Standard versus Dose-Intensified Chemotherapy with Sequential Reinfusion of Hematopoietic Progenitor Cells in Small Cell Lung Cancer Patients with Favorable Prognosis

Erika Buchholz, MD, Christian Manegold, MD,* Lothar Pilz,†*
Nick Thatcher, MD, BChir, PhD,‡ and Peter Drings, MD§

Purpose: The combination of ifosfamide, carboplatin, and etoposide (ICE) is highly effective in treating small cell lung cancer (SCLC). Myelosuppression resulting in leukopenia and thrombocytopenia is the dose-limiting toxicity.

Patients and Methods: This phase 3 study assessed 2-year survival improvement with dose intensification of ICE chemotherapy (ICT) in patients with good-prognosis SCLC. Patients received up to six cycles of ICT with filgrastim-supported sequential reinfusion of peripheral blood progenitor cells every 14 days, or standard ICE (SCT) every 28 days.

Results: Eighty-three patients were randomized to ICT ($n = 42$) or SCT ($n = 41$). Median survival was significantly improved with ICT (30.3 mo) versus SCT (18.5 mo; $p = 0.001$); 2-year survival was 55% for ICT and 39% for SCT ($p = 0.151$). Time to progression (TTP) was significantly improved, with 15 months for ICT versus 11.1 months for SCT ($p = 0.0001$). Overall response rates were 100 and 88% for ICT and SCT, respectively ($p = 0.0258$). SCT was associated with significantly less grade 3 and 4 leukopenia at day 8 ($p < 0.0001$), less thrombocytopenia at day 14 ($p < 0.0001$), and more favorable platelet nadir ($p < 0.0001$). The need for platelet and red blood cell transfusions significantly increased in the ICT group ($p < 0.0001$). Nonhematologic adverse events in both groups were comparable and mostly grade 1 or 2.

Conclusion: Patients receiving ICT with filgrastim achieved significant increases in median survival and TTP despite an increased need for transfusions.

Key Words: Small cell lung cancer, Hematopoietic progenitor cells, Filgrastim, ICE, Chemotherapy.

(*J Thorac Oncol.* 2007;2: 51–58)

*Department of Surgery and Interdisciplinary Thoracic Oncology, Klinikum Mannheim, Mannheim, Germany; †German Cancer Research Center, Department of Biostatistics, Heidelberg, Germany; ‡Department of Medical Oncology, Christie Hospital NHS Trust, Manchester, United Kingdom; §Department of Oncology, Thoraxklinik Heidelberg, Heidelberg, Germany.

Address for correspondence: Erika Buchholz, M.D., Klinikum Mannheim, Department of Surgery and Interdisciplinary Thoracic Oncology, Theodor-KutzerUfer 1-3, D-68167 Mannheim, Germany; E-mail: erika-buchholz@t-online.de

ISSN: 1556-0864/07/0201-0051

Standard combination chemotherapies for the treatment of small cell lung cancer (SCLC) achieve response rates in up to 80% of patients, with a higher rate of complete response for patients with limited disease and better prognosis.[1–3] Combination regimens containing highly active ifosfamide, carboplatin or cisplatin, and etoposide (ICE), often in combination with vincristine (V-ICE), are common treatment options for SCLC.[2,4–7] Despite therapeutic improvements for patients with limited disease, overall median 5-year survival rates have been reported as only approximately 25%.[8,9] Therefore, novel treatments and strategies are needed to improve response and survival for patients with SCLC. Various investigated strategies are high-dose versus standard chemotherapy, prolonged initial treatment, or maintenance therapy, which may provide some survival benefits but often with increased toxicity.[10–12]

This study was designed to compare the feasibility and safety of dose-intensified ICE (ICT) with filgrastim support and peripheral blood progenitor cell (PBPC) reinfusion with standard-dose ICE (SCT) and to determine overall and 2-year survival for both regimens.

PATIENTS AND METHODS

Patient Characteristics

Eligible patients were no older than 70 years and had newly diagnosed and previously untreated histologically or cytologically proven SCLC. Patients needed an Eastern Cooperative Oncology Group score of 0 or 1, a prognostic Manchester score of 0 or 1,[13] a white blood cell count (WBC) of at least 3×10^9/liter, a platelet count of at least 100×10^9/liter, and normal cardiac, hepatic, and renal function. Before the study, all patients underwent disease staging that included a chest radiograph, liver and brain scan, bone marrow aspiration, and bone marrow biopsy (if the patient agreed). Patients with brain metastases or bone marrow metastases were excluded. Patients with prior treatment with cytokines or interferons and steroid dependency were not excluded. All patients provided signed informed consent. This study was approved by the local ethics committee and conducted according to the Declaration of Helsinki and the International Conference on Harmonisation.

Study Design and Treatment

This single-center study was initially planned as a phase 2 pilot study in 1996 with a sample size of 40 patients. After an interim analysis in 1999, the study design was amended to a phase 3 study to possibly detect statistically significant difference in 2-year survival observed at the interim analysis. The amendment was approved by the University of Heidelberg ethics committee. At that time it was believed that 2-year survival rate was about 10% in standard therapy and should be 25% or higher in intensified therapy. Therefore, with a power of 80% and a significance level of $\alpha = 0.05$, our planning indicated that 58 eligible patients per treatment arm should be recruited. Assuming a loss to follow-up of 20%, 64 patients in each treatment arm were recruited. Five interim analyses were planned, and the study was to be stopped if the 2-year survival time of the intensified therapy was significantly higher ($p < 0.01$) using the one-sided log-rank test. The third interim analysis of 70 patients (35 patients in each arm) showed a 22% increase in the 2-year survival rate for patients receiving ICT. This finding was statistically significant ($p = 0.003$), and patient recruitment was halted.

