Concomitant Granulocyte Colony-Stimulating Factor and Induction Chemoradiotherapy in Adult Acute Lymphoblastic Leukemia: A Randomized Phase III Trial


This prospective multicenter study examined whether simultaneous administration of granulocyte colony-stimulating factor (G-CSF; Filgrastim) and induction chemotherapy for adult acute lymphoblastic leukemia (ALL) could prevent treatment-related neutropenia, infections, and resulting treatment delays. Seventy-six patients were randomly assigned to receive either G-CSF (n = 37) or no growth factor (n = 39) in conjunction with a uniform chemotherapy consisting of cyclophosphamide, cytarabine, mercaptopurine, intrathecal methotrexate, and cranial irradiation. The median duration of neutropenia (absolute neutrophil count <1 × 10^9/L) during chemotherapy was 8 days in patients receiving G-CSF, compared with 12.5 days in the control group (P = .002). A similar reduction from 11.5 to 7 days was observed in patients with T-ALL receiving additional mediastinal irradiation (P = .13). Infections occurred in 43% and 56% of patients in the G-CSF and control arm, respectively (P = .25).

The incidence of nonviral infections was reduced by 50%, from 32 episodes in the control arm to 16 episodes in the G-CSF arm. Prolonged interruptions of chemotherapy administration were less frequent, with delays of 2 weeks or more occurring in only 24% of patients receiving G-CSF as opposed to 46% in the control arm (P = .01). Accordingly, chemotherapy was completed significantly earlier with the use of G-CSF (39 vs 44 days, P = .008). With a median follow-up of 20 months, the probability of disease-free survival was 0.45 in the G-CSF group and 0.43 in the control group (P = .34). In conclusion, adult ALL patients appear to benefit by the simultaneous administration of G-CSF with induction chemotherapy because of a significant reduction in the duration of neutropenia, a trend to fewer infections, and a more rapid completion of chemotherapy.

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Materials and Methods

Patients. Seventy-six consecutive patients with newly diagnosed ALL were enrolled between January 1992 and April 1993 in 19 participating centers. The patient's clinical characteristics are shown in Table 1. The diagnosis of B-precursor, T-lineage, or Null-ALL was based on immunophenotypic analysis of the leukemic blasts by flow cytometry, which was performed routinely in a central laboratory in addition to the standard morphologic and cytochemical evaluation as described previously. Patients not achieving a complete or partial remission after the first 4 weeks of induction therapy were not eligible for study entry. All patients or their legal guardians gave prior informed written consent. The study was approved by the local ethics committee of the University of Frankfurt.

Induction therapy. All patients were treated according to the protocol of the German multicenter ALL trials. The study period encompassed the second phase of induction therapy, scheduled for...
weeks 5 to 8 of treatment, as described earlier. Sufficient regeneration of hematopoiesis (neutrophils $>1.5 \times 10^9/L$; platelets $>50 \times 10^9/L$) was required before beginning this treatment phase. Cytotoxic chemotherapy consisted of cyclophosphamide (650 mg/m$^2$ intravenously [IV]) on days 29, 43, and 57; cytosine-arabinoside (75 mg/m$^2$ IV) on days 31 through 34, 38 through 41, 45 through 48, and 52 through 55; mercaptopurine (60 mg/m$^2$ orally [PO]) on days 29 through 57; and intrathecal methotrexate (15 mg) on days 31, 38, 45, and 52. In the event of infections or cytopenias (white blood cell count [WBC] $<1.5 \times 10^9/L$; platelets $<25 \times 10^9/L$), cytotoxic chemotherapy was interrupted until the infection resolved or neutrophils and platelets recovered to greater than $1.5 \times 10^9/L$ and greater than $25 \times 10^9/L$, respectively. Reduction of the chemotherapy dosage was avoided if possible. Prophylactic antibiotic administration consisted of oral trimethoprim/sulfamethoxazole (320 mg/1,600 mg) and amphotericin B solution ($4 \times 100$ mg). Additional supportive care was provided according to standard clinical guidelines at the discretion of the participating centers, excluding the use of heparinoid growth factors other than G-CSF as specified by the study protocol.

Prophylactic cranial irradiation with a total dose of 24 Gy was administered in 12 fractions of 2 Gy per day. Patients with T-ALL received additional mediastinal irradiation with a total dose of 24 Gy delivered over the same 12-day period.

