Fatal Stimulation of Acute Myeloid Leukemia Blasts by Pegfilgrastim

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Abstract. *We herein report the case of a male patient with acute myeloid leukemia with fatal outcome attributable to pharmacokinetics of pegfilgrastim. Case Report: An unexplained blast proliferation in a patient with acute myeloid leukemia following cytotoxic induction chemotherapy was investigated in depth. Myeloblast hyperstimulation was likely related to pegfilgrastim, the long half-life of which extended the duration of side-effects, resulting in massive and rapidly fatal leukemia cell proliferation. Conclusion: Pegfilgrastim can cause unexpected deleterious effects in acute myeloid leukemia. We, thus, recommend administering drugs with a shorter half-life, such as filgrastim or lenograstim, to reduce infection incidence in patients receiving myelosuppressive chemotherapy associated with a clinically significant incidence of febrile neutropenia.*

Pegfilgrastim, a recombinant form of granulocyte colony-stimulating factor (G-CSF), is indicated for reducing neutropenia duration and fever incidence in patients receiving myelosuppressive chemotherapy. G-CSF receptors (G-CSFRs) are displayed in each maturation stage of myeloid lineage cells. After binding to G-CSFRs and following receptor complex internalization, pegfilgrastim is effective in sustaining myeloid cell maturation and proliferation. Seven G-CSFR messenger RNA (mRNA) isoforms produced by alternative splicing of a single-gene transcript have been identified in humans. The expression of various isoforms or mutated G-CSFR expressed on myeloid cell membranes likely affects G-CSF action (1). The conjugation of filgrastim to a polyethylene glycol moiety, as seen in pegfilgrastim, prolongs the drug's half-life and action.

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We herein report the first pegfilgrastim-induced case of fatal blastic hyperstimulation in a patient with leukemia.

Case Report

A 46-year-old male was referred because of anemia, thrombocytopenia, increased white blood cell (WBC) count (17.1×10^9/l), and presence of blasts (1.8×10^9/l). Bone marrow smear was hypercellular, with 41% myeloblasts, and acute myeloid leukemia (AML) FAB-type 2 with intermediate risk (normal cytogenetic and no molecular abnormality) was diagnosed. Fifteen days after initiating chemotherapy (daunorubicine at 60 mg/m^2 on days 1-3 and cytarabine at 200 mg/m^2 on days 1-7), the marrow smear showed persistence of 51% myeloblasts with a decreased cellularity. On day 19 of reinitiating chemotherapy (daunorubicine at 35 mg/m^2 on days 17-18 and cytarabine at 1,000 mg/m^2 bid on days 17-19), the WBC count was 2.2×10^9/l with 0.07×10^9 blasts/lt. Twenty-four hours after completing chemotherapy, 6 mg pegfilgrastim was administered subcutaneously. Six days after pegfilgrastim administration (Figure 1), the WBC count increased to 283.9×10^9/lt, with 230.0×10^9 blasts/lt, despite hydroxyurea therapy initiation. The patient complained of headache. Computed tomographic scan showed diffuse meningeal hemorrhage. The patient died two days later.

Discussion

G-CSF induces proliferation of AML cells *in vitro* (1-2). Although the number of G-CSFRs is lower on myeloblasts than on granulocytes, their affinity for G-CSF is increased, leading *in vitro* to potent induction of DNA synthesis. The resulting cell proliferation has so far been found to have had low impact in practice. Heil *et al.* compared filgrastim to placebo during myelosuppressive chemotherapy in 521 patients with AML (3), with similar 3-year overall survival rates in both groups. G-CSF administration is presently

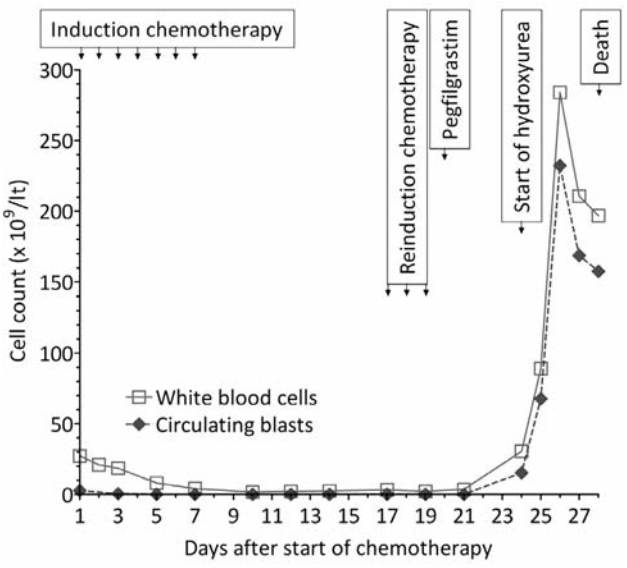

Figure 1. *White blood cell and blast counts from induction chemotherapy until death.*

considered the standard-of-care for intensive chemotherapy for patients with AML. AML blast cells exhibit different expression of G-CSFR isoforms compared to normal $CD34^+$ (cluster of differentiation) cells. Isoform IV overexpression, observed in more than 50% of AML cases, has been linked to defective signaling in cell differentiation, with persistence of the proliferative response, resulting in a G-CSF-dependent myeloblastic proliferation (1). Following G-CSF treatment, there was an increased incidence of relapse in children with AML-overexpressing G-CSFR isoform IV, whereas this isoform overexpression was not correlated to relapse incidence in patients not receiving G-CSF (4).

In our case, isoform IV overexpression or G-CSFR mutation might explain the high proliferative signal. The excessive hyperleukocytosis, not reported before, was probably linked to prolonged pegfilgrastim-induced stimulation on account of its pharmacokinetic features. While filgrastim has a serum half-life of 3 to 4 h, the added polyethylene glycol hampers renal clearance of pegfilgrastim, resulting in several days' exposure. Only one study has previously compared pegfilgrastim to filgrastim in patients with AML (5), with no difference in response rates. G-CSF is an integral part of managing AML and other hematological malignancies in order to reduce infection in patients undergoing intensive chemotherapy. Although experience with pegfilgrastim in patients with AML is limited, no increased toxicity compared to filgrastim has been to our knowledge reported so far. Based on our experience, we recommend administering non-pegylated G-CSF to patients with AML.

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