Recombinant Human Granulocyte-Colony Stimulating Factor (rh G-CSF) After Induction and Consolidation Therapy in Acute Myeloid Leukemia

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Neutropenia and subsequent susceptibility to infection are the major side effects of cytotoxic chemotherapy. Although colony stimulating factors have been shown to accelerate recovery from severe neutropenia after intensive chemotherapy, their use in acute leukemia has been controversial because they stimulate leukemic colonies in vitro. To determine the safety and efficacy of recombinant human granulocyte colony-stimulating factor (rh G-CSF), we evaluated 21 periods of rh G-CSF treatment in 15 patients with acute myeloid leukemia (AML) who received induction or consolidation therapy (9 female, 6 male). rh G-CSF (5μ/kg daily subcutaneously) was begun 24 hours after the end of the chemotherapy consisting of Daunorubicin (45 mg/m^2 daily intravenously for 3 days) and Ara-C (100 mg/m^2 by continuous infusion for 7 days) and continued until the neutrophil count rose above 1000/mm^3 for two consecutive days. The historical control group consisted of 19 AML patients who received same chemotherapy regimen but without rh G-CSF. Compared with control group patients treated with rh G-CSF had a significantly faster neutrophil recovery. The number of days to granulocyte recovery above 1000/mm^3 was 11±0.81 in the rh G-CSF group versus 20±1.58 days in control group (p<0.001). In conclusion, these results suggest that rh G-CSF as an adjunct to induction and consolidation chemotherapy in AML is safe, accelerating neutrophil recovery after chemotherapy without effecting the regrowth of leukemic cells. [Journal of Turgut Özal Medical Center 1998;5(1):1-6]

Key Words: *G-CSF, AML, neutropenia, infection*

Akut miyeloid lösemide indüksiyon ve konsolidasyon tedavisinden sonra rekombinant human granulosit - koloni stimüle edici faktör (rh G-CSF) kullanımı

Nötropeni ve yol açtığı enfeksiyona yatkınlık sitotoksik kemoterapinin önde gelen yan etkisidir. Koloni stimüle edici faktörlerin yoğun kemoterapiden sonra gelişen ciddi nötropeninin düzelmesini hızlandırdığı gösterilmiş olmakla birlikte, in vitro olarak lösemik klonları stimüle ettiklerinden akut lösemideki kullanımları tartışmalıdır. Rekombinan human granülosit koloni stimüle edici faktör (rh G-CSF)'ün emniyetini ve etkinliğini saptamak için indüksiyon ya da konsolidasyon tedavisi alan 15 akut miyeloid lösemi (AML)li hastada (9 kadın, 6 erkek) 21 G-CSF tedavi peryodunu değerlendirdik. rh G-CSF (5μ/kg/gün, cilt altı), Daunorubisin (45 mg/m^2/gün, 3 gün, intravenöz) ve Ara-C (100 mg/m^2/gün, 7 gün, sürekli infüzyon) dan oluşan kemoterapiden 24 saat sonra başlandı ve 2 gün arka arkaya nötrofil sayısı 1000/mm^3 ün üstünde oluncaya kadar devam etti. Daha önceden aynı tedaviyi G-CSF'siz almış olan 19 olgu historik kontrol grubu olarak alındı. Kontrol grubu ile karşılaştırıldığında G-CSF alan hastalarda nötrofil toparlanma süresi anlamlı olarak kısaydı. Granülosit sayısının 1000/mm^3'ün üstüne çıkması için geçen süre G-CSF grubunda 11±0.81 günken, kontrol grubunda 20±1.58 gündü (p<0.001). Eritrosit sayısı ve trombosit toparlanması üzerine herhangi bir etki saptanmadı. Sonuç olarak, bu bulgular AML de indüksiyon ve konsolidasyon tedavisine eklenen G-CSF'nin, lösemik hücre çoğalmasını etkilemeksizin nötrofil toparlanmasını hızlandırması açısından güvenle kullanılabileceğini telkin etmektedir. [Turgut Özal Tıp Merkezi Dergisi 1998;5(1):1-6]

Anahtar Kelimeler: *G-CSF, AML, nötropeni, infeksiyon*

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Myelosupression from chemotherapy results in a substantial morbidity related primary to infectious complications (1). The risk of infection is directly related to the severity and duration of neutropenia (2) despite the use of broad spectrum antibiotics, death from sepsis is not infrequent (3). This also results in delays or modifications of chemotherapy and frequently dictates the schedule of treatment protocols (1). In order to reduced neutropenia-related morbidity and mortality, a number of treatment concepts have been utilized (1). Hematopoietic growth factors, recently, were approved for this aim in patients receiving myelosupressive chemotherapy (4-8) or undergoing bone marrow transplantation (BMT) (9-13).