**Study design.** The study was a prospective, randomized, open-label multicenter phase III study designed to assess the efficacy of concurrent chemotherapy and r-metHuG-CSF in patients with ALL. Patients achieving a complete or partial remission after phase I of induction therapy were randomly assigned to either receive G-CSF or no growth factor during the second half of induction therapy (phase II, scheduled for weeks 5 through 8), during which G-CSF and chemotherapy were administered concomitantly (Fig 1).

**Recombinant metHu-G-CSF (Filgrastim).** Recombinant human G-CSF was supplied by Amgen Inc (Thousand Oaks, CA). G-CSF was administered as a daily subcutaneous (SC) injection at a dose of $5 \mu$g/kg, starting on day 7 after the start of phase II of induction therapy, i.e., 1 day after the first cycle of ara-C (Fig 1). G-CSF was continued until a neutrophil count of greater than $3 \times 10^9/L$ was reached after the final leukocyte nadir but for at least 7 days after the last cyclophosphamide dose. r-metHuG-CSF was stopped only when an absolute neutrophil count (ANC) of greater than $25 \times 10^9/L$ or a leukocyte count greater than $50 \times 10^9/L$ was recorded; it was re instituted when neutrophils reached a level less than $3 \times 10^9/L$.

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Control (n = 39) (%)</th>
<th>G-CSF (n = 37) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>26 (64)</td>
<td>26 (70)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (36)</td>
<td>11 (30)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>30</td>
<td>27</td>
</tr>
<tr>
<td>Range</td>
<td>16-58</td>
<td>16-65</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B-precursor ALL</td>
<td>26</td>
<td>25</td>
</tr>
<tr>
<td>T-lineage ALL</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>T-NHL</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Null-ALL</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nor evaluable</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Karnofsky status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>11 (28)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>90</td>
<td>17 (44)</td>
<td>21 (57)</td>
</tr>
<tr>
<td>80</td>
<td>7 (18)</td>
<td>9 (24)</td>
</tr>
<tr>
<td>70</td>
<td>4 (10%)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

The primary study endpoint was the duration of neutropenia during chemotherapy (ANC <1.1 \times 10^9/L). Secondary study parameters were the incidence and duration of fever (oral temperature $>38^\circ$C), treatment delays, and the time to end of chemotherapy. In addition, the incidence of infections was analyzed. For analysis of safety, the incidence and duration of thrombocytopenia and anemia, transfusions, and adverse events were assessed. Duration of neutropenia was the number of days during induction phase II when the ANC was less than 1.0 \times 10^9/L and was compared between the treatment groups using the Wilcoxon rank sum test. The scheduled frequency of blood counts including manual differential counts was three times per week. Linear interpolation was used to estimate ANC for days with no counts. To determine whether estimating over longer gaps (more than 5 days) would introduce bias into the actual comparison between the two arms, an analysis was performed both excluding and including the patients with long gaps. Chemotherapy dose intensities were also compared using the Wilcoxon rank sum test. The incidence of fever, thrombocytopenia, and platelet transfusions were compared by means of the $\chi^2$ test.

The duration of a delay for patients who did not receive all chemotherapy (day 28 of induction phase II) until the last actual day of chemotherapy. The duration of a delay for patients who did not receive all chemotherapy for any reason was considered as indefinite. The number of patients that experienced a delay of more than 14 days was compared between the treatment groups by using the $\chi^2$ test.

The time to the end of chemotherapy (phase II) was defined as the number of days from the first to the last dose of cyclophosphamide (day 28 of induction phase II). The time to the end of chemotherapy was censored at the last dose of cytosine arabinoside.

Treatment outcome was assessed after a median follow-up of 20 months from time of randomization. Disease-free survival in the two treatment groups was compared using Kaplan-Meier survival curves and the log-rank test.
Table 2. Duration of Neutropenia (ANC <1.0 × 10^9/L) During Chemotherapy

| All Patients | Patients Receiving Medial statistical duration of neutropenia in all patients and the subgroup receiving additional medialized irradiation. In an intent to treat approach, linear interpolation was used to substitute for missing ANC values.

\* in 1 patient, available ANC values were insufficient to calculate duration of neutropenia.

