Prospective Randomization Trial of G-CSF-Primed Induction Regimen versus Standard Regimen in Patients with AML

Yoo Jin Lee, Joon Ho Moon, Jong Gwang Kim, Yee Soo Chae, Byung Woog Kang, Soo Jung Lee, Jun Young Choi, Ho Chul Shin, Jong Won Seo and Sang Kyun Sohn*

Department of Hematology/Oncology and Stem Cell Transplantation Unit, Kyungpook National University Hospital, Kyungpook National University School of Medicine, Daegu, Korea

The sensitization of leukemia cells with hematopoietic growth factors can enhance the cytotoxicity of chemotherapy in acute myeloid leukemia (AML). Therefore, the current trial attempted to evaluate the efficacy of granulocyte colony-stimulating factor (G-CSF) priming in remission induction chemotherapy with an intensified dose of Ara-C for newly diagnosed AML. Patients with newly diagnosed AML were randomly assigned to receive idarubicin (12 mg/m^2/24 hr, days 1-3) plus Ara-C (500 mg/m^2/12 hr, days 4-8) with G-CSF (250 μg/m^2/d, days 3-7) (IAG group) or standard idarubicin (12 mg/m^2/24 hr, days 1-3) plus Ara-C (100 mg/m^2/12 hr, days 1-7) without G-CSF (IA group). There were no significant differences in sex, age, subtype, or cytogenetic risk between the two groups. Complete remission was achieved in 15 patients (88.2%) from the IAG group and in 14 patients (82.4%) from the IA group (p=0.31). The median time to complete remission was 26 vs. 31 days (p=0.779) for the IA and IAG groups, respectively. The median time to neutrophil recovery ($>1\times10^9$/L) and platelet recovery ($>20\times10^9$/L) did not differ significantly between the two groups (26 vs. 26 days, p=0.338; 21 vs. 16 days, p=0.190, respectively). After a median follow-up of 682 days, the 3-year overall survival rate for the IA group was 64.7%, whereas that for the IAG group was 45.6% (p=0.984). No improved clinical outcomes were observed for the AML patients subjected to intensified remission induction with G-CSF priming when compared with standard induction chemotherapy.

Key Words: *Acute myeloid leukemia; Cytarabine; Granulocyte colony-stimulating factor; Induction of remission*

Corresponding Author:
Sang Kyun Sohn
Department of Hematology/Oncology,
Kyungpook National University
Hospital, Kyungpook National
University School of Medicine, 200
Dongduk-ro, Jung-gu, Daegu
700-721, Korea
TEL: +82-53-420-5587
FAX: +82-53-426-2046
E-mail: sksohn@knu.ac.kr

INTRODUCTION

Although the treatment outcomes for patients with acute myeloid leukemia (AML) have substantially improved over the past decades, treatment failure and relapse remain major concerns.[1-3] This high rate of recurrence is due to the reemergence of leukemic cells from a residual leukemic burden that escaped the cytotoxic effect of chemotherapy. Thus, several strategies are used to intensify the induction therapy, including the use of hematopoietic growth factors or an intensified dose of Ara-C.[4-6]

Hematopoietic growth factors have attracted considerable interest as the result of *in vitro* evidence showing that growth factors may recruit leukemic cells into the cell cycle and enhance their susceptibility to chemotherapy.[7,8] Nonetheless, attempts to improve the response rate by sensitizing leukemic cells with growth factors have yielded conflicting results.[8,9] In a previous pilot study, the current authors reported that the sensitization of leukemic cells with growth factors and dose intensification seemed to be a clinically applicable means of enhancing the efficacy of remission induction (RI) chemotherapy.[10]

Accordingly, in the current prospective trial, patients were randomly assigned to receive a granulocyte colony-stimulating factor (G-CSF)-primed RI regimen with an intensified dose of Ara-C or a standard idarubicin plus

Ara-C regimen (IA) to determine the efficacy of growth factor priming and an increased dose of Ara-C for patients with newly diagnosed AML.