Patients were randomized (1:1) to receive up to six cycles of either ICT with filgrastim support and PBPC reinfusion every 2 weeks, or SCT every 4 weeks (Figure 1). The study design was based on a 1995 study by Pettengell et al.[14] Patient randomization was not stratified and was conducted as an intramural randomization provided by an external randomization list conducted by WiSP (Wissenschaftlicher Service Pharma, GmbH, Dr. Axel Hinke, Langenfeld, Germany). No dose reduction was allowed. Chemotherapy was administered if the WBC was at least 3×10^9/liter, the platelet count was at least 30×10^9/liter, and creatinine clearance was at least 50 ml/min; chemotherapy could be delayed for up to 1 week without PBPC reinfusion. Patients could receive transfusions to maintain a hemoglobin level of at least 8 g/dl and a platelet count of at least 20×10^9/liter. Patients in the ICT group who needed a 2-week treatment delay reverted to SCT for the remaining cycles. Filgrastim was administered to patients receiving ICT on days 4 to 13 of each cycle (the study protocol required administration of 300 μg/day for patients who weighed less than 70 kg and 5 μg/kg per day for patients who weighed at least 70 kg; in practice, patients who weighed less than 65 kg received 300 μg, and patients who weighed more than 65 kg received 480 μg). Venesection was used to collect 750 ml of whole blood into standard blood donor bags. The collection and storage of blood was done by the Institute for Immunology of the Ruprecht-Karls University of Heidelberg. Whole blood was stored at 4°C and reinfused as a normal blood transfusion for a 1-hour period within 56 hours of harvest and at least 24 hours after the next ICT cycle.

The primary endpoint of this study was the 2-year survival rate for SCT compared with that of ICT. Secondary efficacy endpoints included the median overall and 1-year survival rate and time to progression (TTP) in both treatment arms. Response was assessed according to prespecified criteria.[15] Briefly, complete response was defined as the disappearance of all clinical evidence of tumor at two assessments at least 4 weeks apart; partial response was a decrease of at least 50% in the sum of products of biperpendicular diameters without new or enlarged lesions at two assessments at least 4 weeks apart; progressive disease was defined as an increase of at least 25% in the sum of products of biperpendicular diameters and the appearance of a new lesion.

Secondary safety endpoints included grade 3 and 4 hematologic adverse events (hemoglobin, WBC, and platelet count on days 8 and 14 and at nadir), including transfusion requirements. Nonhematologic adverse events were assessed according to National Cancer Institute Common Toxicity Criteria, version 2.0.[16] Response and hematologic and renal

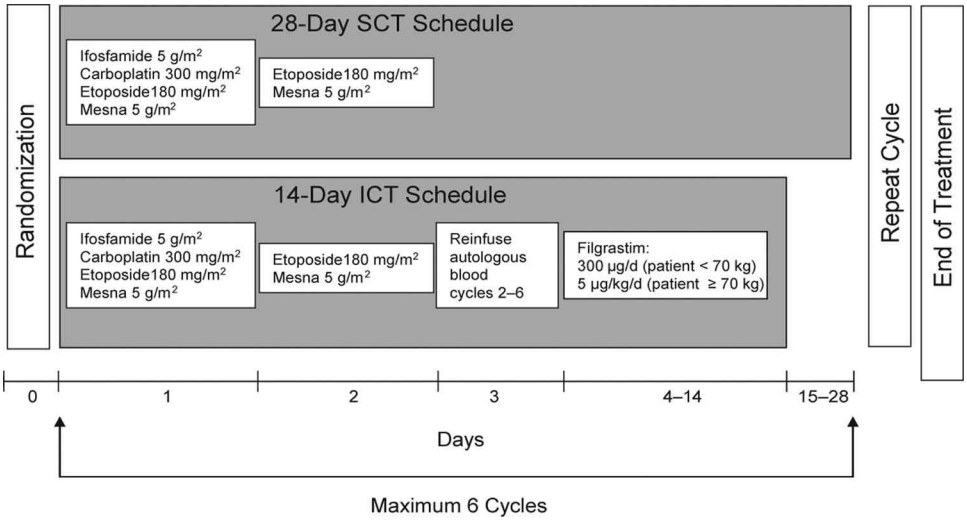

FIGURE 1. Ifosfamide, carboplatin, and etoposide (ICE) chemotherapy schedules. The *upper panel* shows the 28-day standard ICE (SCT) schedule, and the *lower panel* shows the dose-intensified ICE (ICT) schedule. In the ICT group, filgrastim was given on days 4 to 14, and hematopoietic progenitor cells in 750 ml of whole blood were collected on day 1 of cycle 2, with reinfusion on day 3 of cycles 2 to 6.

parameters were assessed before each cycle, and transfusion requirements and adverse events were assessed at each visit. Follow-up assessments, including type of second-line therapy where available, were performed every 6 months until death.

