The Efficacy and Safety of DA-3030 (Recombinant Human Granulocyte Colony-Stimulating Factor) in Neutropenia after the Remission Induction Chemotherapy in Patients with Acute Myelogenous Leukemia

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Purpose: This study was conducted to determine the efficacy and safety of DA-3030 (a recombinant methionyl human granulocyte colony-stimulating factor, rhG-CSF), after remission induction chemotherapy, in patients with acute myelogenous leukemia (AML).

Materials and Methods: After the remission induction chemotherapy, with idarubicin (12 mg/m²/day for 3 days) and cytarabine (200 mg/m²/day for 7 days), 26 patients with newly diagnosed AML were assigned to receive DA-3030 (200μg/m²/day), starting 24 hours after the completion of the remission induction chemotherapy, until their neutrophil count recovered to greater than 1,000/μL for 3 consecutive days.

Results: The median time from the initiation of the chemotherapy to the neutrophil recovery of 1,000/μL was 21 days (range, 12–41). Treatment with DA-3030 was not associated with significant adverse side effects. The most frequently reported side effects were musculo-skeletal pain (13%) and headache (13%).

Conclusion: The DA-3030 is a safe rhG-CSF for the treatment of neutropenia after remission induction chemotherapy in patients with AML. (Cancer Research and Treatment 2003;35:66-68)

Key Words: Acute myelogenous leukemia, rhG-CSF, Neutropenia

INTRODUCTION

Acute myelogenous leukemia (AML) has become a curable disease with the use of chemotherapy and bone marrow transplantation. However, intensive therapy is required for the cure of this disease, and a high degree of myelosuppression and resultant infectious complications are major obstacles in the cure-oriented treatment (1).

Granulocyte colony-stimulating factor (G-CSF) is a glycoprotein hormone of the hemopoietin family, which primarily influence the proliferation and differentiation of neutrophilic granulocytic precursors. G-CSF has also been effective in reducing neutropenia and its complications (2).

The administration of G-CSF to patients with AML has been proven to be safe, since no trial has demonstrated evidence of leukemic stimulation with this drug. However, the application of myeloid growth factor in AML had been limited by the theoretical concerns about their ability to stimulate the growth of leukemic cells (3,4).

DA-3030 (Leucostim® provided by Dong-A Pharm, Co., Seoul, Korea), a recombinant methionyl human G-CSF produced in Escherichia coli, is tolerable and reduces the duration of neutropenia after chemotherapy for solid tumors (5–7).

We conducted this study to determine whether DA-3030 was efficacious and safe for the treatment of severe and prolonged neutropenia after remission induction chemotherapy in patients with AML.

MATERIALS AND METHODS

1) Patients

Twenty-six patients, from 2 institutions (Asan and Samsung Medical Centers), were enrolled in this study between July
Table 1. Patients characteristics

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Leukocyte (median, mm$^3$) 12,000
Hb (median, g/dL) 9.1
Platelet (median, mm$^3$) 47,500
Blasts % in bone marrow (median) 38

*the French-American-British classification system.

1998 and November 1999. All 26 patients received idarubicin and cytosine arabinoside followed by DA-3030, and were under 70 years of age, with de novo AML, as defined by the French-American-British (FAB) classification system (8). The following criteria had to be met for the patients to qualify for the study; adequate renal (serum creatinine < 1.5 x normal) and hepatic (serum bilirubin and transaminases < 2 x normal) functions, and an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 3. The institutional review board approved the protocol, and written informed consents were obtained from all patients. Of the twenty-six patients receiving DA-3030, two patients were withdrawn, one due to acute mixed leukemia after review of bone marrow, and the other because of the administration of an incorrect dose of DA-3030. Therefore, 24 of the 26 patients qualified for testing the efficacy and safety of the DA-3030.

The characteristics of the 24 patients are listed in Table 1.

2) Treatment protocol

All patients received induction chemotherapy consisting of a 30-minute infusion of idarubicin, 12 mg/m$^2$/day for 3 days (D1-3), and a continuous infusion of cytarabine, 200 mg/m$^2$/day for 7 days (D1-7). From 24 hours after the completion of the induction chemotherapy, DA-3030 was administered by intravenous infusion at a daily dose of 200µg/m$^2$, and the process continued until neutrophil recovery became evident [absolute neutrophil count (ANC) more than 1,000/µL for three consecutive days].

RESULTS

1) Recovery of leukocyte and neutrophil

A leukocyte recovery above 1,000/µL, for 3 consecutive days, was evident at a median of 21 days (ranging from 10 to 39 days) after the initiation of the remission induction chemotherapy. The median number of days at which the ANC exceeded 500/µL and 1,000/µL were both 21 days (ranges, 10 to 39 and 12 to 41 days, respectively) after chemotherapy (Fig. 1). The median absolute neutrophil counts (ANC) during and following the induction chemotherapy are shown in Fig. 2.

2) Incidence of febrile episode and microbiologically defined infection

Twenty (83.3%) patients were reported to have had febrile episodes at the time of the enrollment; 4 developed fevers prior to the induction chemotherapy. Microbiologically defined infections were observed in 11 (45.8%) patients. The median duration of intravenous antibiotic therapy was 20.8 days (range, 6 ~ 45 days).

3) Hospitalization

The median duration of hospitalization for the induction chemotherapy among the 24 patients able to be evaluated was
43.8 days (range, 26–98 days).

4) Side effects of DA-3030

Musculo-skeletal pain and headache were reported by three patients, and numbness, tremors and nausea/vomiting by another one after the injection of DA-3030.

5) Response to remission induction chemotherapy

Fifteen of the 24 (62.5%) patients successfully obtained a complete remission after the remission induction chemotherapy.

DISCUSSION

The objective of this study was to determine the efficacy and safety of DA-3030. The DA-3030 was generally well tolerated, with the most frequently reported side effects being musculo-skeletal pain (13%) and headache (13%). A previous study reported that the use of DA-3030 in patients with solid tumors was effective in preventing chemotherapy-induced neutropenia (7).

Several randomized studies have been performed to evaluate the role of G-CSF, or granulocyte-macrophage colony-stimulating factor (GM-CSF), in combination with induction and consolidation chemotherapy in AML patients (1,3,4,9–11). In these studies, the duration of neutropenia (ANC ≥1,000/μL) in the G-CSF treatment groups ranged from 15 to 24 days, and the G-CSF groups showed a significantly faster recovery of neutrophil compared to the control groups. In addition, the administration of G-CSF was accompanied by reductions in the duration of fever, parenteral antibiotic use and hospitalization.

Our clinical data were comparable with the previously reported data, even though our study was not a controlled trial. Despite the beneficial effects, the role of G-CSF as a supportive care for AML patients remains to be proved. There has been no randomized study that clarifies the best time to start the G-CSF treatment after the induction chemotherapy in AML patients. It still remains to be determined whether the G-CSF should be used almost immediately after induction chemotherapy, after the onset of fever, or after the development of severe infection.

The American Society of Clinical Oncology (ASCO) panel recommended that the primary administration of G-CSF could be after the completion of the induction chemotherapy in patients ≥55 years of age (12). Although there are fewer data, the results showing a shortening of the neutropenic period, following the administration of G-CSF, means that it may be applied to younger patients also. G-CSF given before and/or concurrently with chemotherapy for priming effects still cannot be recommended outside of a clinical trial.

CONCLUSIONS

DA-3030 (Dong-A Pharmaceutical Co.) is a safe rhG-CSF for the treatment of neutropenia following induction chemotherapy in patients with AML.

REFERENCES