The hematopoietic growth factors (HGF) are glucoprotein hormones that regulate the proliferation and differentiation of hematopoietic progenitor cells and the function of mature blood cells (14-17). The purification and subsequent moleculer cloning of these factors has allowed their use in clinical trials (18,19). These factors are expected to be useful in treating patients with acute myeloid leukemia (AML) for severe neutropenia after chemotherapy (20-22). However, clinical application of these factors in AML has been controversial, because they stimulate leukemic colonies in vitro (23-25). Whether growth factors used in such ways will have beneficial or in fact adverse effects on the treatment outcome for AML is not yet known. As such, the use of growth factors in the management of myeloid leukemia is still experimental.

G-CSF is one of the growth factors that has been shown to accelerate neutophil recovery after chemotherapy and reduce mortality from neutropenia-related complications (14,26,27). The presumed target cells of this regulator molecule include a late precursor committed to the neutrophil lineage and the mature neutrophil. Therefore, G-CSF may stimulate leukemia stem cells less in vivo (16,24).

The goals of this study were; 1) to evaluate the effects of G-CSF on duration of neutropenia after chemotherapy 2) to investigate the effects on clinical parameters such as number of days of febril neutropenia, antibiotic necessity, and documented infections; 3) to evaluate the potantial side effects such as leukemic regrowth.

MATERIALS and METHODS

Patients

From August 1992 to March 1995 fifteen patients with acut myeloid leukemia were entered in this study at Hematology Clinic of Uludağ University Medical Faculty Hospital. We evaluated 21 periods of rh G-CSF treatment in these patients who received induction or consolidation therapy. The characteristics of the patients are summarized on Table 1. There were 9 females and 6 males whose ages range from 14 to 65 years (median 36).

Historical control group

The results of this study were compared with 19 patients with AML treated in January 1988 and April 1992 with the same chemotherapy schedule without G-SCF or other cytokines. This group consisted of 6 males and 13 females, ranged in age from 14 to 63 years (median 37). The characteristics of control group are also given on Table 1.

The entry criteria on both groups were the same and patients in the historical control group received similar supportive care therapy (platelet, red cell, antibiotic regimen) as the study population. Data on both groups were collected and evaluated by the same investigators.

Study design

This was a prospective, open-lable, nonrandomized trial to evaluate the effects of G-CSF on hemotopoietic recovery, on the regrowth of leukemic cells in vivo, on the incidence of febril episodes and infectious complications after induction or consolidation chemotherapy. Compled blood counts were performed daily. Biochemical profile

Table 1. The characteristics of study and control patients

	G-CSF group (n=15)	Control group (n=19)
Median age (range)	36 (14-65)	37 (14-63)
Sex		
Female	9	13
Male	6	6
FAB classification		
FAB M1	2	2
FAB M2	2	2
FAB M3	1	2
FAB M4	9	12
FAB M5	1	1
Cycles of G-CSF therapy	21	

including electrolytes, renal and liver function tests, uric acid, serum lipids, cholesterol, and serum creatinine were performed weekly. When the patient's axillary temperature was higher than 38.5°C once or higher than 38°C twice within 6 hours and absolute neutrophil count (ANC) was below 1000 per cubic millimeter, empirical antibiotic therapy was started immediately after collecting-three blood samples for blood culture, getting sample for urine culture, and performing chest X-ray (3,38). When the results of antibiotic sensitivity tests were known, antibiotic therapy was changed accordingly. Antifungal treatment was given if fever had persisted more than 5 days after the starting of antibiotic therapy and without evidence of bacterial infection. Packed red blood cell transfusions were administered to maintain hemoglobin level of more than 8 gr/dL and random platelets were administered when the platelet count had decreased to less than 20.000 per cubic millimeter.

Treatment protocol and G-CSF

All the patients were hospitalized through the study. Induction or consolidation chemotherapy consistend of Daunorubicin (45 mg/m^2 daily, intravenously for 3 days) and Ara-C (100 mg/m^2 by continuous infusion for 7 days). Recombinant human G-CSF (r Met hu G-CSF; Neupogen, Roche, Amgen) at a dose of 5 μg/kg/day, was administered subcutaneously 24 hours after the end of the chemotherapy and continued until the neutrophil count rose above 1000 per cubic millimeter for two consecutive days.

Statistical methods

Results were given as median/mean values and standard errors of the mean. Student t test and Mann-Whitney-U test was used for continuous variables, Wilcoxon's rank-sum test for time dependent variables, and Fisher's exact test for propotions were performed.