### RESULTS

**Patients.** Of 76 patients enrolled in the study, 37 were assigned to the G-CSF and 39 to the control group. Clinical features of the patients in the two treatment arms were well balanced regarding sex, age, immunophenotype, and performance status (Table 1). Mean time intervals from start of phase I of induction to start of phase II were 41.3 days (range, 29 to 77 days) in the G-CSF group versus 40.5 days (range, 28 to 69 days) in the control group, indicating similar degrees of myelosuppression during treatment before study entry. All 76 patients were evaluable for safety. Seventy-five patients completed induction therapy and were evaluable for the primary efficacy endpoint (duration of neutropenia). One patient in the control group was excluded from this analysis because of insufficient available ANC values. Five patients were excluded from analysis of the duration of therapy. Of these, 1 patient in the G-CSF arm and 4 in the control arm had received only two of three scheduled doses of cyclophosphamide; reasons for this change were chemotherapy-induced hepatic toxicity in the patient in the G-CSF arm and persisting pancytopenia, psychiatric reasons, a protocol violation, and death during induction due to pneumonia in 1 patient each in the control arm. All 10 patients with T-ALL in the control group and 9 of 10 T-ALL patients in the G-CSF arm received medialized irradiation (24 Gy) in addition to the 24 Gy prophylactic central nervous system (CNS) irradiation administered to all patients. There was no death in the G-CSF group during the study period; 1 patient in the control group died of pneumonia during chemotherapy 1 month after the start of phase II.

**Neutrophil response.** Patients in the G-CSF arm responded initially with a prompt increase in neutrophils on initiation of G-CSF despite the preceeding administration of cyclophosphamide and ara-C and ongoing 6-mercaptopurine. This increase was followed by a reduction in ANC values that was shorter and less pronounced than in the control group. The median duration of neutropenia (ANC <1 × 10^9/L) during chemotherapy was 8 days in the G-CSF group, compared with 12.5 days in the control group (P = .002, Wilcoxon rank sum test; Table 2). In an analysis excluding the patients with gaps of more than 5 days with no complete blood counts (12 G-CSF and 19 control), the median durations of neutropenia were 8 days and 12 days for the G-CSF and control groups, respectively (P = .011). Recovery of ANC to greater than 1 × 10^9/L after the final chemotherapy dose was also more rapid. A comparable reduction of neutropenia of less than 1 × 10^9/L with G-CSF was observed in the patients with T-ALL who received medialized irradiation. In these patients, the number of days with an ANC of less than 1 × 10^9/L was reduced from 11.5 days in the control to 7 days in the G-CSF groups (Table 2); this difference did not reach statistical significance (P = .13).

From categorization of the duration of neutropenia (Table 3) it is evident that G-CSF primarily reduces the incidence of more prolonged neutropenias: 42% of patients in the control arm experienced neutropenia exceeding 2 weeks, compared with 22% of patients receiving G-CSF.

Thrombocytopenia occurred in the majority of patients but did not differ significantly between the two groups. Platelet counts less than 25 × 10^9/L occurred in 24 (65%) and 22 (58%) patients in the G-CSF and control arms, respectively (P = .54). Platelet counts less than 50 × 10^9/L occurred in 34 (92%) and 33 (87%) patients, respectively (P = .48). Accordingly, platelet transfusions were administered to 25 patients receiving G-CSF (68%) and to 24 control patients (62%) (P = .58, x^2 test). Among these patients, the median number of platelet transfusions administered in the G-CSF and control arms were 2 (range, 1 to 22) and 1 (range, 1 to 23), respectively (P = .2). There were no major bleeding complications in either of the two treatment groups.

**Fever and infections.** A smaller proportion of patients in the G-CSF group (n = 13; 35%) had fever ≥38°C than in the control group (n = 18; 47%). This difference did not reach statistical significance (P = .28). Among the patients who had fever, the median duration of fever was slightly shorter in the G-CSF group (3 days; range, 1 to 13 days) than in the control group (4 days; range, 1 to 21 days).

Twenty-one infections were observed in 16 of 37 patients (43%) in the G-CSF arm and 37 infections were seen in 22 of 39 (56%) control patients (P = .25). There were 9 severe bacterial infections (pneumonia and septicemia) in the control group as opposed to 2 episodes in the G-CSF group. Fever of unknown origin (FUO) occurred in 16 and 11 patients, respectively. Overall, the number of nonviral infections was reduced by 50%, from 32 to 16 episodes in the control and G-CSF groups, respectively. There was no relevant difference in the frequency of viral or candida infections. One patient died in the control group due to pneumonia, whereas no death occurred in the G-CSF group during the study period.