Statistics

Survival probabilities and TTP were calculated according to the Kaplan–Meier method.[17] Differences in the distribution of continuous and categorical variables were assessed using the Wilcoxon, Fisher's exact, chi-square, and log-rank tests. Median exposures to each treatment were calculated as described above and summarized as box plots.[15]

RESULTS

Patient Characteristics

Of the 83 patients enrolled from October 1996 to June 2002 at the Thoraxklinik, Heidelberg, Germany, 42 received ICT and 41 received SCT. Baseline and disease characteristics of the two groups were generally balanced (Table 1). The majority of patients were male (75%), with a median age of 54.2 years (higher for the SCT group). Only three ICT patients and one SCT patient had extensive disease. A total of 33 ICT patients (79%) and 26 SCT patients (63%) completed this study; six ICT patients (14%) and nine SCT patients (22%) discontinued because of adverse reactions. Four patients in the SCT group discontinued because of progressive disease, and one patient in each group withdrew consent. Ten patients were switched from ICT to SCT because of hematologic toxicity (two patients), patient request (three patients), two treatment delays (two patients), hepatitis C infection (one patient), or other reasons that were not study drug related (two patients). No patients died during the study.

TABLE 1. Baseline Characteristics

Characteristic	ICT (n = 42)	SCT (n = 41)
Median age, years (range)	50.9 (28–64)	56.9 (36–69)
Male sex, *n* (%)	30 (71)	32 (78)
Mean weight, kg (SD)	75.3 (12.5)	81.6 (13.1)
Disease stage, *n* (%)		
Limited	39 (93)	40 (98)
Extensive	3 (7)	1 (2)
ECOG performance status, *n* (%)		
0	1 (2)	3 (7)
1	41 (98)	38 (93)
Manchester score, *n* (%)		
0	21 (50)	21 (51)
1	21 (50)	20 (49)
Serum sodium level < normal, *n* (%)	6 (14)	6 (15)
Serum lactate dehydrogenase >200, *n* (%)	20 (48)	20 (49)
Alkaline phosphatase, grade 1, *n* (%)	0	1 (2)
Median time to treatment from SCLC diagnosis, days (range)	9 (0–22)	10 (1–25)

ECOG, Eastern Cooperative Oncology Group; SCLC, small cell lung cancer; SD, standard deviation.

Treatment Exposure and Dose Intensity

The study protocol did not allow any dose reductions. The median treatment durations were 2.5 and 4.7 months for ICT and SCT, respectively (Table 2). A total of 446 cycles were administered, with a median of six cycles in both groups. Significantly more patient-cycles were administered in the ICT group than in the SCT group ($p = 0.0038$; Table 2), and more ICT patients than SCT patients received all six cycles (79 versus 63%). The median dose received in milligrams per meter squared of body surface area per week of ifosfamide was 2484 (range, 475–2761) in the ICT group and 1250 (range, 493–2917) in the SCT group; for carboplatin it was 148 (range, 29–162) for ICT and 75 (range, 30–175) for SCT, and for etoposide it was 178 (range, 34–229) for ICT and 90 (range, 35–210) for SCT (Figure 2). The ratio of weekly median doses of ICE in ICT compared with SCT were 1.99, 1.97, and 1.98, respectively, and the overall ratio of administered doses (mean of the ratios) was 1.98 for all drugs. Seventeen (6.7%) and 35 (14.2%) cycles were missed in the ICT and SCT groups, respectively. All patients in the ICT group and nine (22%) in the SCT group received filgrastim for a median of 10 and 5.5 days, respectively. More treatment delays were reported for the ICT compared with the SCT group (51 versus 15). The majority (82%) of treatment delays for ICT patients were attributable to hematologic toxicities, with a median duration of 3 days. Nonhematologic delays totaled a median of 2 days for ICT and 5 days for SCT.

Because it was the standard in 1996, patients achieving at least a partial response at the end of chemotherapy treatment were offered thoracic radiation as consolidation treatment and prophylactic cranial radiation, if indicated. The numbers of patients receiving radiation therapy were similar in both treatment arms: brain (25 [60%] ICT and 23 [56%] SCT), chest (40 [95%] ICT and 35 [85%] SCT), and brain and chest in the same patient (25 [57%] ICT and 22 [54%] SCT).

Survival and Response

The median length of follow-up for the ICT group was 23.9 (range, 0.4–87.0) months versus 13.7 (range,

TABLE 2. Exposure

	ICT, *n* (%)	SCT, *n* (%)
Number of patient-cycles	235	211
Median treatment duration, mo	2.5	4.7
Reason for delay, *n* (median days)		
Hematologic toxicity	42 (3)	6 (7.5)
Not study related	9 (2)	9 (5)
Median number of cycles delivered	6	6
6, *n* (%)	33 (79)	26 (63)
5, *n* (%)	1 (2)	6 (15)
4, *n* (%)	8 (17)	2 (5)
3, *n* (%)	0	4 (10)
2, *n* (%)	0	2 (5)
1, *n* (%)	0	1 (1)

ICT, dose-intensified ICE (ifosfamide, carboplatin, and etoposide); SCT, standard ICE.