RESULTS

Fifteen patients with AML were admitted the study. In these patients, 21 periods of G-CSF treatment were evaluated. The patients were aged from 14 to 65 years (median 36). There were 6 males and 9 females. The historical control group consisted of 19 AML patients who received same chemotherapy regimen without G-CSF. There was no statistical differences between the two groups in age, sex, type of leukemia, or stage. The characteristics of study and control patients are shown on Table 1. G-CSF treatment was begun 24 hours after chemotherapy and continued until the ANC rose above 1000/mm^3 for two consecutive days. G-CSF was given over a median of 12 (range 4 to 20) days. Two patients did not complete the course of G-CSF therapy because of early death. One patient died of infection and one of intracranial bleeding within 30 days follow up. All other patients received the planned doses and time of G-CSF treatment.

In the study patients the number of days to recovery of neutrophils above 500/mm^3 was 8$\pm$0.77$\pm$ SE days, compared with 16$\pm$1.5 days for the historical control group ($p<0.001$). The results were also significantly different for the time to recovery of neutrophils above 1000/mm^3, the mean number of days being 11$\pm$0.81 with G-CSF and 20$\pm$1.56 in control group ($p<0.001$). The mean neutrophil count at day 7th after chemotherapy was 276±68/mm^3 in patients given G-CSF and was 96±21 in controls. Difference was not significant. But after 14th day, the numbers of neutrophils were significantly higher for patients received G-CSF than for control patients (5053$\pm$2091/mm^3 vs 454$\pm$131/mm^3; $p<0.001$).

No effects on red blood cell counts, reticulocytes, and platelets were observed. Platelet counts more than 100.000/mm^3 were reached on days 15.9±1.18 in the patients treated with G-CSF versus days 17±1.81 in the historical controls ($p>0.05$).

Six of 21 cycles in the study group before G-CSF therapy and 3 of 19 cycles in control group before chemotherapy had febrile episodes probably due to primary disease. These patients exluded for evaluation of febrile neutropenic episodes and documented infections. Among the remaining 15 cyles in the study group and remaining 16 in the control group, febrile neutropenia (temperature above 38°C and ANC below 1000/mm^3) developed in 9 and 11, respectively. The mean number of febrile days in G-CSF was 3.14±0.89 days, and in the control group was 4.47±0.98. The difference was not statistically significant ($p>0.05$). There was no difference in the incidence of documented infections: 4 patients in the G-CSF group and 4 in the controls. Similar organisms were cultured in both groups, the majority being gram (+) organisms. Intravenous antibiotic treatment was necessary in 9 of the 15 (60%) patients treated with G-

CSF and in 11 of 16 (68%) of the controls, with a mean duration of 4.25±7.35 and 6.9±7.6 days, respectively. The difference was not statistically significant ($p>0.05$). In two patients, two or more types of infection were observed. Oral candidiasis was noted in three patients in the G-CSF group and two in the control group. Clinical results of G-CSF and control groups are shown on Table 2.

G-CSF was generally well tolerated by patients. Bone pain was the predominant side effect attributed to G-CSF and occured in 5 patients. In one patient, a mild generalized maculopapular rash was observed. No significant increase in the number of leukemic blast cells was observed. Biochemical abnormalities that could be attributed to G-CSF included the elevation in levels of lactate dehidrogenase (in 6 patients), alkalen phosphatase (in 3 patients), and reduction in the levels of total cholesterol. The mean values of total cholesterol was 122±6.8 mg/dL after the G-CSF treatment versus 157±9.5 pretreatment ($p<0.01$).

DISCUSSION

Neutropenia-related infection is the major side effect of cytotoxic chemotherapy (1). Despite the availability of new broad spectrum antibiotics, infection is still the major fatal complication in neutropenic patients (3). Studies by Bodey et al. (2) have clearly shown a direct correlation between severity and duration of neutropenia and the incidence of infection. Hematopoietic growth factors such as G-SCF may have a clinical benefit by alleviating chemotherapy-associated neutropenia, thereby reducing the probability and severity of neutropenia associated complications (1,2,25).

The maximum tolerable doses of G-CSF was not identified. Generally, doses of 1 to 20 μg per kilogram per day are toleraled very well and should be suitable for most indications (14). Because the drug appears to have a very broad therapeutic index, we chose an average dose of 5 μg/kg body weight. The question of optimal schedule for adiministration of G-CSF also remains an answered (14,16,28). All presently reported schedules (prior, coadmitted, or after chemotherapy) are effective in stimulating granulopoiesis (16,17). In our study, G-CSF was started 24 hours after the end of the induction chemotherapy in 16 cycles. G-CSF may also be of benefit by reducing the mortality and morbidity of postremission therapy for AML. More et al. (29) have demonstrated that G-CSF reduced the duration of granulocytopenia after consolidation therapy in AML. Based on this study, G-CSF was administered after consolidation chemotherapy in five cycles.

