

A Multicenter, Double-Blind, Randomized, Phase II Trial Comparing Pegfilgrastim With Filgrastim as an Adjunct to Chemotherapy for Acute Myeloid Leukemia

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Origin of Study	Italy, Australia, Canada, Spain, the UK, and the US
Type of Study	MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PHASE II CLINICAL TRIAL
Objectives	<p>Compare time to recovery from severe neutropenia (absolute neutrophil count [ANC] $< 0.5 \times 10^9/L$) in the first induction chemotherapy cycle in patients with acute myeloid leukemia (AML) treated with pegfilgrastim or filgrastim.</p> <p>Compare the safety of pegfilgrastim with that of filgrastim in patients with AML receiving idarubicin/cytarabine induction chemotherapy.</p>
Study Design	<p>Patients with de novo AML received one or two courses of induction chemotherapy, consisting of idarubicin (12 mg/m^2) IV on days 1–3 and cytarabine (100 mg/m^2) IV every 12 hours on days 1–7.</p> <p>Subsequently, patients in remission were given consolidation chemotherapy, consisting of cytarabine 3 g/m^2 (for patients < 55 years of age) or 2 g/m^2 (for patients ≥ 55 years) IV every 12 hours on days 1, 3, and 5.</p> <p>In addition, patients received either a single dose of pegfilgrastim (6 mg) or daily administration of filgrastim ($5 \mu\text{g/kg}$) starting 24 hours after the completion of chemotherapy and continuing until the patients' neutrophil count recovered.</p> <p>Time to recovery from severe neutropenia was defined as the number of days from the first day of chemotherapy until the first of two consecutive ANC values after the nadir was $\geq 0.5 \times 10^9/L$.</p> <p>Duration of severe neutropenia was defined as the total number of days during the cycle with an ANC $< 0.5 \times 10^9/L$.</p>
Patients	<p>Of 84 patients enrolled into the study and randomized to one of the two treatment arms, 83 received study drugs (42 received pegfilgrastim, 41 filgrastim).</p> <p>The two treatment groups were generally well balanced for demographics and baseline characteristics.</p>
Observations	<p>All patients developed severe neutropenia (ANC $< 0.5 \times 10^9/L$) during the first induction chemotherapy cycle. The median time to recovery from severe neutropenia in this cycle was 22 days in both treatment groups (95% CI for treatment difference = $-1.9, 1.9$).</p> <p>No statistically significant difference was observed in the median duration of severe neutropenia between the two treatment groups (21 days for pegfilgrastim vs 20 days for filgrastim).</p> <p>Patients in the filgrastim treatment group required a median of 16 daily injections during the induction chemotherapy phase and 13 daily injections in the consolidation phase, compared with a single dose of pegfilgrastim per cycle for patients in both induction and consolidation phases.</p> <p>The median serum concentration of pegfilgrastim in the first induction chemotherapy cycle remained above clinically relevant concentrations until approximately 21 days after the start of chemotherapy, results that are consistent with the neutrophil-mediated clearance of pegfilgrastim.</p>

Pegfilgrastim Compared With Filgrastim as an Adjunct to Chemotherapy for AML

Most patients (20/22 receiving pegfilgrastim and 21/24 receiving filgrastim) had severe neutropenia during the consolidation phase. There was no difference in time to recovery of the ANC between the two treatment groups (median of 17.0 days for pegfilgrastim vs 16.5 days for filgrastim; 95% CI = -1.1, 2.1).

The incidence of serious adverse events was comparable between the two treatment groups, except for infectious complications, which were more frequent among patients receiving filgrastim (22%) than among those treated with pegfilgrastim (12%).

The durations of fever, anti-infective use, and hospitalization were comparable between pegfilgrastim and filgrastim during both induction chemotherapy and the consolidation phase.

Conclusions

A single dose of pegfilgrastim (6 mg) per cycle and daily administration of filgrastim (5 $\mu\text{g}/\text{kg}$) result in a similar median time to recovery of the ANC to $\geq 0.5 \times 10^9/\text{L}$ in patients with AML receiving idarubicin/cytarabine induction chemotherapy.

There is no statistically significant difference between pegfilgrastim and filgrastim in the duration of severe neutropenia in this setting.

Pegfilgrastim was well tolerated in this patient population and had a safety profile similar to that of filgrastim.

Discussion

Previous studies have demonstrated that the duration of neutropenia and its clinical consequences following induction chemotherapy for AML were significantly reduced by the addition of filgrastim, with no increased risk of death, second malignancy, or death (*Heil et al. Blood* 1997;90:4710; *Heil et al. Proc Am Soc Hematol*; December 7–10, 2002; Philadelphia, Pa. Abstract 1325). Myelosuppression caused by both the disease and the chemotherapy treatment results in sustained durations of neutropenia, fever, and hospitalization and greater anti-infective use. The purpose of this study was to compare the efficacy and safety of pegfilgrastim with filgrastim in patients with AML.

AML patients, treated with one to two courses of induction therapy (idarubicin and cytarabine) and one course of consolidation therapy (cytarabine) in remission, were assigned to receive a single dose of pegfilgrastim (6 mg subcutaneously) or daily doses of filgrastim (5 $\mu\text{g}/\text{kg}$).

During the first course of induction, all patients developed severe neutropenia. The median time to ANC recovery was identical in the pegfilgrastim and filgrastim treatment groups—22 days in each (95% CI for difference, -1.9, 1.9). During consolidation, 20/22 (91%) and 21/24 (88%) of patients in the pegfilgrastim and filgrastim groups, respectively, developed severe neutropenia. Again, the median time to ANC recovery did not differ between groups—17.0 vs 16.5 days (95% CI for difference, -1.1, 2.1).

Pegfilgrastim and filgrastim seem to be similarly safe and efficacious when used as an adjunct to chemotherapy in patients with AML, the investigators concluded, but pegfilgrastim has the advantage of requiring fewer injections. In future studies, Dr. Bosi commented, these agents may be evaluated for their usefulness during mobilization before peripheral blood stem cell transplantation.

Key Points

- A single dose of pegfilgrastim is equivalent to daily administration of filgrastim in restoring the ANC before the next chemotherapy cycle in patients with AML.
- Pegfilgrastim is safe and well tolerated in this clinical setting.

References

Bosi A, Szer J, Kassis J, Sierra J, Desborough C, Buchanan K. A multicenter, double-blind, randomized, phase 2 trial comparing pegfilgrastim with filgrastim as an adjunct to chemotherapy for acute myeloid leukemia (AML). Poster presented at the 46th Annual Meeting of the American Society of Hematology; December 4–7, 2004; San Diego, Calif. Abstract 866.