria (29).

Statistical Analysis

The primary endpoint was overall survival based on time from random assignment to death. Secondary endpoints included 1) progression-free survival based on time from random assignment to death or disease progression (local or metastatic), whichever occurred first; 2) overall response rate; and 3) toxicity. Percentages of events over time were calculated with the Kaplan–Meier method (30). Greenwood's formula (31) was applied to obtain the corresponding standard errors. Each comparison of survival results is presented with P values from the log-rank test (32). Response rates and other percentages were compared with the χ^2 test. All probability values are from two-sided tests, and P values less than .05 were considered to be statistically significant. All analyses were performed according to the intention-to-treat principle, after the exclusion of five patients (see "Results"). Exploratory subgroup analyses were performed according to sex and to the factors used to stratify randomization (see above, "Study Design"). Patients who were lost to follow-up or refused treatment were not excluded from the analysis. An independent data monitoring committee (IDMC) was set up to review toxic events and to issue recommendations for continuation or modification of the study.

It was expected that High-ICE treatment would raise the 3-year survival from 12% to 24%. A power of 90%, a statistical significance level of 5%, 3 years of accrual, and 1 year of follow-up were considered; thus, the study required 270 deaths for 360 patients accrued (33). The study began accruing patients in 1997, but the accrual rate was much lower than expected, and in 2004, it was agreed with the IDMC to convert the original fixed sample design to a sequential design with three equally spaced interim

analyses. The maximum number of events was adjusted to 311 due to the introduction of the stopping rule. The latter was based on boundaries for early stopping in favor of a difference (O'Brien–Fleming error spending function) or of lack thereof (Pocock Fleming error spending function) (33). At the time of the first interim analysis, the boundaries for early stopping with 114 events corresponded to type I and II error probabilities of 0.0004267 and 0.0488374, respectively. The following decision rule applied: stop in favor of the null hypothesis of no treatment difference if the log-rank test statistic is in the range of −0.500 to 0.500, stop in favor of the alternative hypothesis if this statistic is smaller than −3.523 or larger than 3.523, otherwise continue the trial.

Results

Patient Characteristics

A total of 145 patients from 18 centers were randomly assigned between June 19, 1997, and December 20, 2005, to High-ICE (n = 74) or Std-ICE (n = 71). Four patients in the High-ICE arm never started protocol treatment because they were identified as being clearly ineligible for the study after random assignment and were therefore excluded from all analyses (two had brain metastases, one had low ejection fraction, and one had acute coronary syndrome). One additional patient in the High-ICE arm was excluded from the analyses because the center never provided any data (Table 1). Baseline characteristics (Table 2) were well balanced across the treatment arms.

Peripheral Blood Progenitor Cell Mobilization and Collection

PBPCs were mobilized in all 69 patients in the High-ICE arm, but leukapheresis was not performed in four patients (toxic death, n = 2 [see below]; disease progression, n = 1; refusal, n = 1). A median of 16.7 (range = 7–52) × 10^6 CD34+ cells per kg were obtained after one, two, or three or more rounds of leukapheresis in 27 patients, 27 patients, and 11 patients, respectively.

Toxicity during mobilization consisted of neutropenia and reached grade 3/4 in 41 (59%) patients, with severe infections in 4 (6%). Two toxic deaths occurred related to sepsis (n = 1) and severe lysis syndrome (n = 1). Other toxicities included grade 3/4 thrombocytopenia in seven patients (10%), grade 3/4 anemia in five patients (7%), mucositis in six patients (9%), and severe nausea in four patients (6%).

Table 1. CONSORT flowchart of the trial*

Category	No. in each trial arm (N = 145)	
	High-ICE	Std-ICE
Allocated to intervention	74	71
Received allocated intervention	69	71
Did not receive allocated intervention	5	0
Reasons		
Ineligible	4	0
Absence of data	1	0
Lost to follow-up but analyzed	0	1
Chemotherapy was discontinued	26	19
Reasons		
Toxic death during mobilization	2	0
Progression during mobilization	3	0
Refusal	5	3
Toxicity	9	2
Progression	1	10
Clinically indicated	1	2
Insufficient PBPC collection	1	0
Toxic death	4	2
Completed all cycles	43	52
Analyzed for efficacy and toxicity	69	71

* High = high-dose; Std = standard-dose; ICE = ifosfamide, carboplatin, and etoposide; PBPC = peripheral blood progenitor cells.

