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

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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.

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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

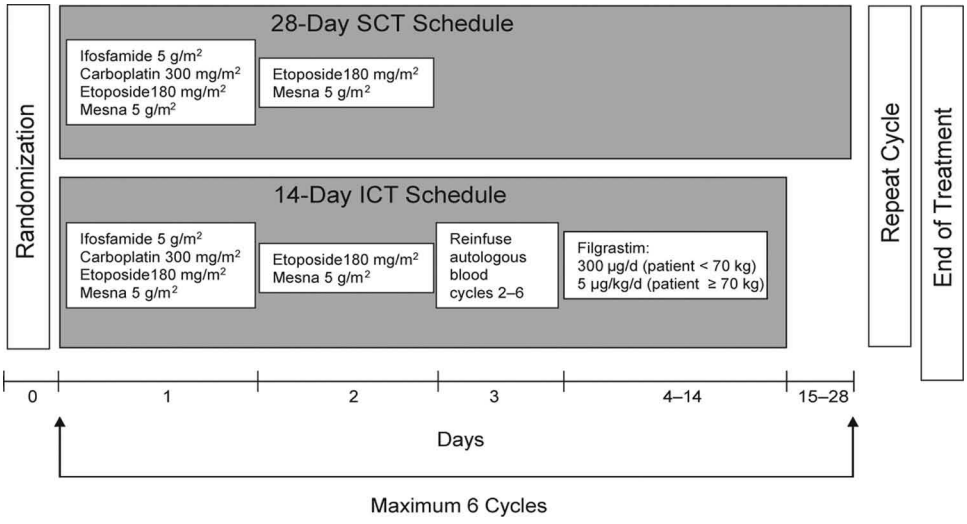

FIGURE 1. Ifosfamide, carboplatin, and etoposide (ICE) chemotherapy schedules. The *upper panel* shows the 28-day standard ICE (SCT) schedule, and the *lower panel* shows the dose-intensified ICE (ICT) schedule. In the ICT group, filgrastim was given on days 4 to 14, and hematopoietic progenitor cells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