MATERIALS AND METHODS

1. Patient eligibility

A total of 34 patients aged 15 to 64 years with newly diagnosed AML were randomly assigned to the G-CSF priming group or the no priming group. Patients with acute promyelocytic leukemia and a poor performance status (ECOG $\geq$ 3) were excluded from this trial. The primary end point was the complete remission (CR) rate and the secondary end point was the overall survival (OS) rate of the patients. The current study was approved by the local institutional review board of Kyungpook National University Hospital, and each patient gave written informed consent in line with the Helsinki declaration.

2. Treatment protocol

The G-CSF-primed intensified RI chemotherapy (IAG group) consisted of idarubicin (12 mg/m^2 intravenously over a period of 15 minutes on days 1 to 3), an intermediate dose of Ara-C (500 mg/m^2/12 hr given intravenously over a 3-hour period on days 4 to 8), and G-CSF (lenograstim 250 μg/m^2 intravenous infusion on days 3-7). For patients over 50 years of age, the idarubicin dose was reduced to 8 mg/m^2/day and ara-C to 350 mg/m^2/12 hr. If the white blood cell (WBC) count remained higher than 30×10^9/L after 2 days of chemotherapy, the administration of G-CSF was postponed or interrupted until the WBC count decreased to 20×10^9/L. G-CSF was also discontinued in the case of serious toxicity considered to be attributable to the growth factor. The nonpriming induction (IA group) consisted of idarubicin (12 mg/m^2 intravenously over a period of 15 minutes on days 1 to 3) and Ara-C (100 mg/m^2/12 hr given intravenously over a 3-hour period on days 1 to 7). For patients over 50 years of age, the dose of idarubicin was reduced to 8 mg/m^2/day.

Both groups were given G-CSF during nadir periods after chemotherapy. Stem cell transplantation was recommended for patients with an intermediate or unfavorable cytogenetic risk after RI chemotherapy.

3. Response criteria

The response criteria followed the revised recommendations of the international working group for therapeutic trials in AML.[11] CR was defined as morphologically normal marrow with less than 5% blasts, no evidence of extramedullary leukemia, and the recovery of peripheral blood values to platelet counts of at least 100×10^9/L and an absolute neutrophil count of more than 1.0×10^9/L. CR with incomplete platelet recovery (CRp) was defined as for CR, yet with a platelet count below 100×10^9/L. Partial remission (PR) was defined as a decrease of at least 50% in the percentage of blasts to 5% and 25% in the bone marrow aspirates and normalization of the blood counts. Patients failing to achieve CR were considered treatment failures. Relapse following CR was defined as the reappearance of leukemic blasts in the peripheral blood or more than 5% blasts in the bone marrow.

4. Statistical analysis

OS was measured from the initiation of RI therapy until death from any cause. Event-free survival (EFS) was defined as the time from the initiation of RI therapy until treatment failure, relapse from CR, or death from any cause, whichever occurred first. The time to CR was the time from the start of induction until the achievement of CR.

The continuous variables were compared by using a two-sample t-test, whereas the categorical data were analyzed by using a Chi-square test. The OS and EFS rates were analyzed by using a Kaplan-Meier test and both groups were compared by using a log-rank test or Breslow test. A p-value of less than 0.05 was considered significant. For the statistical analyses, SPSS software ver. 15 (SPSS Inc., Chicago, IL, USA) was used.

RESULTS

1. Patient characteristics

Between March 2006 and June 2008, a total of 34 patients were equally randomly assigned into the IA and IAG groups. The patients' ages ranged from 15 to 64 years, with a median age of 44 years for the IA group and 47 years for the IAG group. The initial presentation in terms of the WBC count, peripheral blood and bone marrow blast counts, and cytogenetic risk groups was not significantly different between the two groups.

For the IA group, consolidation chemotherapy was administered to 5 patients (29.4%), an autologous stem cell transplantation (SCT) to 3 patients (17.6%), and allogeneic SCT to 8 patients (47.1%), whereas for the IAG group, consolidation chemotherapy was administered to 7 patients (35.3%), an autologous SCT to 3 patients (5.9%), and allogeneic SCT to 9 patients (52.9%) (p=0.765). The patient characteristics are summarized in Table 1.