Treatment Cycles

High-Dose Chemotherapy With Ifosfamide, Carboplatin, and Etoposide Arm. Eight of the 69 patients never started chemotherapy (refusal, n = 2; tumor progression, n = 3; toxic death, n = 2; preexisting clotting disorder, n = 1). A total of 43 patients (62%) underwent the entire course of three sequential cycles. Reasons for not completing all three treatment cycles included refusal

Table 2. Patient characteristics*

Characteristic	High-ICE (n = 69)	Std-ICE (n = 71)	Total (N = 140)
Disease extent, No.			
Limited disease	49	48	97
Extensive without liver involvement	14	16	30
Extensive with liver involvement	6	7	13
Sex, No.			
Male	52	51	103
Female	17	20	37
LDH concentration at registration, No.			
Normal	45	45	90
Elevated	24	26	50
ECOG performance status, No.			
0	41	41	82
1	28	30	58
Age, mean (range), y	52 (31–68)	54 (33–66)	53 (31–68)
Weight loss, mean (range), kg	2.5 (0–16)	2.1 (0–12)	2.3 (0–16)

* High = high-dose; Std = standard-dose; ICE = ifosfamide, carboplatin, and etoposide; LDH = lactate dehydrogenase; ECOG = Eastern Cooperative Oncology Group; limited disease = disease restricted to the ipsilateral hemithorax that can be encompassed within a radiation treatment plan. Elevated LDH values are defined as greater than the upper normal value given by the laboratory of each participating center.

(n = 3), toxicity (n = 9), toxic death (n = 4), progression (n = 1), and insufficient stem (CD34+) cells (n = 1). A total of 158 cycles were administered overall. Transfusion with PBPCs was applied with a median 5.1 (range = 2.1–12.7) × 10^6 CD34+ cells per kg per cycle.

Standard-Dose Chemotherapy With Ifosfamide, Carboplatin, and Etoposide Arm. One of the 71 patients died before chemotherapy was begun. A total of 52 patients (73%) underwent the entire treatment course of six cycles. Reasons for not completing all six cycles included refusal (n = 3), toxicity (n = 2), toxic death (n = 2), disease progression (n = 8), tumor-related death (n = 2), and discontinuation for clinical reasons (n = 2). A total of 365 cycles were administered overall.

Dose Intensity

Compliance with the treatment plan was good. Compared with the dose levels that were defined in the protocol, the median dose intensities administered reached 91% (range = 90%–97%) in the High-ICE arm and 99% (range = 99%–100%) in the Std-ICE arm. Median relative dose intensification for patients in the High-ICE arm compared with that in patients in the Std-ICE arm was 293%, with a range of 174%–392%.

Toxicity

Toxic events were mainly hematologic in nature. In the Std-ICE arm, grade 3/4 leukopenia was observed in 49 patients (70%). A total of 17 patients (25%) in this arm exhibited grade 3/4 thrombocytopenia and anemia. In the Std-ICE arm, grade 3/4 infections occurred in four (6%) patients and toxic deaths occurred in three patients (4%). In the High-ICE arm, all 61 patients exhibited grade 4 leukopenia and thrombocytopenia and 54 patients (88%) had grade 3/4 anemia. Grade 3/4 infections affected 19 (31%) patients in the High-ICE arm, and five (8%) toxic deaths occurred. Other toxicities (eg, nausea and vomiting, diarrhea, mucositis, renal, neurological) were more prevalent and severe in the High-ICE arm than the Std-ICE arm (Table 3). Patients in the High-ICE arm remained hospitalized for a median of 19.6 (range = 8–91) days vs 4.3 (0–32) days for patients in the Std-ICE arm.