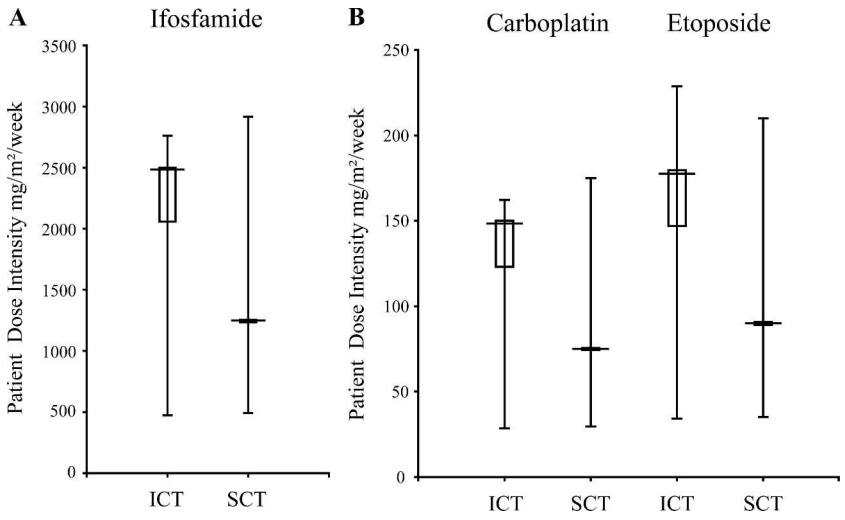

FIGURE 2. Patient dose intensity in milligrams per meter squared per week for the ICT and SCT groups. Patients in both groups received a weekly dose of ifosfamide (*A*), carboplatin (*B*), and etoposide (*B*). ICT, dose-intensified ICE; SCT, standard ICE.

2.2–53.0) months for SCT. At the last follow-up, 26 of the 62 (62%) patients who had died were in the ICT group, and 36 (88%) were in the SCT group, representing a significantly improved survival for ICT ($p = 0.0107$). The median overall survival was statistically significantly prolonged for ICT compared with SCT (30.3 versus 18.5 months; $p = 0.001$) (Figure 3). The 2-year survival rate of 55% (23 patients) for ICT was numerically but not significantly higher compared with the 2-year survival rate of 39% (16 patients) for SCT ($p = 0.151$). The 1-year survival rate for ICT was slightly increased compared with that for SCT (81 versus 78%).

A total of 61 patients had experienced disease progression at the last follow-up (27 for ICT and 34 for SCT). The median TTP was significantly prolonged in favor of ICT ($p = 0.0001$), with 15.0 (range, 12.7–31.9) months for ICT and 11.1 (range, 9.1–11.9) months for SCT (Figure 4). In the follow-up period, there were statistically significantly fewer ICT patients showing progressive disease compared with SCT-treated patients ($p = 0.0197$, Fisher's exact test). For ICT, 16 of 27 patients showed local progression, and 14 of 27 had distal progression, with three of 27 patients having both local and distal progression. In the SCT group, 22 of 34 patients showed local and 18 of 34 had distal progression, with six of 34 demonstrating both local and distal progression. There was no statistically significant difference between local ($p = 0.21$) and distal progressions ($p = 0.62$) within treatment arms.

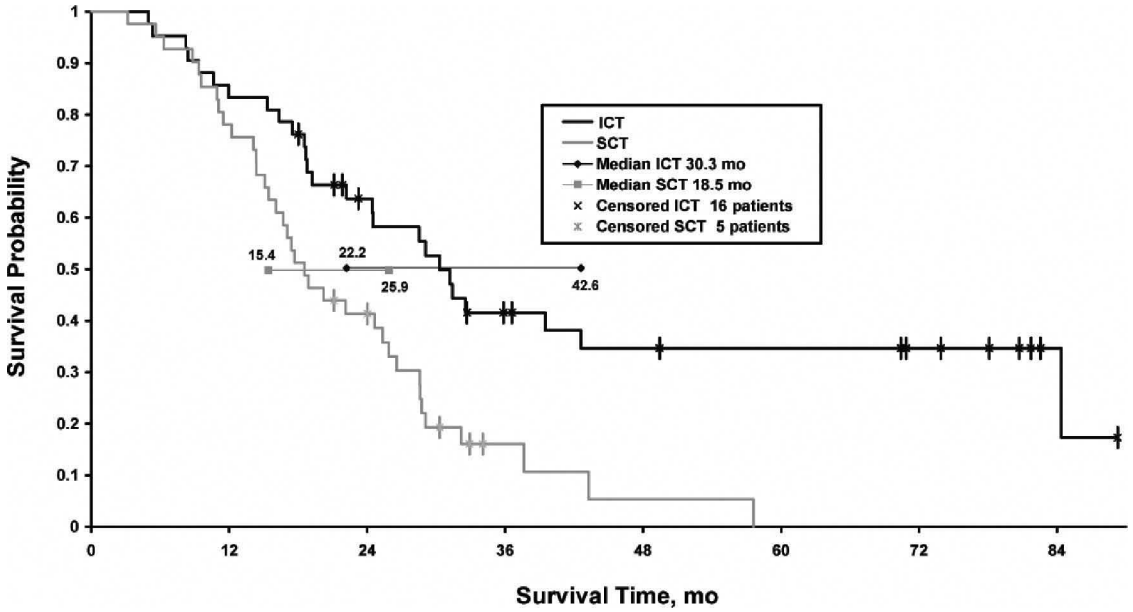

FIGURE 3. Median overall Kaplan–Meier survival curves for patients receiving ICT (censored = 16) and SCT (censored = 5). Median overall survival was statistically significantly improved for patients receiving ICT ($p = 0.001$). ICT, dose-intensified ICE (ifosfamide, carboplatin, and etoposide); SCT, standard ICE.