2. Response to induction treatment

For the IA group, CR was achieved in 14 (82.4%) of 17 patients, whereas for the IAG group, CR was achieved in 15 (88.2%) of 17 patients; 2 patients were refractory to the RI therapy. The median time to CR achievement was 26 days (range, 22-72 days) for the IA group and 31 days (range, 22-55 days) for the IAG group (p=0.779) (Table 2).

The median time to neutrophil recovery was 26 days (range, 20-39 days) versus 26 days (range, 22-56 days, p=0.338) and that for platelet recovery was 21 days (range, 13-189 days) versus 16 days (range, 12-29 days, p=0.190) for the IA and IAG groups, respectively. The incidence of febrile neutropenia was 76.5% for the IA group and 70.6% for the IAG group (p=0.679) (Table 2). There were no cases of TRM during RI therapy in either group.

TABLE 1. Patient characteristics

	IA (n=17)	IAG (n=17)	p
Sex, M/F, n (%)	8/9 (47.1/52.9)	9/8 (52.9/47.1)	0.732
Age, median years (range)	44 (26-63)	47 (15-63)	0.939
FAB classification, n (%)			
M0	0	2 (11.8)	0.136
M1	0	1 (5.9)	
M2	9 (52.9)	8 (47.1)	
M4 (+M4E)	2 (11.8)	2 (11.8)	
M5	3 (17.6)	1 (5.9)	
M6	0	2 (11.8)	
Mixed	3 (17.6)	1 (5.9)	
Cytogenetic risk group, n (%)			
Good	4 (23.5)	3 (17.6)	0.651
Intermediate	11 (64.7)	10 (58.8)	
Poor	2 (11.8)	4 (23.5)	
Peripheral blood (range)			
WBC ($\times 10^9$/L)	20.8 (1.5-162.3)	15.8 (0.5-241.4)	0.291
Hb ($\times 10^6$/L)	7.7 (3.6-12.0)	8.4 (4.5-12.2)	0.654
Platelets (10^9/L)	39.5 (6.0-289.0)	43.0 (15.0-166.0)	0.346
PB blast %	24.5 (2.0-94.0)	42.5 (1.0-94.0)	0.329
BM blast %	56.0 (26.0-90.6)	49.2 (25.2-94.8)	0.480
LDH, IU/L	793 (218-5,779)	868 (223-3,545)	0.257
Post-remission therapy, n (%)			
Chemotherapy	5 (29.4)	6 (35.3)	0.765
Autologous-SCT	3 (17.6)	1 (5.9)	
Allogeneic-SCT	8 (47.1)	9 (52.9)	

IA: cytarabine plus idarubicin chemotherapy, IAG: G-CSF-primed cytarabine plus idarubicin chemotherapy, WBC: white blood cells, Hb: hemoglobin, PB: peripheral blood, BM: bone marrow, LDH: lactate dehydrogenase, SCT: stem cell transplantation.

TABLE 2. Treatment outcomes of the IA and IAG groups

	IA group (n=17)	IAG group (n=17)	p
Response to RI therapy			
CR	14 (82.4)	15 (88.2)	0.306
PR	2 (11.8)	0	
Refractory	1 (5.9)	2 (11.8)	
Time to CR, days (range)	26 (22-72)	31 (22-55)	0.779
Hematologic recovery			
ANC ($>1\times 10^9$/L)	26 (20-39)	26 (22-56)	0.338
Platelet ($>20\times 10^9$/L)	21 (13-189)	16 (12-29)	0.190
Febrile neutropenia	13 (76.5)	12 (70.6)	0.697
Relapse after 1st remission (%)	2 (11.8)	4 (23.5)	0.368
Death (%)	6 (35.3)	8 (47.1)	0.486
Cause of death			
Refractory	1 (5.9)	1 (5.9)	0.515
Relapse	2 (11.8)	1 (5.9)	
GVHD	1 (5.9)	3 (17.6)	
Infection	1 (5.9)	3 (17.6)	
Hemorrhage	1 (5.9)	0	

IA: cytarabine plus idarubicin chemotherapy, IAG: G-CSF-primed cytarabine plus idarubicin chemotherapy, RI: remission induction, CR: complete remission, PR: partial remission, CRp: CR with incomplete platelet recovery, ANC: absolute neutrophil count, GVHD: graft-versus-host disease.

