The value of PegFilgastrim for the therapy of acute myeloid leukemia

Acute myeloid leukemia (AML) is a malignant disease resulting from acquired mutations that block the differentiation of primitive hematopoietic cells and thereby cause immature myeloid precursors to accumulate. Patients are often neutropenic as a result of the disease, and intensive chemotherapy will unavoidably exacerbate myelosuppression. However, since the life expectancy is directly correlated to the achievement of complete remission (CR), the goal of induction and consolidation treatment is to induce CR and prevent relapse. Infectious complications, mostly occurring during the first course of treatment, are one of the major causes of death and the risk and severity of chemotherapy-induced myelosuppression increases with age. Older adults are less able to tolerate intensive chemotherapy regimens, often have pre-existing hematologic disorders, and are more likely to have poor-risk cytogenetic abnormalities or expression of the multidrug resistance phenotype. The proportion of patients achieving CR decrease with advancing age due either to the frailty of the elderly patients or to the persistence of leukemia.

Happily, hematopoietic growth factors such as recombinant granulocyte colony-stimulating factor (G-CSF, filgrastim) demonstrated to be effective in older individuals affected by cancer who had to receive curative chemotherapy: in a retrospective review of clinical practices in the USA filgrastim was associated with a 40% reduction in the risk of febrile neutropenia in CHOP treated non-Hodgkin lymphoma patient.1

The application of myeloid growth factors in AML has been delayed by their potential ability to stimulate the growth of myeloid blast cells since in vitro studies showed that the myeloid blasts expressed receptors for G-CSF and GM-CSF. Two were the major concerns in the use of colony stimulating factors during AML therapy: the potential stimulation of leukemic cell growth and the stimulation of residual normal precursors in the marrow, leading to increased susceptibility to chemotherapy and consequent prolonged neutropenia. However the safety of administration of growth factors before, during and after induction chemotherapy has now been borne out by the results of large randomized studies.2

Use of growth factors after chemotherapy

Over the last decade, several randomized trials have analyzed whether recombinant growth factors can reduce the duration of chemotherapy-induced neutropenia in AML patients without compromising the clinical outcome. These studies varied in methodology, assessed varied patient populations in terms of refractory or de novo AML, and produced somewhat inconsistent results. Generally, they showed that the use of growth factors significantly shortened the duration of severe neutropenia, which also reduced the need for hospitalization and intravenous antibiotic use.3,4 Recently, data of a large randomized, double-blind, placebo-controlled, phase III study of filgrastim in remission induction and consolidation therapy for adults with de novo acute myeloid leukemia have been published.5 The authors, while confirming previous data on the safety and efficacy of filgrastim in reducing the morbidity associated with AML treatment, demonstrated, after a median follow-up of 7 years, that filgrastim supportive therapy had no detrimental effect on either disease free survival (DFS) or overall survival (OS). Patients receiving filgrastim achieved the same CR rate as those receiving placebo, and the remissions were of similar duration. In conclusion, myeloid growth factors given after chemotherapy can consistently reduce the duration of neutropenia although they did not significantly modify the overall outcome of AML. While some studies demonstrate an increase in CR rate and OS,6,7 others did not confirm these results.7,8
Concomitant use of growth factors with chemotherapy

In patients who are able to avoid therapy related mortality, relapse is the most important cause of treatment failure. The likely cause of such failure is related to the existence of a small proportion of quiescent clonogenic blasts which has escaped the toxic effects of chemotherapy. In vitro and in vivo studies have demonstrated the ability of growth factors to recruit these quiescent cells into a phase of cell cycle where these are more susceptible to the cytotoxic drugs. Exposure of leukemic cells to growth factors before cytarabine increases intracellular ara-CTP and DNA uptake of radiolabeled cytarabine into the leukemic cells.

These preclinical studies provided the rationale for a number of trials investigating the safety and efficacy of concomitant administration of colony-stimulating factors with chemotherapy. Lowenberg et al. conducted a multicenter trial where patients age 18-60 years with newly diagnosed AML received cytarabine-based chemotherapy with or without G-CSF. Overall, a higher DFS was reported in the patients who received G-CSF (42% vs 33% at 4 years, \( p = 0.02 \)) but the OS was not significantly better. A real advantage in the OS was registered in the subset of standard risk patients ( OS at 4 years 45 vs 35%, \( p = 0.02 \)). The outcome for patients with unfavorable prognosis was not improved and the small number of patients in the favorable subgroup limited a meaningful analysis.