In this study, patients with AML received G-CSF compaired with those of a historical control group who received the identical chemotherapy regimen without G-CSF, showed a significantly decreased duration of neutropenia ($p<0.001$). The mean neutrophil recovery time was reduced by about 1 week. Similar data reported by Ohno et al (20). In their study treatment with G-CSF, in patients with acute leukemia shortened the duration of neutropenia by aproximately 1 week. In our study G-CSF also shortened the period of severe neutropenia (ANC < 500/mm^3) by about five days. In a study by Kantarjian et al. (8) almost equal to the shortened recovery time produced by the G-CSF in patient with ALL. Similar results on the effect of G-CSF on myeloid recovery have also been reported in allogenic or autologous bone marrow transplantation (8,30,31). This and other clinical studies clearly demonstrated that rh G-CSF administered as an adjunct to chemotherapy in patients with AML or other malignancies resulted in a significant reduction in the incidence, duration, and severity of neutopenia.

Different reports are present about the effects of growth factors on febrile episodes, documented infections, and on days of treated with parenteral antibiotic use. In patients with refractory or relapsed leukemia-treated with G-CSF, Ohno et al. (20) found reduced neutropenia and documented infection, but little difference in the incidence of febrile episodes and the number of days taking antibiotics. However, Pettengel et al. (5) showed that G-CSF significantly reduced the duration of neutropenia and incidence of

Table 2. Clinical results of study and control group

	G-CSF group	Control group	p
Neutropenic period (<1000/mm^3, day)	11	19	< 0.001
Severe neutropenia (< 500/mm^3, gün)	8	16	< 0.001
After chemotherapy 7th day mean ANC/mm^3	276	96	< 0.05
After chemotherapy 14th day mean ANC/mm^3	5053	454	< 0.001
Incidence of febril episodes (%)	60	68	< 0.05
Mean febril neutropenic days	3.14	4.47	< 0.05
Documented infection (%)	27	31	< 0.05

febrile episodes, but there was little difference in the incidence of culture-confirmed infections. In patients with NHL underwent chemotherapy Silverstri et al. (32) showed that the use of G-CSF resulted, a significantly shorter period of neutropenia, a lower incidence of febrile episodes and the documented infections. Similar data have been reported by Crawford et al. (4) in patients with small cell lung cancer. In our study, 9 patients in the G-CSF group and 11 in the control group had febrile episodes, mean of febrile days was 4.25 days in G-CSF and 6.9 days in controls. There were no significant differences in the incidence of febrile episodes and in the number of febrile days. No significant differences were also observed in the incidence of documented infections and days of antibiotic therapy. While the duration of granulocytopenia was reduced, this did not translate in to a lower incidence of febrile episodes or documented infections. This observation has also been reported by Kantarjian et al. (33) in patient with refractory acute lymphoblastic leukemia.

Since the receptor for G-CSF have been reported on AML blast cells (31) and these factors stimulate leukemic colonies in vitro (23-25,34) their clinical application in AML has been controversial. In two recent randomized study, no evidence of accelerated regrowth of leukemia due to administration of G-CSF was observed in patients with AML (20,22). Whereas Theshima et al. (35) observed an increase in the number of blasts in one patient with chronic myeloid leukemia (CML) in myeloid crisis after the administration of G-CSF. Similary, in two different centers, in two patients with promyelocytic leukemia, increases in the number of leukemic blasts after G-CSF therapy were reported (36,37). In our study no evidence of G-CSF-accelerated regrowth of leukemic cells and no relaps after concolidation chemotherapy were observed. Confirmation of these findings will require further randomised trials.

G-CSF was generally well tolerated. No serious side effects attributable to the G-CSF treatment were recorded. As previously reported, the bone pain was the predominant side effect. However, we observed a significant reduction in serum cholesterol level during G-CSF administration. Similar results was reported by Nimer (38) et al using GM-CSF in patients with aplastic anemia, and Miles (39) et al using G-CSF in patients with AIDS.

In conclusion, our data provides good evidence for beneficial effect of G-CSF treatment on duration and severity of neutropenia. But no effect on neutropenia related morbidity was observed. The effect of G-CSF treatment on clinical parameters such as febrile episodes and documented infections, and the optimal dose and time schedules must be addressed by, some large randomized trials.

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