3. Survival

With a median follow-up duration of 682 days (range, 61-1,365 days), 6 deaths (35.4%) occurred in the IA group and 8 deaths (47.0%) in the IAG group (p=0.486). The causes of death included 1 primary refractory disease (5.9%), 2 relapse-related deaths (11.8%), 1 graft-versus-host dis-

A
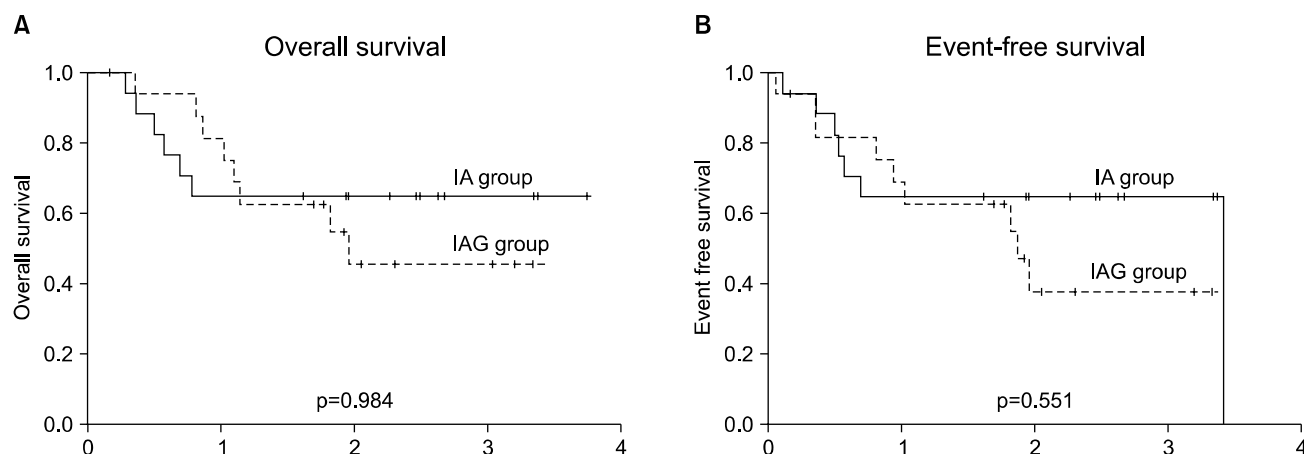
Overall survival

B

Event-free survival

FIG. 1. Overall survival and event-free survival in the IA and IAG groups. IA: cytarabine plus idarubicin chemotherapy, IAG: G-CSF-primed cytarabine plus idarubicin chemotherapy. (A) The 3-year overall survival rate was 64.7±11.6% for the IA group and 45.6±13.6% for the IAG group. (B) The 3-year event-free survival rate was 64.7±11.6% for the IA group and 37.6±13.5% for the IAG group.

ease (GVHD; 5.9%), and 1 infection (5.9%) in the IA group, and 1 primary refractory disease (5.9%), 1 relapse-related death (5.9%), 3 GVHD (17.6%), and 3 infections (17.6%) in the IAG group (Table 2). The OS and EFS rates were not significantly different between the two groups. The 3-year OS was 64.7±11.6% for the IA group and 45.6±13.6% for the IAG group (p=0.984). The 3-year EFS was 64.7±11.6% for the IA group and 37.6±13.5% for the IAG group (p=0.551, Fig. 1).