Response to Treatment

The response rates are based on the entire sample of 140 patients. Antitumor responses were observed in 54 of 69 patients in the High-ICE arm and 48 of 71 patients in the Std-CE arm. These rates (78%, 95% confidence interval [CI] = 67% to 87%, and 68%, 95% CI = 55% to 78%) were not statistically significantly different (P = .156). The number of complete responders was 27 (39%, 95% CI = 28% to 52%) in the High-ICE arm and 24 (34%, 95% CI = 23% to 46%) in the Std-ICE arm. Response rates were also not different between the two arms when looking at disease extension subgroups. Among patients with limited disease, overall response (complete plus partial reponses) was seen in 39 of 49 patients (80%, 95% CI = 66% to 90%) and 33 of 48 patients (69%, 95% CI = 54% to 81%) (P = .25) in the High- and Std-ICE arms, respectively. Similarly, among patients with extensive disease, the proportions were 15 of 20 (75%, 95% CI = 51% to 91%) and 15 of 23 (65%, 95% CI = 43% to 84%) (P = .49), respectively.

Radiotherapy

Forty-four patients in the High-ICE arm and 48 in the Std-ICE arm were treated with thoracic radiotherapy; 34 and 35, respectively, were the responding patients with limited disease at baseline. Twenty-seven patients in each of the two study arms received PCI; 20 and 21, respectively, had limited disease at baseline. Based on this selected group of patients, the overall response after thoracic radiotherapy was 40 of 44 (91%) in the High-ICE arm vs 39 of 48 (81%) in the Std-ICE arm.

Progression-Free and Overall Survival

A total of 121 patients exhibited disease progression at the time of analysis, including 63 in the High-ICE arm vs 58 in the Std-ICE arm. The first progression site was local in 29 (42%) vs 27 patients (38%) and distant in 36 (52%) vs 30 patients (42%). Overall, sites of first distant progression included liver in 30 (28%), brain in 23 (21%), lung in 22 (20%), and bone in 9 (8%) of all patients, with many patients having disease progression at more than one site.

Median progression-free survival was 10.5 months overall (12.2 months in the High-ICE arm vs 8.8 months in the Std-ICE arm; P = .972) (Figure 1). At 3 years, 9% (95% CI = 4% to 18%) and

Table 3. Nonhematologic toxicity in both arms of the trial*

	High ICE (n = 158 cycles)					Std ICE (n = 365 cycles)				
	WHO grade, No.					WHO grade, No.				
Toxicity	**1**	**2**	**3**	**4**	**3/4, %**	**1**	**2**	**3**	**4**	**3/4, %**
Ototoxicity	–	4	2	–	3	–	1		–	–
Mucosal	14	16	13	3	26	9	2	2	–	3
Nausea–vomiting	15	18	17	3	33	18	13	4	–	6
Gastrointestinal	12	16	12	4	26	10	4	1	–	1
Bleeding	10	7	5	–	8	6	–	1	–	1
Infections	3	10	15	4	31	1	10	3	1	6
Cardiac	2	4	3	–	5	1	–	1	2	4
Neurologic	7	6	2	3	8	8	2	2	1	4
Renal	3	11	4	1	8	3	–	–	1	1

* High = high-dose; Std = standard-dose; ICE = ifosfamide, carboplatin, and etoposide; WHO = World Health Organization (24); – = none reported. Only patients who had any chemotherapy were considered, that is, n = 8 in the High-ICE arm and n = 1 in the Std-ICE arm were excluded.

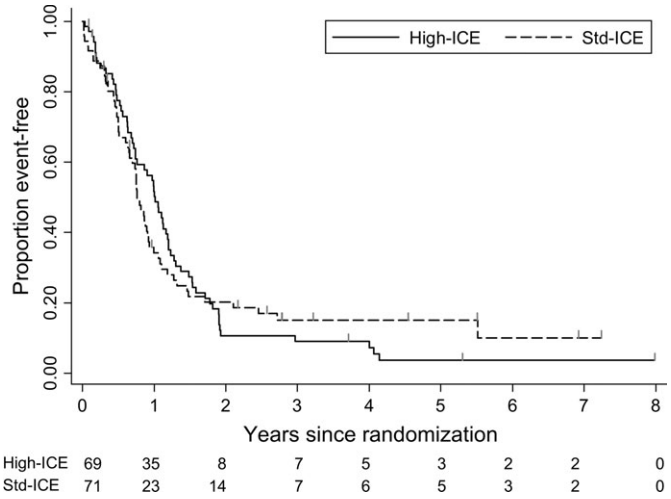

Figure 1. Progression-free survival among patients in the trial. Kaplan–Meier analyses of progression-free survival. **Vertical lines** are censored observations. *P* = .972 (two-sided) was calculated using the log-rank test. High-ICE = high-dose chemotherapy with ifosfamide, carboplatin, and etoposide; Std-ICE = standard-dose chemotherapy with ifosfamide, carboplatin, and etoposide.