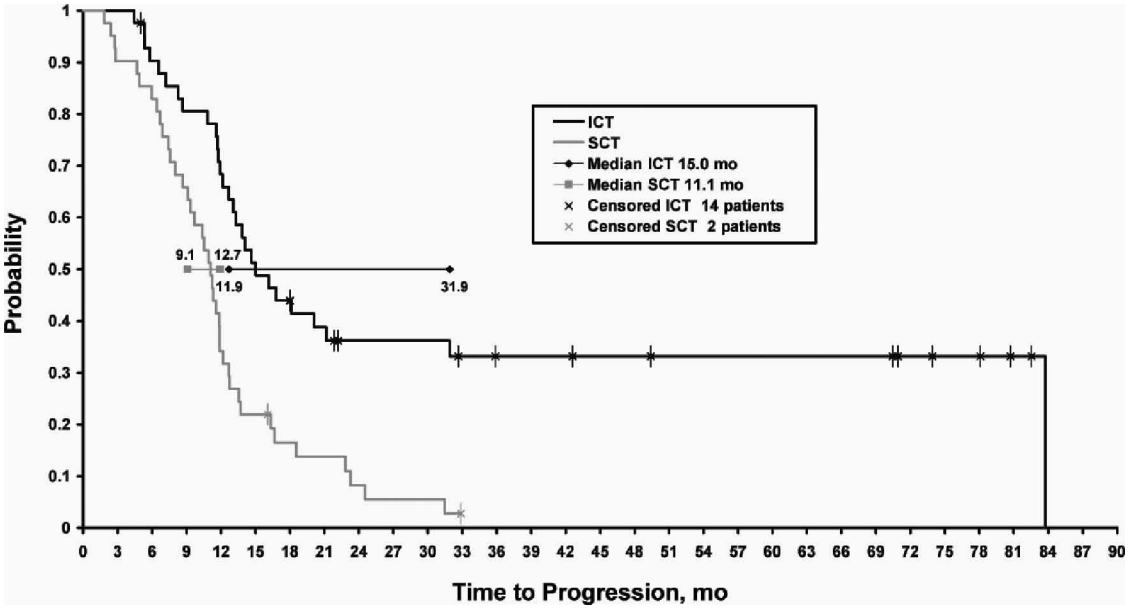

FIGURE 4. Median time-to-progression Kaplan–Meier curves for patients receiving ICT (censored = 14) and SCT (censored = 2). Median time to progression was statistically significantly improved for patients receiving ICT ($p = 0.0001$). ICT, dose-intensified ICE (ifosfamide, carboplatin, and etoposide); SCT, standard ICE.

All patients receiving ICT achieved a partial or complete response, and the overall response rate was higher (100%) than that for SCT (88%; $p = 0.0258$) (Table 3). Three patients in the SCT group experienced stable disease, and four had progressive disease while receiving study treatment. At the last follow-up, statistically fewer ICT patients compared with SCT patients (20 versus 35) had received second-line treatment ($p = 0.0004$, Fisher's exact test). Second-line treatments for progressive disease included radiotherapy of the chest received by no ICT patients and six SCT patients ($p = 0.0119$), radiotherapy of the brain received by five ICT patients and five SCT patients ($p > 0.05$), and all other antitumor therapies received by 18 ICT patients and 32 SCT patients ($p = 0.0016$). The most common therapies were radiation (11 versus 26%), ICE reexposition (14 versus 11%), and doxorubicin, cyclophosphamide, and vincristine (11 versus 14%).

Toxicity and Supportive Care

All 446 administered cycles were analyzed for grade 3 and 4 myelotoxicity on days 8 and 14 and for hematologic nadirs in each cycle. There was no significant difference in the occurrence of febrile leucopenia; the incidence was 15 (36%) and 15 (37%) for patients and 23 (10%) and 16 (8%) for cycles in the ICT and SCT arms, respectively. SCT was associated with a lower incidence of grade 3 and 4 hemoglobin nadir (15.9 versus 20.4%; $p = 0.00605$) and platelet nadir (46.4 versus 73.2%; $p < 0.0001$) compared with ICT, whereas the WBC nadirs were similar in both groups.

Because of the increased myelotoxicity with ICT, significantly more patients receiving ICT required platelet and red blood cell (RBC) transfusion packs per cycle than did those on SCT. Significantly more platelet and RBC transfusion packs were needed in the ICT group ($p < 0.0001$; Table 4). The median patient transfusion requirement was 10 packs of platelets and nine packs of RBCs for patients receiving

TABLE 3. Treatment Response

	ICT *n* (%)	SCT *n* (%)
Overall response	42 (100)	36 (88)
Complete response	22 (52)	15 (37)
Partial response	20 (48)	21 (51)
Stable disease	0	3 (7)
Progressive disease	0	2 (5)

ICT, dose-intensified ICE (ifosfamide, carboplatin, and etoposide); SCT, standard ICE.