DISCUSSION

Although the combination of anthracycline and Ara-C has been established as the standard 3+7 induction regimen since the 1980s, several strategies have also been introduced to improve the CR rate for AML, including an intensified dose of ara-C and G-CSF priming.[1,3] In the case of a higher dose of Ara-C, two previous large cooperative clinical trials found that patients receiving induction therapy with a high dose of Ara-C (2-3 g/m^2/12 hr for a total of 24 g/m^2) experienced equivalent rates of complete remission yet a higher treatment-related mortality and more neurologic toxicity when compared with patients receiving a standard dose of Ara-C.[12,13]

Meanwhile, attempting to improve the response rate by sensitizing leukemic cells with growth factors, administered before or concurrently with RI therapy, is also an attractive concept. *In vitro* evidence indicates that G-CSF may increase the susceptibility of blast cells to cell cycle-specific agents, such as Ara-C, in the S-phase.[7,8] However, in contrast to *in vitro* data, these attempts have yielded conflicting results in *in vivo* studies.[8,9]

Based on the results of a previous pilot study, although the clinical outcomes in terms of OS and EFS were similar between the G-CSF priming group and the historical control group, the modulation of leukemic cells with growth factors and a dose intensification of Ara-C would seem to be a clinically applicable means of therapy for newly diag-

nosed AML patients.[10] Plus, the use of G-CSF priming before chemotherapy did not increase the risk of leukocytosis. Therefore, the present study was conducted to determine whether priming with G-CSF and a dose intensification of Ara-C in anthracycline-based RI therapy improves the clinical outcomes for newly diagnosed AML patients.

We found that priming with an increased dose of G-CSF produced no beneficial outcomes in terms of the achievement of CR, hematologic recovery, and OS; in addition, the risk of leukocytosis and interruption of chemotherapy were negligible (Table 2, Fig. 1). In a study focused on older AML patients, priming with G-CSF was found to improve the CR rate, yet the use of G-CSF during chemotherapy was not found to have any effect on the long-term outcomes of AML in older patients.[14] Meanwhile, in a study conducted by Lowenberg and colleagues, the rates of response and OS were not found to be significantly different, regardless of G-CSF priming. However, in a subgroup analysis, treatment with G-CSF priming reduced the probability of relapse and improved the OS and disease-free survival in patients with a standard risk, as defined by a cytogenetic analysis. Plus, although a previous pilot study by the current authors revealed a possible beneficial effect of G-CSF-primed RI therapy on disease-free survival, no positive results were observed in the current prospective trial.[10]

Bishop et al. previously reported that a dose intensification of Ara-C during induction therapy did not improve the CR rate, yet prolonged the remission duration and disease-free survival in *de novo* AML.[15] Plus, G-CSF priming has not been found to produce any positive effects in previous studies when administered with a standard dose of Ara-C. Therefore, because a dose escalation of Ara-C may affect the killing of leukemic cells sensitized by G-CSF, this study used an intermediate dose of Ara-C (500 mg/m^2), because exposure to a more intensified dose of Ara-C may increase the mortality due to overwhelming sepsis when compared with a standard dose of Ara-C. Nonetheless, whereas

the previous pilot study suggested the possibility of improved disease-free survival with G-CSF priming, the current randomized study did not produce a favorable response rate with G-CSF-primed RI therapy. Plus, G-CSF priming may even have a negative impact on subsequent allogeneic or autologous SCT, because the IAG group showed more GVHD and infection-related death, although this difference was not statistically significant (Table 2).

In conclusion, no improved clinical outcomes were observed for the AML patients subjected to G-CSF-primed RI therapy with an increased dose of Ara-C compared with the standard induction chemotherapy.