**Treatment delays and duration.** Thirty-five patients in the control group and 36 patients in the G-CSF group were evaluable. Five patients were excluded from this analysis because of omission of the final cyclophosphamide dose. With G-CSF administration, there was a conspicuous reduction in the incidence of chemotherapy delays exceeding 2 weeks, which occurred in only 9 (24%) patients as opposed to 18 (46%) patients in the control group (Table 4). Delays exceeding 4 weeks occurred in 4 patients, all in the control
G-CSF AND INDUCTION CHEMORADIOThERAPY IN ALL

Table 3. Frequency Distribution of Neutropenia Duration

<table>
<thead>
<tr>
<th>Duration (d)</th>
<th>Control (n = 38)</th>
<th>G-CSF (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>1 (3%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>1-7</td>
<td>6 (18%)</td>
<td>17 (46%)</td>
</tr>
<tr>
<td>8-14</td>
<td>15 (39%)</td>
<td>11 (30%)</td>
</tr>
<tr>
<td>15-21</td>
<td>8 (21%)</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>22-28</td>
<td>6 (16%)</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>&gt;28</td>
<td>2 (5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

The duration of neutropenia less than 1 x 10^9/L occurring during chemotherapy was categorized based on weekly time periods. The frequency distribution shows that G-CSF leads to a predominant reduction of the more prolonged neutropenic episodes.

Table 5. Frequency and Type of Infectious Episodes

<table>
<thead>
<tr>
<th>No. of patients with infection</th>
<th>Control Arm (n = 39)</th>
<th>G-CSF Arm (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonia</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Septicemia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>FUO</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Otitis media</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Skin infection</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Candida</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Herpes infection</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Common cold</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No. of episodes</td>
<td>37</td>
<td>21</td>
</tr>
</tbody>
</table>

G-CSF AND INDUCTION CHEMORADIOThERAPY IN ALL

group. Chemotherapy was completed according to schedule in 19% of patients with G-CSF and in 8% of patients in the control arm. Overall, induction therapy was completed 5 days earlier with G-CSF treatment, after a median of 39 treatment days (interquartile range, 32 to 43 days) as opposed to 44 days (interquartile range, 36 to 49 days) in the control group (P = .008). This resulted in an increase in the dose intensity of chemotherapy. Assuming equipotency of cyclophosphamide and cytosine arabinoside, the overall median chemotherapeutic dose intensity was 75% in the G-CSF arm and 66% in the control arm (P = .023).

Toxicity. Nearly all patients (39 [100%] in the control arm and 34 [92%] in the G-CSF arm) reported side effects during the study period, ie, until 4 weeks after the final day of G-CSF administration. The majority of events were mild or moderate (WHO grades I and II). Nonhematologic and noninfectious adverse events of WHO grades III and IV occurred in 11 patients in the control arm (13 events) and 5 patients in the G-CSF arm (7 events). None of these severe adverse events was considered to be G-CSF related. The only adverse event attributed to G-CSF administration was musculoskeletal pain of WHO grades I and II, which occurred in 5 patients in the G-CSF group. However, this side effect was also experienced by 7 patients in the control group. Infectious events are presented separately in Table 5.

Treatment outcome. Thirty-seven of 39 patients in the control arm and 35 of 37 patients in the G-CSF arm were in complete remission (CR) at the time of randomization. Two patients in each group had achieved a partial remission (PR). At the end of the study period, 36 control patients and 36 G-CSF—treated patients were in CR. One patient in the G-CSF group remained in PR and was considered a treatment failure. There were 2 early relapses and 1 death during induction caused by a bilateral pneumonia of unknown etiology in the control group. The most recent analysis of outcome was conducted in December 1994 after a median follow-up of 20 months; 7 high-risk patients with an HLA-compatible sibling donor who were transplanted in first CR according to the GMALL protocol were excluded from this analysis. By Kaplan-Meier analysis, the probability of disease-free survival calculated from the time of randomisation is 0.45 for the G-CSF and 0.43 for the control group (P = .34 by log rank test). Death in CR occurred in 2 patients in the control group, 1 of an infectious complication during induction therapy and 1 of a complication after intrathecal chemotherapy, as opposed to no deaths in CR in the G-CSF group. A total of 32 patients have relapsed, 18 in the control arm and 14 in the G-CSF arm. The median time from randomization to treatment failure was 6 months (range, 2 to 31 months) in the G-CSF group and 5.5 months (range, 1 to 19 months) in the control group. Among patients with T-ALL, there were 2 relapses in the G-CSF group and 5 relapses plus 1 death in CR in the control group. The Ph1 chromosome or a bcr/abl translocation were present in 3 relapsed patients in the G-CSF arm (time to relapse 4.5, 6, and 7.5 months) and in 5 relapses in the control arm (time to relapse 2, 4.5, 5, 5.5, and 8 months).

