Recombinant Human Granulocyte-Colony Stimulating Factor (rh G-CSF) in Standard Chemotherapy of Hodgkin's Disease

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The aim of this study was to evaluate the effectiveness of recombinant granulocyte colony stimulating factor (rhG-CSF) administered following cytotoxic chemotherapy in Hodgkin's disease. Total number of 26 courses of rhG-CSF were applied in 19 patients with Hodgkin's disease aged 15 to 61 (median 44) years. They received MOPP (Nitrogen Mustard, Vincritine, Procarbazine, Prednisone) chemotherapy every 28 days. rhG-CSF was given at a dose of 5μ/kg daily and subcutaneously from day 2nd to 6th day 8th to 20th unless the neutrophil count exceeded 10.000/mm^3, in which case rhG-CSF discontinued. The outcome was compared with 24 prognostically similar control patients treated with the same chemotherapy without rhG-CSF. Recovery of granulocyte counts above 1000/ mm^3 was significantly faster in the rhG-CSF treated group (3±0.72 days vs 7±0.81 days; p<0.001). The incidence of febrile neutropenia and empiric parenteral antibiotic use were lower in study patients (%36 vs %64 ; p<0.05). But there was no reduction in the incidence of documented infections. Full doses of chemotherapy could be given on time to 26/26 (%100) rhG-CSF patients but to only 18/24 (%75) controls (p<0.01). All patients tolerated cytokine treatment well. Our results showed that rhG-CSF has an important role in decreasing period of neutropenia maintaining chemotherapy schedule and allowing patients to receive full doses of chemotherapy on time. [Journal of Turgut Özal Medical Center 1998;5(1):24-29]

Key Words: *G-CSF, Hodgkin's disease, neutropenia, infection*

Hodgkin hastalığının standart tedavisinde rekombinant human granülosit koloni stimüle edici faktör kullanımı

Bu çalışmanın amacı Hodgkin hastalığında sitotoksik kemoterapiyi takiben rekombinant human granülosit koloni stimüle edici faktör (rhG-CSF) uygulamasının etkinliğini değerlendirmekti. Yaşları 15 ile 61 (median 44) arasında değişen 19 Hodgkin hastasında toplam 26 rhG-CSF kürü uygulandı. Hastalar 28 günde bir MOPP (Nitrojen Mustart, Vinkristin, Prokarbazine, Prednizolon) aldılar. rhG-CSF subkutan olarak günde 5μ/kg dozunda 2. günden 6. güne ve 8. günden 20. güne kadar nötrofil sayısı 10.000/mm^3'ü geçmediği sürece uygulandı, bu değerin üstüne çıkanlarda rhG-CSF kesildi. Sonuç prognostik açıdan benzer özelliklere sahip daha önceden aynı kemoterapi ile fakat rhG-GSF'siz olarak tedavi edilmiş 24 kontrol hastası ile karşılaştırıldı. Granülosit sayısının 1000/mm^3'ün üstüne çıkma zamanı kontrollere göre anlamlı olarak kısaydı (3±0.72 güne karşı 7±0.81 gün, p<0.001). Febril nötropeni insidansı ve ampirik antibiotik kullanımı çalışma grubunda daha düşüktü (%36 ya karşı %64; p<0.05). Fakat dökümante edilen enfeksiyon sıklığında değişiklik yoktu. Tam doz kemoterapi rhG-CSF alanlarda 26/26 (%100) uygulanırken kontrol grubunda bu oran yalnızca 18/24 (%75) idi. (p<0.01). Tüm hastalar sitokin tedavisini iyi tolere ettiler. Sonuçlarımız rhG-CSF nin kemoterapi sürerken nötropeni süresini kısaltarak hastaların zamanında ve tam doz kemoterapi almalarında önemli rolu olduğunu göstermektedir. [Turgut Özal Tıp Merkezi Dergisi 1998;5(1):24-29]

Anahtar Kelimeler: *G-CSF, Hodgkin hastalığı, nötropeni, enfeksiyon*

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Advanced-stage Hodgkin's disease (HD) can be cured with combination of chemotherapy (1). To increase the complete remission and cure rates, recently more effective chemotherapy schedules and combinations were advanced (2). Modern multi-drug chemotherapy regimens for Hodgkin's disease has significantly increased complete remission rates, but myelosupression from chemotherapy results in a substantial morbidity related to infections. Several studies have shown that the incidence and severity of infection are directly influenced by both the severity and duration of neutropenia (3,4). In addition to increasing the risk of life threatening infections, neutropenia is the commonest reason for modifying the optimal doses and limiting the potential benefit of these regimens (5). Strategies to prevent infections in these patients have been developed in recent years by stimulating the recovery of granulocytopenia with various agents including hematopoietic growth factors.

