

### NO INCREASE OF LEUKEMIA RELAPSE IN NEWLY DIAGNOSED PATIENTS WITH ACUTE MYELOID LEUKEMIA WHO RECEIVED GRANULOCYTE COLONY-STIMULATING FACTOR FOR LIFE-THREATENING INFECTION DURING REMISSION INDUCTION AND CONSOLIDATION THERAPY

To the Editor:

Granulocyte colony-stimulating factor (G-CSF) has proved useful for the recovery of severe neutropenia after intensive chemotherapy or bone marrow transplantation. However, the clinical application of G-CSF in myeloid leukemia has been controversial because it stimulates leukemia cells as well as normal granulocyte progenitors in vitro.<sup>1,2</sup> In a prospective randomized study on patients with refractory acute leukemia, we demonstrated that G-CSF accelerated neutrophil recovery and reduced the incidence of documented infections.<sup>3</sup> The regrowth of myeloid leukemia blasts was not accelerated by G-CSF, and the remission duration of the patients receiving G-CSF did not differ from that of patients receiving no G-CSF.<sup>3</sup> We report here that the remission duration of newly diagnosed patients with acute myeloid leukemia (AML) who received G-CSF for their life-threatening infections during the initial remission induction therapy or consolidation therapy was not shorter than that of patients receiving no G-CSF.

To the AML-87 protocol of the Japan Adult Leukemia Study Group, 265 newly diagnosed adult patients with AML were consecutively registered from 19 institutions from June 1987 to September 1989. The details of this study were reported elsewhere.<sup>4</sup> Patients received an intensive induction therapy consisting of daunorubicin, behenoyl cytarabine, 6-mercaptopurine, and prednisolone with or without vincristine. After achieving complete remission (CR), they received 3 courses of intensive consolidation therapy; they then received either 4 or 12 courses of maintenance therapy administered every 6 weeks.

At the period when this protocol was conducted, it was the general consensus that G-CSF should not be administered to patients with standard-risk AML because of possible stimulation of AML blasts in vivo by this drug. However, among 252 evaluable patients, there were 23 patients who received G-CSF due to life-threatening infections during severe neutropenia after the induction or consolidation therapy. There were 28 infectious episodes for which they received G-CSF: 9 septicemia, 8 pneumonia, 2 septicemia and pneumonia, 4 periodontitis/stomatitis, 4 perianal abscess, and 1 pseudomembranous colitis. Recombinant human G-CSF (Kirin/Sankyo, Tokyo, Japan) 200 µg/m<sup>2</sup> was administered daily by 30-minute intravenous infusion until peripheral neutrophil counts recovered over 1,500/µL. The white blood cell counts at the start of G-CSF therapy ranged from 100 to

800/µL, with a median of 200/µL. Fourteen cases received G-CSF after the induction therapy, 5 cases after the first consolidation, 5 after the second consolidation, and 4 after the third consolidation. They received G-CSF for 2 to 35 days with a median of 8 days per episode, and for 2 to 35 days with a median of 14 days per patient. The neutrophils recovered over 1,500/µL in all but 3 patients within 2 to 20 days, with a median of 8 days. After the induction therapy, 1 patient died of pneumonia, 1 died of cerebral hemorrhage, and 1 died of sepsis. One patient died of septicemia after the third consolidation. The infections were controlled in all but 3 patients described above. Eight of 14 patients (57%) who had received G-CSF after the induction therapy achieved CR, and 188 of 238 (79%) receiving no G-CSF during the induction therapy achieved CR. Nine patients were in CR when they received G-CSF.