TABLE 4. Incidence of Transfusions

	ICT *n* = 42	SCT *n* = 41
Platelet or RBC transfusion		
Patients receiving transfusion, *n* (%)	40 (95)	24 (59)
Patient-cycles with transfusion, *n*/*N* (%)	129/235 (55)	58/211 (27)
Platelet transfusion only		
Patients receiving transfusion	7 (17)	4 (10)
Platelet transfusion packs, *n*	387	327
RBC transfusion only		
Patients receiving transfusion	11 (26)	8 (20)
RBC transfusion packs, *n*	371	166

ICT, dose-intensified ICE (ifosfamide, carboplatin, and etoposide); SCT, standard ICE; RBC, red blood cell.

ICT compared with 12 packs of platelets and eight packs of RBCs for those receiving SCT.

The incidences of grade 1 and 2 nonhematologic adverse events and fever for the two groups were similar. There were no grade 3 or 4 toxicities in this study, with the exception of one grade 3 pulmonary adverse event reported in the SCT group. Differences in the incidence of certain adverse events were observed; fewer grade 1 and 2 pulmonary ($p < 0.001$) and cardiac ($p = 0.0019$) toxicities were reported for ICT, whereas fewer episodes of grade 1 or 2 nausea ($p = 0.0209$) and vomiting ($p = 0.0160$) were reported for the SCT group. Creatinine data were normal for all analyzed cycles in both groups, with the exception of one grade 1 toxicity in a patient receiving SCT. Other toxicities included those previously reported for ICE-based combination regimens.

DISCUSSION

SCLC is known to be highly sensitive to initial therapy, but relapsed SCLC is often resistant to chemotherapy and radiotherapy, emphasizing the importance of complete initial treatment response to minimize the risk of resistant relapse. A promising strategy for increasing initial complete response rates and survival has been the dose intensification of cytotoxic regimens by either increasing the individual dose size or decreasing dose intervals.[18–23] Aggressive, more ICT for patients with SCLC led to higher response rates, prolonged overall survival, and increased 2-year survival rates up to 30 to 33% compared with studies of standard regimens.[24–27]

The introduction of autologous PBPC reinfusion in whole blood or after leukapheresis preparation with filgrastim support allowed for the safe delivery of significantly dose-intensified chemotherapy.[28–31] Multiple studies suggested that single or sequential reinfusion of PBPCs was feasible, allowing for the dose intensification of ICE by a factor of 1.80.[32–41] These studies reported significant improvements for patients with limited-disease SCLC but showed less benefit for patients with extensive-disease SCLC.

Our randomized phase 3 study demonstrated that the dose intensity of six cycles of ICE therapy in patients with limited-disease SCLC can be significantly increased by shortening the therapy from 4 to 2 weeks when proactively treated with filgrastim and reinfusion of autologous PBPC in whole blood at each cycle.

The regimen using six cycles of ICT with repeated hematopoietic progenitor cell support was previously reported to be safe and effective in a phase 2 study of patients with limited-disease SCLC.[39] Therefore, our study not only confirmed the promising results reported in that phase 2 study but, for the first time, reported significantly increased survival. All patients who received ICT achieved a complete or partial response, and the ICT group had a statistically significantly prolonged median overall survival, a statistically significantly prolonged TTP, and a better 2-year survival rate compared with SCT.

In contrast, the larger, similarly designed study by Lorigan et al.[42] in the same patient population reported different results. In the Lorigan et al.[42] study, the delivered median dose intensity was 99% (interquartile range: 96–100%) for the standard arm and 182% (interquartile range: 163–196%) for the dose-dense arm. Median overall survival was 13.9 months (95% confidence interval [CI]: 12.9–15.8 mo) in the standard arm and 14.4 months (95% CI: 12.7–16.0 mo) in the dose-dense arm, and 2-year survival was 22% (95% CI: 16–29%) and 19% (95% CI: 14–27%), respectively.[42] In contrast, our study patients received a higher median number of chemotherapeutic cycles (six cycles), and a higher chemotherapy density (1.98) was achieved. Our study could be criticized for having been performed in a single institution with a small number of patients. However, our positive results find at least some support by the larger study. Of note, in the Lorigan et al.[42] study, there was a trend toward improved outcomes among patients with limited disease in the dose-dense arm.

Two studies demonstrated that the dose intensity of ICE-based regimens could be safely increased 1.26- and 1.34-fold using V-ICE with growth factor support in patients with SCLC.[41,43] Importantly, only the addition of repeated progenitor cell support allowed for increased dose intensification by a factor of 1.80,[39] which is similar to the mean of relative doses of 1.98 for ICT versus SCT achieved in our study. This intensity was not reached in other trials. Overall, despite the increased myelotoxicity, more ICT than SCT cycles were administered. However, an increased incidence of treatment delays, mostly attributable to hematologic events, was observed with ICT compared with SCT.