Hematopoietic growth factors (HGF) are glikoproteins that stimulate the proliferation of bone marrow progenitor cells and their maturation into fully differentiated circulated blood cell (6-9). They have been molecularly cloned and produced in sufficient quantaties to allow their use in clinical trials (10,11). The addition of HGF to cytotoxic chemotherapy in patients with solid and hematologic malignancy has been reported to reduce the intensity and duration of granulocytopenia and related morbidity (6,12,13).

Granulocyte Colony-Stimulating Factor (G-CSF) is a hematopoietic growth factor which stimulates the proliferation and differentiation of neutrophil procursors, leading to the release of mature, and functioning neutrophils into the circulation (14-17). G-CSF also enhances the functional properties of mature neutrophils including fagositic activity, antimicrobial killing, and antibody dependent cell-mediated cytotoxicity (14,15). G-CSF has been succesfully used to ameliorate chemotherapy-related neutropenia in various settings. In recent randomized clinical trials, the administration of G-CSF subsequent to myelosupressive chemotherapy for solid tumors (18,19). Leukemia (20), and lymphoma (21,22) or after bone marrow transplantation (23) resulted in a marked acceleration of myeloid recovery.

Before this study, several trials had suggested that G-CSF and GM-CSF were capable of decreasing the degree and duration of chemotherapy induced neutropenia and related complications in HD (23-25). In majority of these studies, G-CSF had administered after completion of chemotherapy. In our study, G-CSF and chemotherapy were given concurrently. Therefore, the aim of this study was to evaluate the safety of concurrent G-CSF and chemotherapy and to evaluate the effect of G-CSF treatment on duration of neutopenia, incidence of febril episode, documented infections, and maintaining chemotherapy schedules.

MATERIALS AND METHODS

Patients

From September 1992 to February 1995 18 patients with HD were entered the study at Hematology Clinic of Uludağ University Medical Faculty Hospital. We used 21 periods of rh G-CSF treatment in these patients. There were 7 females and 11 males whose ages ranged from 15 to 61 years (median 42). All patients had severe or prolonged neutropenic periods after previous chemotherapy. Exlusion criteria includes congestive heart failure and renal or hepatic disfunction unless the abnormal parameters were directly attributable to lymphomatous infiltration.

Control group

The control group consisted of 23 patients with HD who were treated with the same chemotherapy regimen but without G-CSF. The median age of these patients was 40 years (range 15-62). Patients in the control group had received similar supportive care therapy and identical cytotoxic dose reduction criteria were applied to both the control and G-CSF treatment groups. Data on both groups were collected and evaluated by the same investigators. Characteristics of G-CSF and control patients are shown in Table 1.

Treatment protocol and G-CSF

All patients received MOPP chemotherapy. The MOPP regimen was given as follows: Nitrogen Mustard 6 mg/m^2 body surface area, intravenously (IV) days 1st and 8th; vincristine 1.4 mg/m^2, iv days 1st and 8th; procarbazine 100 mg/m^2, orally days 1st to 14th; and prednisolone 40 mg/m^2, orally days 1st to 14th in cycles 1st and 4th. Each cycle was repeated in 28-day intervals. Recombinant human G-CSF (r-methu G-CSF, Neupogen, Amgen, Roche) was given at a dose of 5 μg/kg daily subcutaneously from day 2nd to 6th and day 8th to 20th unless the neutrophil count

Table 1. Characteristics of G-CSF and control patients

	G-CSF group (n=18)	Control group (n=23)
Mean age (range)	42 (15-61)	40 (15-62)
Sex		
Female	7	12
Male	11	11
Stage of disease		
Stage II-E	3	2
Stage III	6	8
Stage IV	9	14
Histological classification		
Lymphocyte depleted	2	4
Lymphocyte predominant	2	3
Noduler sclerosis	6	6
Mixed cellularity	7	11
Cycles of G-CSF treatment	26	--

exceeded 10.000/mm^3, in which case G-CSF was to discontinued.