ACKNOWLEDGEMENTS

REFERENCES

1. Preisler HD, Rustum Y, Henderson ES, Bjornsson S, Creaven PJ, Higby DJ, et al. Treatment of acute nonlymphocytic leukemia: use of anthracycline-cytosine arabinoside induction therapy and comparison of two maintenance regimens. Blood 1979;53:455-64.
2. Keating MJ, Smith TL, McCredie KB, Bodey GP, Hersh EM, Gutterman JU, et al. A four-year experience with anthracycline, cytosine arabinoside, vincristine and prednisone combination chemotherapy in 325 adults with acute leukemia. Cancer 1981; 47:2779-88.
3. Rai KR, Holland JF, Glidewell OJ, Weinberg V, Brunner K, Obrecht JP, et al. Treatment of acute myelocytic leukemia: a study by cancer and leukemia group B. Blood 1981;58:1203-12.
4. Ohno R, Naoe T, Kanamaru A, Yoshida M, Hiraoka A, Kobayashi T, et al. A double-blind controlled study of granulocyte colony-stimulating factor started two days before induction chemotherapy in refractory acute myeloid leukemia. Kohseisho Leukemia Study Group. Blood 1994;83:2086-92.
5. Zittoun R, Suciu S, Mandelli F, de Witte T, Thaler J, Stryckmans P, et al. Granulocyte-macrophage colony-stimulating factor associated with induction treatment of acute myelogenous leukemia: a randomized trial by the European Organization for Research and Treatment of Cancer Leukemia Cooperative Group. J Clin Oncol 1996;14:2150-9.
6. Löwenberg B, Boogaerts MA, Daenen SM, Verhoef GE, Hagenbeek A, Vellenga E, et al. Value of different modalities of granulocyte-macrophage colony-stimulating factor applied during or after induction therapy of acute myeloid leukemia. J Clin Oncol 1997;15:3496-506.
7. te Boekhorst PA, Löwenberg B, Vlastuin M, Sonneveld P. Enhanced chemosensivity of clonogenic blasts from patients with acute myeloid leukemia by G-CSF, IL-3 or GM-CSF stimulation. Leukemia 1993;7:1191-8.
8. Löwenberg B, van Putten W, Theobald M, Gmür J, Verdonck L, Sonneveld P, et al; Dutch-Belgian Hemato-Oncology Cooperative Group; Swiss Group for Clinical Cancer Research. Effect of priming with granulocyte colony-stimulating factor on the outcome of chemotherapy for acute myeloid leukemia. N Engl J Med 2003;349:743-52.
9. Rowe JM, Neuberg D, Friedenberg W, Bennett JM, Paietta E, Makary AZ, et al; Eastern Cooperative Oncology. A phase 3 study of three induction regimens and of priming with GM-CSF in older adults with acute myeloid leukemia: a trial by the Eastern Cooperative Oncology Group. Blood 2004;103:479-85.
10. Baek JH, Sohn SK, Kim DH, Kim JG, Yang DH, Kim YK, et al. Pilot remission induction therapy with idarubicin, plus an intensified dose of ara-C and priming with granulocyte colony-stimulating factor for acute myeloid leukemia. Acta Haematol 2007;117:109-14.
11. Cheson BD, Bennett JM, Kopecky KJ, Büchner T, Willman CL, Estey EH, et al; International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. J Clin Oncol 2003;21:4642-9.
12. Büchner T, Hiddemann W, Wörmann B, Löffler H, Gassmann W, Haferlach T, et al. Double induction strategy for acute myeloid leukemia: the effect of high-dose cytarabine with mitoxantrone instead of standard-dose cytarabine with daunorubicin and 6-thioguanine: a randomized trial by the German AML Cooperative Group. Blood 1999;93:4116-24.
13. Cahn JY, Labopin M, Sierra J, Blaise D, Reiffers J, Ferrant A, et al. No impact of high-dose cytarabine on the outcome of patients transplanted for acute myeloblastic leukaemia in first remission. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Br J Haematol 2000;110: 308-14.
14. Amadori S, Suciu S, Jehn U, Stasi R, Thomas X, Marie JP, et al; EORTC/GIMEMA Leukemia Group. Use of glycosylated recombinant human G-CSF (lenograstim) during and/or after induction chemotherapy in patients 61 years of age and older with acute myeloid leukemia: final results of AML-13, a randomized phase-3 study. Blood 2005;106:27-34.
15. Bishop JF, Matthews JP, Young GA, Szer J, Gillett A, Joshua D, et al. A randomized study of high-dose cytarabine in induction in acute myeloid leukemia. Blood 1996;87:1710-7.