DISCUSSION

In this prospective randomized trial we show that recombinant G-CSF significantly reduces neutropenia and the overall treatment duration when administered simultaneously with induction chemotherapy in patients with ALL. Previous studies have shown that G-CSF administered after myelosuppressive treatment accelerates hematopoietic recovery and allows a more rapid application of successive chemotherapy cycles. In contrast, parallel administration of G-CSF and chemotherapy has generally been avoided, based on the theo-
Arterial concern that G-CSF could sensitize normal hematopoietic stem cells to the cytotoxic effects of cell-cycle active agents. Additional conceivable risks included a stimulation of leukemic lymphoblast growth and potential interactions between G-CSF administration and simultaneous cranial and mediastinal irradiation. However, there is a rationale for administering hematopoietic growth factors concurrently with profoundly myelotoxic chemotherapy regimens when cytotoxic drugs are administered daily over an extended time, as is the case in the 8-week induction protocol for acute lymphoblastic leukemia of the German Cooperative ALL trials (GMALL).17

This prospective, randomized study now confirms both the safety and the efficacy of concomitant G-CSF and ALL induction chemotherapy using the GMALL protocol, as suggested previously by a pilot study by ourselves14 and a study by Scherrer et al.15 In combination with the two cell-cycle active agents cytosine-arabinoside and 6-mercaptopurine in addition to cyclophosphamide and cranial irradiation, G-CSF maintained neutrophil counts at consistently higher levels than observed in the control group. It is of particular clinical relevance that the duration of neutropenia was significantly reduced not merely after but during ongoing chemotherapy. This finding indicates that the stimulation of additional cell divisions of myeloid progenitor cells in conjunction with an acceleration of neutrophil maturation by G-CSF counterbalances any sensitization of residual normal progenitors to the cytotoxic actions of these drugs.

The potential clinical importance of a shorter duration of neutropenia in this setting is emphasized by a 50% lower infection rate in the G-CSF group. This difference was caused primarily by fewer severe bacterial infections, ie, pneumonias and septicemias. Accordingly, the only death during the study resulted from a pneumonia in 1 patient in the control group. Substantial reductions were also noted regarding fever of unknown origin as well as less severe bacterial infections, eg, otitis media and skin infections, whereas the incidence of viral infections did not differ in the two study groups. These results thus complement the results from previously published studies that show a reduction in the infection rate with the sequential administration of cytotoxic therapy and G-CSF.2,3

As a consequence of shorter neutropenia and fewer infectious episodes, adherence to the chemotherapy schedule was improved, with fewer treatment interruptions and delays caused by granulocytopenia and none caused by intercurrent infections in the G-CSF arm. This finding resulted in a significantly more rapid (median of 5 days) completion of therapy. Being an open-label study, it is conceivable that the treating physicians were more inclined to continue treatment in the G-CSF arm despite infectious complications or to restart chemotherapy sooner, thereby facilitating the more rapid completion of therapy. On the other hand, specific guidelines existed for interrupting or restarting chemotherapy, and, although the bias of some investigators may have been to expect fewer delays with G-CSF, substantial concern remained that the simultaneous administration of G-CSF and chemotherapy might have the opposite effect. Overall, this indicates that the difference in treatment delays reflects the biologic effect of G-CSF rather than investigator bias.