As demonstrated in our study for ICT, only the concurrent use of hematopoietic growth factors with reinfusion of autologous hematopoietic progenitor cells allowed for more significant increases in dose intensity, which translated into increased response, prolonged time to relapse, and significantly increased survival.[32–40]

Dose intensification is an attractive option for increasing the efficacy of treatments for SCLC. Earlier studies using the ICE regimen reported promising results, but their designs provided only limited information about actual survival benefit.[24–27] These earlier studies compared the efficacy and safety of ICE-based regimens in patients with limited and extensive disease or ICT with alternative regimens, or they used historic controls. Dose intensification with hematopoietic growth factor but without hematopoietic progenitor cell support has demonstrated significant median survival benefits for patients with limited disease.[19,27,43]

ICT as used with filgrastim and hematopoietic progenitor cells was safe for patients with limited-disease SCLC. In our study, hematologic toxicities for both groups were generally low but were statistically different for the hemoglobin nadir ($p = 0.006$) and the platelet nadir ($p < 0.0001$), both in favor of SCT. Therefore, contrary to the experience in the phase 2 study, our patients receiving ICT had an increased need for transfusions, which was also significant for RBCs as for platelets.[39] Most of the nonhematopoietic toxicities in the two groups were similar, and there was no difference in the incidence of or reasons for discontinuation. Importantly, no toxicity-related deaths were reported in our study, compared with previously studied dose-intensified V-ICE (six chemo-

therapy-related deaths in the granulocyte colony-stimulating factor arm).[43] In addition, dose intensification of ICE did not affect the choice of second-line therapy.

Summary

In conclusion, our data support the findings of others that dose intensity matters and that, in contrast to Lorigan et al.[42], dose intensification with hematopoietic growth factors may provide survival benefit for patients with limited-disease SCLC.

REFERENCES

1. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol* 1992;10:282–291.
2. Wolff AC, Ettinger DS, Neuberg D, et al. Phase II study of ifosfamide, carboplatin, and oral etoposide chemotherapy for extensive-disease small-cell lung cancer: an Eastern Cooperative Oncology Group pilot study. *J Clin Oncol* 1995;13:1615–1622.
3. Johnson BE, Ihde DC, Bunn PA, et al. Patients with small-cell lung cancer treated with combination chemotherapy with or without irradiation. Data on potential cures, chronic toxicities, and late relapses after a five- to eleven-year follow-up. *Ann Intern Med* 1985;103:430–438.
4. Thatcher N, Lind M, Stout R, et al. Carboplatin, ifosfamide and etoposide with mid-course vincristine and thoracic radiotherapy for 'limited' stage small cell carcinoma of the bronchus. *Br J Cancer* 1989;60:98–101.
5. Shevlin PM, Muers MF, Peake MD, et al. Modified ice study: a phase II study of an intensive, modified ICE regimen (ifosfamide, carboplatin and etoposide) in patients with better prognosis, small cell lung cancer. *Lung Cancer* 1998;21:115–126.
6. Lorigan P, Lee SM, Betticher D, et al. Chemotherapy with vincristine/ifosfamide/carboplatin/etoposide in small cell lung cancer. *Semin Oncol* 1995;22:32–41.
7. Glisson B, Scott C, Komaki R, et al. Cisplatin, ifosfamide, oral etoposide, and concurrent accelerated hyperfractionated thoracic radiation for patients with limited small-cell lung carcinoma: results of radiation therapy oncology group trial 93-12. *J Clin Oncol* 2000;18:2990–2995.
8. Turrisi AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265–271.
9. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20:3054–3060.
10. Giaccone G, Dalesio O, McVie GJ, et al. Maintenance chemotherapy in small-cell lung cancer: long-term results of a randomized trial. European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. *J Clin Oncol* 1993;11:1230–1240.
11. Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994;12:2022–2034.
12. Spiro SG, Souhami RL, Geddes DM, et al. Duration of chemotherapy in small cell lung cancer: a Cancer Research Campaign trial. *Br J Cancer* 1989;59:578–583.
13. Cerny T, Lind M, Thatcher N, et al. A simple outpatient treatment with oral ifosfamide and oral etoposide for patients with small cell lung cancer (SCLC). *Br J Cancer* 1989;60:258–261.
14. Pettengell R, Woll PJ, Thatcher N, et al. Multicyclic, dose-intensive chemotherapy supported by sequential reinfusion of hematopoietic progenitors in whole blood. *J Clin Oncol* 1995;13:148–156.
15. Buyse M, Staquet M, Sylvester Ret al. Cancer Clinical Trials Methods and Practice. Oxford, UK: Oxford University Press, 2005.
16. NCI-CTC. National Cancer Institute Cancer Therapy Evaluation Program Common Toxicity Criteria, version 2.0. Available at: http://ctep.cancer.gov/reporting/ctc.html. Accessed 1997.
17. Kaplan EL, Meier P. Nonparametric estimation for incomplete observation. *J Am Stat Assos* 1958;53:457–481.
18. Ardizzoni A, Tjan-Heijnen VC, Postmus PE, et al. Standard versus intensified chemotherapy with granulocyte colony-stimulating factor support in small-cell lung cancer: a prospective European Organization for Research and Treatment of Cancer-Lung Cancer Group Phase III Trial-08923. *J Clin Oncol* 2002;20:3947–3955.
19. Arriagada R, Le Chevalier T, Pignon JP, et al. Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. *N Engl J Med* 1993;329:1848–1852.
20. Hryniuk W, Bush H. The importance of dose intensity in chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984;2:1281–1288.
21. Sheehan RG, Balaban EP, Frenkel EP. The impact of dose intensity of standard chemotherapy regimens in extensive stage small cell lung cancer. *Am J Clin Oncol* 1993;16:250–255.
22. Tjan-Heijnen VC, Wagener DJ, Postmus PE. An analysis of chemotherapy dose and dose-intensity in small-cell lung cancer: lessons to be drawn. *Ann Oncol* 2002;13:1519–1530.
23. Pasini F, Durante E, De Manzoni D, et al. High-dose chemotherapy in small-cell lung cancer. *Anticancer Res* 2002;22:3465–3472.
24. Evans WK, Stewart D, Logan D, et al. A phase II study of ifosfamide in combination with etoposide and cisplatin in the treatment of extensive small cell lung cancer. *Semin Oncol* 1992;19:51–56.
25. Hand S, Baker J, Smith AP, et al. Outpatient intensive chemotherapy for small cell lung cancer: five years experience of modified 'ICE' ifosfamide carboplatin and etoposide. *Clin Oncol (R Coll Radiol)* 2002;14:367–371.
26. Prendiville J, Radford J, Thatcher N, et al. Intensive therapy for small-cell lung cancer using carboplatin alternating with cisplatin, ifosfamide, etoposide, mid-cycle vincristine, and radiotherapy. *J Clin Oncol* 1991;9:1446–1452.
27. Thatcher N, Lorrigan P, Burt P, et al. Intensive combined-modality therapy in small cell lung cancer. *Semin Oncol* 1994;21:9–22.
28. Pettengell R, Luft T, Henschler R, et al. Direct comparison by limiting dilution analysis of long-term culture-initiating cells in human bone marrow, umbilical cord blood, and blood stem cells. *Blood* 1994;84:3653–3659.
29. Pettengell R, Woll PJ, O'Connor DA, Dexter TM, Testa NG. Viability of haemopoietic progenitors from whole blood, bone marrow and leukapheresis product: effects of storage media, temperature and time. *Bone Marrow Transplant* 1994;14:703–709.
30. Rizzo JD, Elias AD, Stiff PJ, et al. Autologous stem cell transplantation for small cell lung cancer. *Biol Blood Marrow Transplant* 2002;8:273–280.
31. Souhami RL, Hajichristou HT, Miles DW, et al. Intensive chemotherapy with autologous bone marrow transplantation for small-cell lung cancer. *Cancer Chemother Pharmacol* 1989;24:321–325.
32. Bessho A, Ueoka H, Kiura K, et al. High-dose ifosfamide, carboplatin and etoposide with autologous peripheral blood progenitor cell transplantation for small-cell lung cancer. *Anticancer Res* 1999;19:693–698.
33. Calderoni A, von Briel C, Aebi S, et al. Intensive chemotherapy with whole blood stem-cell support and concurrent chest radiotherapy in small cell lung cancer: a phase I/II trial. *Lung Cancer* 2002;36:321–326.
34. Elias AD, Ayash LJ, Wheeler C, et al. High-dose ifosfamide/carboplatin/etoposide with autologous hematopoietic stem cell support: safety and future directions. *Semin Oncol* 1994;21:83–85.
35. Elias AD, Skarin AT, Richardson P, et al. Dose-intensive therapy for extensive-stage small cell lung cancer and extrapulmonary small cell carcinoma: long-term outcome. *Biol Blood Marrow Transplant* 2002;8:326–333.
36. Leyvraz S, Perey L, Rosti G, et al. 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. *J Clin Oncol* 1999;17:3531–3539.
37. Oelmann E, Thomas M, Serve H, et al. Early tandem high-dose ifosfamide, carboplatin, etoposide therapy with stem cell rescue for small-cell lung cancer: brief report on the results of a phase-I/II trial. *Oncology* 2002;63:248–253.

