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Effect of granulocyte colony-stimulating factor on outcomes in patients with non-M3 acute myelogenous leukemia treated with anthracycline-based induction (7+3 regimen) chemotherapies

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ABSTRACT

We analyzed the effects of granulocyte colony-stimulating factor (G-CSF) on outcomes in 315 anthracycline-based induction chemotherapy-treated patients with non-M3 acute myelogenous leukemia (AML). Patients were classified as follows: no G-CSF administration during induction (no G-CSF group; 112 patients); administration immediately upon neutropenia onset (absolute neutrophil counts (ANC) < 1000/μL), but before febrile neutropenia (preemptive group; 74 patients); and administration following febrile neutropenia development (therapeutic group; 129 patients). G-CSF users had a shorter time to ANC recovery than the no G-CSF group ($p < 0.001$). The chemotherapy-induced febrile neutropenia (CIFN) duration was significantly shorter in the preemptive group than in other groups ($p < 0.001$). The incidence of CIFN was not significantly different between preemptive and non-G-CSF users (84.8% versus 82.4%). Preemptive G-CSF administration modestly improved treatment-related mortality (TRM), compared with no G-CSF administration ($p = 0.076$ in multivariate analysis). G-CSF administration did not affect relapse-free or overall survivals or the cumulative relapse incidence among the groups. In conclusion, preemptive G-CSF administration reduced CIFN duration and modestly improved TRM without affecting chemotherapy outcomes. These effects were not observed in the therapeutic group; therefore, initiation of G-CSF during induction therapy before the development of febrile neutropenia may be desirable.

1. Introduction

Induction chemotherapy comprising a combination of anthracycline and cytarabine is a standard treatment for newly diagnosed patients with acute myelogenous leukemia (AML) [1]. Although this combination regimen provides fair anti-leukemic efficacy, it is associated with a fairly high incidence of treatment-related mortality (TRM) [2,3]. Notably, most TRMs occur in response to neutropenia-related infections [2,4].

In the first phase III clinical trial of filgrastim in patients with small-cell lung cancer, reductions in both the duration of neutropenia and the incidence of febrile neutropenia was reported [5]. Since then, several studies have reported similar benefits [6,7], and most current guidelines recommend primary granulocyte colony-stimulating factor (G-CSF) prophylaxis in patients with solid cancer, who have a ≥20% risk of febrile neutropenia [8–10]. However, the recommendations for patients with AML are less clear-cut. For instance, the 2015 American Society of Clinical Oncology guidelines do not address the use of G-CSF in patients with AML [8]. The most recent National Comprehensive Cancer Network (NCCN) guidelines recommend G-CSF mainly as a part of supportive care for post-remission therapy rather than for induction therapy, except for patients with sepsis and those with life-threatening infections [10].

Abbreviations: AML, acute myelogenous leukemia; ANC, absolute neutrophil counts; CCI, Charlson comorbidity index; CI, confidence interval; CIFN, chemotherapy-induced febrile neutropenia; CR, complete remission; G-CSF, granulocyte colony-stimulating factor; NCCN, National Comprehensive Cancer Network; OS, overall survival; RFS, relapse-free survival; TRM, treatment-related mortality.

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The unclear guidelines regarding G-CSF use may be attributed to several factors. First, there is a relative dearth of relevant clinical trials. Several studies have demonstrated that the use of G-CSF during induction chemotherapy leads to reductions in neutrophil recovery time without a negative effect on the prognosis of patients with AML [13–15]. However, the initiation of G-CSF administration in these trials was based on fixed time schedules (e.g. day 8 after induction chemotherapy initiation), and not on clinical situations such as the development of febrile neutropenia. Second, despite reductions in the incidence and duration of neutropenia, the role of G-CSF in reducing TRM during the induction phase remains controversial [16]. Finally, because leukemic myeloblasts express G-CSF receptors to varying degrees [17,18], G-CSF administration may induce myeloblast proliferation [19]. Although this potential adverse effect was not observed during clinical trials involving patients with AML, many hematologists remain hesitant to administer G-CSF to patients with AML during induction therapy.

To identify the role of G-CSF in induction therapy for patients with newly diagnosed AML, we analyzed the efficacy of G-CSF administration based on the clinical status of the patient (e.g., development of neutropenia or fever). We further investigated the effect of G-CSF administration on the anti-leukemic efficacy of induction chemotherapy.