The disease-free survival (DFS) of 17 CR patients who received G-CSF was compared with that of patients who did not receive G-CSF. Although there is no statistical significance, patients who received G-CSF tended to have a better DFS ( $P = .0785$  by the log-rank test) (Fig 1). At the median follow-up of 37 months, the predicted 40-month DFS rate of 17 CR patients who received G-CSF was 60%, whereas that of 179 CR patients who did not receive G-CSF was 33%. There was no significant difference between the two groups in age or French-American-British classification, but there was significantly more females in the G-CSF group. Because this is not a prospective randomized study and comparison of a small subset receiving G-CSF with a much larger group not receiving it may provide results that can be misleading, no conclusion should be drawn from this analysis. However, the results may indicate that the patients who developed life-threatening infections and subsequently received G-CSF had more profound myelosuppression by the chemotherapy and, as a result, obtained more leukemia cell kill. At least one can say that the cautious use of G-CSF to life-threatening infections caused no increased incidence of leukemia relapse in newly diagnosed patients with AML. Because G-CSF definitely stimulates AML cells in vitro, the clinical use of this drug should be limited to life-threatening infections in severely neutropenic states in case of standard-risk AML. In cases of high-risk AML, it is allowable to use G-CSF for the prophylaxis of infection, because early recovery from neutropenia will permit a dose-intensified chemotherapy in these patients, which will possibly result in better therapeutic outcome. However, the issue should be answered by a prospective randomized study.

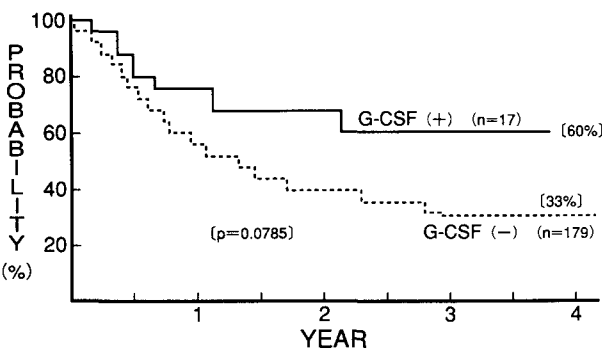


Fig 1. Kaplan-Meier curves of DFS of CR patients who received G-CSF and of those who did not receive G-CSF in the AML-87 study of the Japan Adult Leukemia Study Group.

RYUZO OHNO  
AKIRA HIRAOKA  
MITSUNE TANIMOTO  
NORIO ASOU  
KAZUTAKA KURIYAMA  
TOHRU KOBAYASHI  
MINORU YOSHIDA  
HIROFUMI TESHIMA  
HIDEHIKO SAITO  
KOJI FUJIMOTO  
Japan Adult Leukemia Study Group  
Nagoya, Japan

#### REFERENCES

1. Souza LM, Boone TC, Gabrilove JL, Lai PH, Zsebo KM, Murdoch DC, Chazin VR, Bruszewski J, Lu H, Chen KK, Barendt J, Platzer E, Moore MAS, Mertelsmann R, Welte K: Recombinant

Downloaded from http://ashpublications.org/blood/article-pdf/81/12/561/609596/561.pdf by guest on 01 June 2023

human granulocyte colony-stimulating factor: Effects on normal and leukemic myeloid cells. *Science* 232:61, 1986

2. Griffin JD, Löwenberg B: Clonogenic cells in acute myeloblastic leukemia. *Blood* 68:1185, 1986

3. Ohno R, Tomonaga M, Kobayashi T, Kanamura A, Shirakawa S, Masaoka T, Omine M, Oh H, Nomura T, Sakai Y, Hirano M, Yokomaku S, Nakayama S, Yoshida Y, Miura AB, Morishima Y, Dohy H, Niho Y, Hamajima N, Takaku F: Effect of granulocyte

colony stimulating factor after intensive induction therapy in relapsed or refractory acute leukemia: A randomized controlled study. *N Engl J Med* 323:871, 1990

4. Ohno R, Kobayashi T, Morishima Y, Hiraoka A, Imai K, Asoh N, Tsubaki K, Tomonaga M, Takahashi K, Kodaera K, Omine M, Yoshida Y, Naoc T: Randomized study of individualized induction therapy with or without VCR, and of maintenance of 4 or 12 courses in adult AML; JALSG-AML-87. *Leukemia* 6:92, 1992 (suppl 2)

---