38. Perey L, Rosti G, Lange A, et al. Sequential high-dose ICE chemotherapy with circulating progenitor cells (CPC) in small cell lung cancer: an EBMT study. *Bone Marrow Transplant* 1996;18(suppl 1):S40–S43.
39. Woll PJ, Thatcher N, Lomax L, et al. Use of hematopoietic progenitors in whole blood to support dose-dense chemotherapy: a randomized phase II trial in small-cell lung cancer patients. *J Clin Oncol* 2001;19:712–719.
40. Takahashi M, Yoshizawa H, Tanaka H, et al. A phase I dose escalation study of multicyclic, dose-intensive chemotherapy with peripheral blood stem cell support for small cell lung cancer. *Bone Marrow Transplant* 2000;25:5–11.
41. Woll PJ, Hodgetts J, Lomax L, et al. Can cytotoxic dose-intensity be increased by using granulocyte colony-stimulating factor? A randomized controlled trial of lenograstim in small-cell lung cancer. *J Clin Oncol* 1995;13:652–659.
42. Lorigan P, Woll PJ, O'Brien MER, et al. Randomized phase III trial of dose-dense chemotherapy supported by whole-blood hematopoietic progenitors in better-prognosis small-cell lung cancer. *J Natl Cancer Inst* 2005;97:666–674.
43. Steward WP, Von Pawel J, Gatzemeier U, et al. Effects of granulocyte-macrophage colony-stimulating factor and dose intensification of V-ICE chemotherapy in small-cell lung cancer: a prospective randomized study of 300 patients. *J Clin Oncol* 1998;16:642–650.