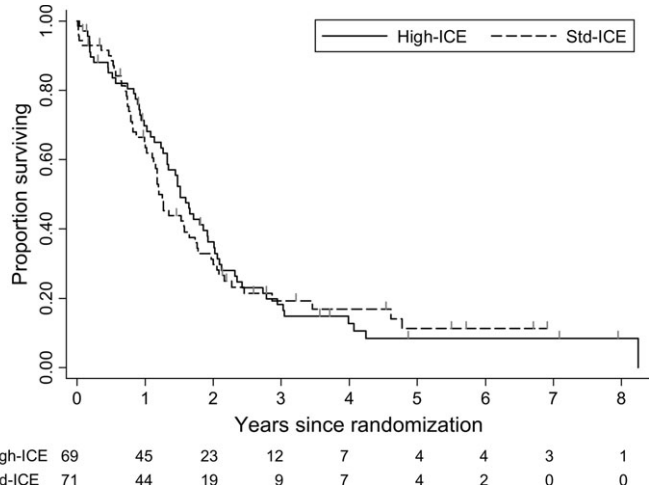

Figure 2. Overall survival among patients in the trial. Kaplan–Meier analyses of progression-free survival. **Vertical lines** are censored observations. *P* = .767 (two-sided) was calculated using the log-rank test. High-ICE = high-dose chemotherapy with ifosfamide, carboplatin, and etoposide; Std-ICE = standard-dose chemotherapy with ifosfamide, carboplatin, and etoposide.

15% (95% CI = 8% to 25%) of patients in the High-ICE and Std-ICE arms, respectively, had not developed disease progression.

A total of 114 deaths were reported, including 58 and 56 patients in the High- and Std-ICE arms, respectively. The deaths were due to tumor progression in 45 and 43 patients, respectively, and to toxicity in 10 and 5 patients, respectively; other or unreported causes of death accounted for three and eight deaths, respectively.

Log-rank testing on the accumulated data yielded a statistic with a value of .09 (*P* = .767), which was well within the stopping range of −0.500 to 0.500. Thus, no evidence for a potential treatment effect was present. Three-year overall survival rates were 18% (95% CI = 10% to 29%) in the High-ICE arm vs 19% (95% CI = 11% to 30%) in the Std-ICE arm. Overall median survival was 17.3 months (18.1 months in the High-ICE arm vs 14.4 months in the Std-ICE arm; Figure 2).

Exploratory analysis by disease extension, limited disease level, sex, and performance status did not suggest a benefit of High-ICE. In particular, the 2-year survival rate was 39% (95% CI = 25% to 53%) vs 37% (95% CI = 23% to 50%) in the High-ICE vs Std-ICE arms, respectively, when analyses were restricted to patients with limited disease.

Discussion

This study is the first, to our knowledge, to test in a randomized fashion the role of early intensification of chemotherapy administered repeatedly with sequential courses supported by hematopoietic stem cells for the treatment of SCLC. The EBMT designed the present trial to include a standard-dose arm as one of the most effective regimens available and a high-dose arm that would offer the maximum dose intensity. The trial was designed prospectively to test the hypothesis that increasing the dose intensity of the ICE regimen by a factor of three would double the long-term 3-year survival. Such a level of dose intensification has never been tested previously, but despite good compliance to the treatment plan, this therapeutic strategy failed to overcome the intrinsic chemoresistance of SCLC. Such a level of chemotherapy dose intensification has been continuously advocated in the past until very recently, and it has subjected patients to clinically significant toxicities without creating a basis for solid conclusions (34–37); with the results of this study, this strategy should now be discarded.

The study was limited by its slow accrual rate. The decreasing incidence of SCLC in western Europe (2) and the fading interest in intensification for the treatment of solid tumors (38,39) had a negative impact on the accrual rate. To overcome this limitation, the EBMT was forced to modify the statistical design by introducing points of interim analysis with strong boundaries to draw solid definitive conclusions. The present trial showed no differences between the High- and Std-ICE arms. Similar rates of overall (78% vs 68%) and complete (39% vs 34%) response were obtained. These results are in accord with those of our previous trial (23) and with other early intensification regimens in small phase II studies (23,34). Also, the proportion of complete responders in the Std-ICE arm was consistent with rates of 39%–54% that have been documented for other Std-ICE regimens (15,40).