In a more recent study, 722 newly diagnosed AML elderly patients (age >60 years) were randomized into four arms: no G-CSF, G-CSF after chemotherapy until neutrophils recovery, G-CSF during and after chemotherapy. Patients who received G-CSF after chemotherapy had a shorter time to neutrophil recovery (median, 20 vs 25 days; \( p < 0.001 \)), a shorter hospitalization (mean, 27.2 vs 29.7 days; \( p = <0.001 \)). CR rate was 58.3% for patients receiving G-CSF during chemotherapy (groups 2+4) vs 48.6% for the others (groups 1+3) \( p = 0.009 \), suggesting a possible priming effect. However, no significant differences were observed between the various groups in terms of OS. The authors conclude that although priming with G-CSF can improve the CR rate, the use of G-CSF during and/or after chemotherapy has no effect on the long-term outcome of elderly AML patients. Even less satisfactory results have been reported in a recent update of the AMLCG 1999 trial by the German group.

In this study, patients 16 to 85 years of age with de-novo or secondary AML received two induction regimens, TAD/HAM or HAM/HAM, standard consolidation, prolonged maintenance or autologous stem cell transplantation. By randomization, G-CSF was given with all chemotherapy courses during the first year and started 48 hours before each course. Confirming a previous report (14), CR rate, OS and DFS were not affected in either younger or elderly patients. Differences in the design of these trials and patients characteristics make comparison of these studies difficult. However, this strategy has not been consistently effective and no significant clinical benefit has been reported in the majority of the studies. Thus, the priming with growth factors in AML could not be recommended as standard of care.

Pegylated filgrastim

The application of pegylation technology has created a second generation molecule, pegfilgrastim, with significantly altered pharmacokinetic properties. Pegfilgrastim has the same mechanism of action as filgrastim but the pegylation markedly reduces renal clearance, leaving neutrophil-mediated clearance as the major route of elimination. As a result, clearance of pegfilgrastim is decreased and serum concentrations are sustained throughout the duration of neutropenia. In clinical studies with standard, multicyle chemotherapy, a single subcutaneous (sc) dose of pegfilgrastim has been shown to have similar efficacy and safety as daily sc doses of filgrastim in patients with solid tumors. Emerging evidence also suggests that pegfilgrastim may be equally employed in the setting of chemotherapy for AML, dose-dense chemotherapy and peripheral stem cell mobilization.

A double-blind, randomized, active-controlled, clinical trial was conducted to assess the efficacy and safety of pegfilgrastim relative to filgrastim in patients with de novo AML. To minimize inter-patient variability, patients with FAB M7 subtype, high-risk cytogenetics or leukemia secondary to myelodysplastic syndrome were excluded. Patients received 1 or 2 courses of standard induction chemotherapy, and 1 course of consolidation therapy if complete remission was achieved. During days 6 through 8 of induction, patients were randomized to receive either pegfilgrastim or filgrastim (plus placebo-matched comparator) in a 1:1 ratio. Pegfilgrastim was administered as a single, 6 mg, fixed dose, 24 hours after completing chemotherapy. Filgrastim 5 \( \mu g/kg \) was administered daily, beginning 24 hours after chemotherapy and continuing until the absolute neutrophil count (ANC) was \( \geq 10\times 10^9/L \) for 3 consecutive days or \( \geq 10\times 10^9/L \) for 1 day. Median time to recovery from severe neutropenia was 22.0 days for each treatment group during induction and 17.0 and 16.5 days during consolidation for pegfilgrastim and filgrastim, respectively.

After a single injection, median pegfilgrastim serum concentrations remained above clinically relevant concentrations throughout the prolonged neutropenia and declined upon ANC recovery, consistent with a neu-
Peptphil-mediated clearance mechanism. Compared with 1 pegfilgrastim injection, a median of 16 filgrastim injections were required in induction and 13 in consolidation to ensure ANC recovery. Pegfilgrastim was well tolerated, with a safety profile similar to that of filgrastim. The results from this study show the efficacy of pegfilgrastim to assist in neutrophil recovery following chemotherapy in de novo AML patients with low to intermediate risk cytogenetics.

The German Cooperative group for AML used sequential high dose ARA-C as accelerated dose dense induction therapy (S-HAM, 66% dose). Pegfilgrastim was applied subcutaneously to all patients with complete blast clearance on day 18 after start of S-HAM. After a single injection, measurable pegfilgrastim plasma levels were observed up to day 14. In patients who received a second injection 10 days after the first, measurable plasma levels were seen up to day 20. Pegfilgrastim clearance was significantly correlated with neutrophil recovery. Median time to neutrophil recovery was 12.7 days after injection. With this approach using an accelerated, dose dense regimen plus pegfilgrastim, the duration of severe neutropenia was 30.7 days, vs 45 days with the conventional HAM/HAM regimen. Due to the shortened neutropenia with no excess of toxicity or early deaths, the AMLCG is now testing the S-HAM regimen at 100% dose for AML induction.

In conclusion, once–per-cycle administration of pegfilgrastim is safe and at least as effective as daily filgrastim in accelerate ANC recovery after chemotherapy in AML patients. Further studies are advisable to establish the proper role and the best timing of pegfilgrastim administration in the AML treatment.

References