2. Patients and methods

2.1. Patients

Patients with newly diagnosed AML who were enrolled in the Korea University AML registry between September 2001 and June 2016 were retrospectively analyzed. Patients treated with anthracycline-based induction chemotherapies (a 7+3 regimen comprising cytarabine 100 mg/m^2 daily for 7 days plus idarubicin 12 mg/m^2 daily for 3 days, or cytarabine 100 mg/m^2 daily for 7 days plus daunorubicin 60–90 mg/m^2 daily for 3 days) were included for further analysis. Patients with acute promyelocytic leukemia and those in the blast phase of chronic myelogenous leukemia were excluded. Bone marrow aspiration and biopsies were performed to confirm the persistence of leukemia if the patients' absolute neutrophil counts (ANC) increased to >1000/μL at 14–21 days after the completion of induction chemotherapy. Patients were segregated into favorable risk, intermediate risk, and poor risk groups based on the cytogenetic and molecular abnormalities, according to the NCCN guidelines. Patients in complete remission (CR) were scheduled to receive 3–4 cycles of consolidation chemotherapy. Some patients in the favorable risk group received 1–2 cycles of consolidation chemotherapy followed by autologous stem cell transplantation, whereas those in the intermediate and poor risk groups received allogeneic transplantation based on donor availability. Consolidation chemotherapy comprised high-dose cytarabine (3 g/m^2 every 12 h on days 1, 3, and 5), or a combination of intermediate-dose cytarabine (1 g/m^2 every 12 h for 3 days) and anthracycline (idarubicin 12 mg/m^2 or mitoxantrone 12 mg/m^2 daily for 2 days).

Based on the G-CSF administration strategies used during induction therapy, patients enrolled in the study were classified into 3 subgroups. First was the no G-CSF group that included patients who did not receive G-CSF during induction chemotherapy. Second was the preemptive G-CSF group that included patients who immediately after induction chemotherapy completion received G-CSF upon the onset of neutropenia (ANC <1000/μL), but before developing febrile neutropenia. Third was the therapeutic G-CSF group that included patients who immediately after induction chemotherapy completion received G-CSF upon developing febrile neutropenia. G-CSF administration strategies were decided by the attending physicians, and the doses and routes of filgrastim or lenograstim administration were decided according to FDA guidelines. Patients who were febrile before induction chemotherapy received empirical or therapeutic antibiotics, whereas afebrile patients received either quinolone-based prophylactic antibiotics or no antibiotics. The same components of supportive care, including nutritional support, isolation policies, and antibiotics for febrile neutropenia, were provided to all enrolled patients.

2.2. Clinical endpoints

The primary endpoint was the time to ANC recovery, defined as the median number of days from the start of induction chemotherapy to the time when an ANC >1000/μL was achieved and maintained for 3 days in a row. Secondary endpoints included the duration and incidence of chemotherapy-induced febrile neutropenia (CIFN), the duration of hospitalization, TRM, rate of CR, relapse-free survival (RFS), and overall survival (OS). The duration of CIFN was defined as the time period during which the following conditions were met: (1) development of fever after induction chemotherapy initiation; (2) an ANC <500/μL or an ANC <1000/μL with a predicted decline to ≤500/μL within the next 48 h; and (3) a temperature of >38.3 °C or >38.0 °C sustained over an 1-h period, as measured by a tympanic thermometer. The duration of hospitalization was calculated as the median number of days from the start of induction chemotherapy to the date of discharge from the hospital. TRM was defined as mortality within 8 weeks of induction chemotherapy initiation. CR was defined as <5% blasts in the bone marrow with normal trilineage regeneration, per the revised International Working Group criteria [20]. Relapse was defined as the reappearance of leukemic blasts in the peripheral blood or ≥5% blasts in the bone marrow after a CR phase. For patients who had achieved CR, the duration of RFS was defined as the time from the date of CR to the date of relapse or death. OS was defined as the time from the date of AML diagnosis to the date of death. The comorbidity score was generated using a previously published, adapted form of the Charlson comorbidity index (CCI) [21].

2.3. Statistical analysis

The IBM Statistical Package for Social Sciences (SPSS) version 21.0 (IBM Corp., Armonk, NY, USA), SAS version 9.4 (SAS Inc., Cary, NC, USA), and R version 3.3.1 (The R Project for Statistical Computing, Vienna, Austria) were used for data analysis. Patient demographics and baseline characteristics were compared among the three G-CSF groups using the Kruskal–Wallis H test or chi-square test, as appropriate. The Mann–Whitney *U* test was used to compare the timing of G-CSF initiation between the preemptive and therapeutic G-CSF groups. A post hoc analysis with Bonferroni correction was performed when a statistical difference was identified among the three groups using the Kruskal–Wallis H test.

The median ANC recovery time, CIFN duration, and hospitalization duration were compared using a Kruskal–Wallis H test with post hoc Bonferroni correction. For study variables, associations with the incidence of CIFN were assessed using univariate and multivariate logistic regression analyses, and associations with the incidence of TRM were assessed using univariate and multivariate personalized logistic regression analyses. The following variables were included: age, sex, performance status, CCI, cytogenetic risk categories, type of anthracycline, any use of antibiotics, fever, or neutropenia before induction chemotherapy, lactate dehydrogenase and C-reactive protein levels, and G-CSF administration.

Prognostic factors affecting the rate of CR were assessed using univariate and multivariate logistic regression analyses with the following variables: age, sex, performance status, CCI, cytogenetic risk categories, type of anthracycline, and G-CSF administration.