Progression-free survival was 12.2 months in the High-ICE arm and 8.8 months in the Std-ICE arm (*P* = .972). Similar values, ranging from 8.5 to 10.9 months, have been obtained with the dose-densification approach, in which the increase in the dose intensity is obtained by reducing the interval between cycles without increasing the dose per cycle (28,41,42). Sites of disease progression were similar in both treatment arms, with the brain being affected first in 20% of patients. PCI and thoracic radiotherapy were delivered at the end of treatment to 42% and 71%, respectively, of patients with limited disease. It has been proposed that the rate of brain metastases can be reduced by early concomitant radiotherapy (43) and that the effect of radiotherapy on tumor control and ultimately on survival depends on the timing of radiotherapy, time to completion, dose, and fractionation schedule (44–46). Our radiotherapy schedule was designed at a time when these issues were not settled.

The primary endpoint of our study was 3-year overall survival, which was attained by 18% of patients in the High-ICE arm vs 19% in the Std-ICE arm. Median overall survival was 18.1 vs 14.4 months (P = .767), with no advantage of High-ICE in any subgroup analyses. Patients with limited disease showed 2-year survival rates of 39% vs 37%. These rates are consistent with the most active treatment strategies and a strategy combining minimal increase of chemotherapy with early radiotherapy (43%) (47) or concomitant chemotherapy with bifractionated radiotherapy (47%) (48). Median 2-year survival values from 20% to 33% were obtained in dose-dense arms of various randomized trials (15,40,41). Our results are similar to those obtained by doubling the dose intensity (15,40,41). It is, however, difficult to compare different studies in general due to different patient selection.

The combination of paclitaxel and epidoxorubicin was unable to improve the results of High-ICE treatment but was a good regimen for mobilizing PBPCs. Transfusion of PBPCs allowed the relative dose intensity of High-ICE to be maintained in 91% of cycles and the median dose intensity to be increased to almost 300% compared with Std-ICE treatment. This dose intensity was similar to that reached in our previous EBMT phase II study (23) and higher than in any previous trial. Although the High-ICE regimen led to more severe toxicity, the Std-ICE regimen was still toxic, involving grade 3 and higher infection in 6% and toxic death rate in 4% of patients. Other triplet regimens based on ifosfamide are also complicated by toxic effects, with severe leukopenia in 71%–96% of patients, grade 3 and higher infection in 15%–84%, and toxic death in 2%–12% (15,16,28,40,42). In comparison, PE caused grade 3 and greater neutropenia in 47%–85% of patients and toxic death in 5.5% of patients (16,49). Severe myelosuppression associated with High-ICE treatment was an expected finding, and in this arm, we observed grade 3 and higher infection in 31% and toxic death in 8% of patients. Other severe toxicities in this group included diarrhea and abdominal pain (26%), mucositis (26%), renal failure (8%), and neurological events (8%). This profile is consistent with a previous EBMT trial (23). The densification strategy used elsewhere (28) for doubling dose intensity also caused severe leukopenia and thrombopenia in 94% of patients and anemia in 71% (28,42). However, in these trials, neutropenic sepsis and toxic death were confined to 18%–56% and 3% of patients, respectively. Toxicity was also observed in the PBPC mobilization phase of the present trial, with toxic death in 3% (n = 2) of patients, compared with the collection of PBPCs by the whole-blood technique of the dose-densification approach, for which no toxicity was recorded (28).

The concept of dose intensification has now been studied exhaustively. Higher total doses involving more cycles and longer treatment periods have not improved survival (50), although some progress has been made through moderate enhancements, such as escalating doses over a few cycles, reducing cycle intervals, or combining more agents (40,47,49,51–54). Increases of chemotherapy dose intensity in SCLC clinical trials have only been able to raise dose by 30%–70%. Doubling the relative dose intensity by densification of chemotherapy could not improve the results (28). The approach explored in the present trial succeeded in raising the peak dose, total dose, and dose intensity of ICE by threefold but has clearly been ineffective and highly toxic. In addition, this regimen is costly. As a result, this strategy should be abandoned. Research should now focus on other treatment approaches.

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