As a result of the decrease in treatment duration, there was a moderate albeit statistically significant increase in chemotherapy dose intensity. Dose intensity may affect treatment results in ALL21,22 and chemotherapy dose reductions have been associated with an inferior duration of CRs in childhood ALL.23 This current study was not designed and therefore lacks statistical power to detect potential clinical benefits of this incremental increase in dose intensity. Conversely, our data strongly suggest that simultaneous G-CSF and chemotherapy do not adversely affect treatment outcome in the patient population under study, as indicated by similar probabilities of disease-free survival, and that there is no aggravation of cytopenias during or after cytotoxic therapy. As a caveat, paradoxical myelosuppression has been reported in tumor patients treated simultaneously with G-CSF and 5-FU plus leucovorin.24 This finding indicates that the clinical benefit of the concomitant administration of G-CSF and cytotoxic chemotherapy may be critically dependent on the specific chemotherapy regimen. Theoretically, the beneficial effects of G-CSF could also be patient specific, although this cannot be assessed in the current study because of the relatively small number of patients with T-ALL or the Ph1 chromosome.

Theoretical concern that thrombocytopenia could be aggravated in the G-CSF group due either to sensitization of megakaryocyte progenitors to chemotherapy or to an increase in chemotherapy dose-intensity was not substantiated. Neither the incidence of thrombocytopenia nor platelet transfusion requirements differed significantly between the two treatment groups. However, due to the decrease of neutropenia- and infection-related delays in patients receiving G-CSF, thrombocytopenia became a predominant reason for delaying treatment in the G-CSF group.

An additional important aspect of this study relates to the concurrent administration of G-CSF and prophylactic CNS and mediastinal irradiation. No CNS toxicity attributable to G-CSF was observed with 24 Gy cranial irradiation, and radiotherapy did not appear to compromise the myeloorestorative effect of G-CSF. Similarly, the additional mediastinal irradiation (24 Gy) administered to patients with T-ALL did not abrogate the acceleration of neutrophil recovery by G-CSF seen in those patients receiving only cranial irradiation, although the difference was not statistically significant owing to the small number of patients in this subgroup. In agreement with preclinical25-28 and clinical studies29,31 showing a radioprotective effect of G-CSF administered either before or after radiation, our data indicate that the simultaneous administration of G-CSF with radiation therapy in this setting is safe and may be effective in mitigating the myeotoxicity of combined chemoradiotherapy.

Although the potential of G-CSF to stimulate ALL blasts is of less concern than with myeloid malignancies, functional G-CSF receptors have been shown on blast cells expressing myeloid markers in biphenotypic acute leukemias, in bcr abl-positive ALL,32,33 and on lymphoid cells in non-Hodgkin's lymphoma.34 In vitro, proliferative responses of ALL blasts to G-CSF have been observed in some32,33,35 but not all36 studies. Prospective randomized clinical trials of G-CSF after induction chemotherapy for adult acute leukemias,
including refractory and relapsed leukemias, and in childhood high-risk ALL provided no evidence of growth stimulation of leukemic lymphoblasts by G-CSF. Similar results were obtained in previous studies by ourselves and by Scherrer et al that examined parallel G-CSF and chemotherapy. Our current randomized study now confirms these observations by providing no evidence of G-CSF-stimulated lymphoblast proliferation or accelerated leukemic regrowth as judged by a probability of disease-free survival that showed a small albeit nonsignificant advantage for the G-CSF group.

Although several recent studies have evaluated G-CSF administered before, during, and after chemotherapy for acute myeloid leukemia, our present study is, to our knowledge, the first prospective, randomized trial examining the effects of simultaneous G-CSF and chemotherapy for ALL. We show that G-CSF significantly reduces the severity and duration of neutropenia during ongoing chemotherapy and the length of treatment interruptions, with a trend towards fewer bacterial infections, thereby reducing the duration of treatment by a median of 5 days. The clinical impact of this statistically highly significant difference remains to be elucidated, because treatment outcome and infection rates were not significantly different. In a randomized, double-blind study by the CALGB examining G-CSF versus placebo during remission induction and consolidation treatment of adult ALL, neutropenia was likewise shortened, and there was a trend towards fewer severe infections and a lower rate of death during induction in the G-CSF arm. In contrast to our results, the overall length of treatment was not shortened, which may be due to different scheduling of the cytotoxic agents.

Although a cost benefit analysis was not the intention of our multicenter study, an improved quality of life was evident in these patients whose disease entails hospitalization for many weeks. Further studies are required to determine whether treatment strategies aimed at mitigating therapy-induced myelotoxicity can reduce morbidity and contribute to an improved overall treatment outcome in ALL.

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