Study designe and statistical analysis

This is an open-lable, nonrandomized trial, designed to asses the effectivenes of G-CSF in decreasing the number of neutropenia and maintaining chemotherapy schedules and full dose in time. Complete blood counts were performed daily. Biochemical profile including electrolytes, renal and liver function tests, uric acid, serum lipids and cholesterol, and serum creatinin were obtained weekly. When the patient's axillary temperature was higher than 38.5°C once or higher 38°C twice within 6 hours and absolute neutrophil count (ANC) was below 1000 per cubic millimeter, empirical antibiotic therapy was started immediately after collection of three blood samples for blood culture and urine culture. When the results of antibiotic sensitivity test were known, antibiotic therapy was changed accordingly. Antifungal treatment was given if fever had persisted more than 5 days after starting of antibiotic therapy and without evidence of bacterial infection.

Results were given as median and standard error of the mean. Student t-test and Mann-Whitney U test were used for continuous variables, Wilcoxon's rank-sum test for time dependent variables and Fisher's exact test for proportions (26).

RESULTS

We evaluated 24 periods of G-CSF treatment in 18 patients with HD. The characteristics of the patients and 21 patients in the control group are summarized on Table 1. There were no statistical differences between the two groups in age, sex, and stage of disease. All patients in study group received on the planned time of G-CSF treatment, except one who didn't complete the course of therapy because of severe bone pain.

The time to granulocyte recovery above 1000/mm^3 was significantly shorter for patients who received G-CSF than those who did not (mean number of days to recovery, 3.2±0.72 versus 7.1±0.81, respectively; p <0.001). Severe neutropenia (ANC <500 /mm^3) was also significantly reduced in the G-CSF group. The mean day on which the neutrophil count exceeded 500 per cubic millimeter was 0.9±0.39 day in the G-CSF group and 2.8±0.62 days in the control group (p<0.005). The time to platelet recovery above 50.000/mm^3 was not significantly different with or without G-CSF (mean number of days 14 versus 16, respectively; p>0.05). No significant increase in the number of other series was seen.

The number of days of febrile neutropenia was lower in study patients. The mean duration of febrile epizodes for all cycles was 1.03 ± 0.52 day in the G-CSF group and 2.87 ± 0.66 days in the control group (p<0.05). The incidence of febrile episode was also lower in G-CSF group. Thirty six percent of control patients had febril neutropenia, as compared with 19 percent of patients given G-CSF.

Documented or suspected infections occured with similar frequency in both groups, despite the shorter duration of granulocytopenia among patients treated with G-CSF. Bacteremia confirmed by culture occured in one control patient, but did not in any patient treated with G-CSF. The number of days on iv antibiotic therapy was found to be higher in the control group than in the G-CSF group (p>0.05). Clinical results of G-

Table 2. Clinical results of G-CSF and control group

	G-CSF group (n=18)	Control group (n=23)	p
Neutropenic period (<1000 / mm^3, day)	3.2	7.2	< 0.001
Severe neutropenia (< 500 / mm^3, day)	0.9	2.8	< 0.005
After chemotherapy 7th day mean ANC/mm^3	3615	2295	> 0.05
After chemotherapy 14th day mean ANC/mm^3	3053	1454	< 0.05
İncidence of febrile episodes (%)	19	54	< 0.05
Mean febrile neutropenic days	1.03	2.87	< 0.05
Documented infection (%)	15	16	> 0.05

CSF and Control Group are shown Table 2.

All patients in this study received all the planned doses without dose attenuation, and they received next chemotherapy on time. In the controls, dose reductions and treatment delay up to 25% were required. The difference was statistically significant ($p<0.001$).

G-CSF was in general well tolerated by patients. Bone pain was the predominant side effect attributed to G-CSF and occur in 3 patients. In one patient, the pain was severe, G-CSF was stopped on day 5^{th}. Mild elevation of serum lactate dehydrogenase in 4 patients and serum alkaline phosphatase in 1 patient were observed. No other side effects were reported as directly related the administration of G-CSF.

DISCUSSION

It has been apparent from earlier studies that G-CSF significantly reduced the incidence, severity, and duration of neutropenia after chemotherapy (18,20-22,27-29) and bone marrow transplantation (25). Furthermore; the clinical complication of neutropenia following chemotherapy such as febrile episodes and infection can be significantly ameliorated by G-CSF. In this study, concomittant administration of G-CSF and chemotherapy with MOPP protocol was evaluated. Compared with those of a control group who received the same chemotherapy regimen without G-CSF, patients receiving G-CSF had a shorter duration of neutropenia, a low incidence and duration of febrile episode and parenteral antibiotic use without a reduction in the incidence of documented infections.

The optimum timing for G-CSF administration after chemotherapy has not been defined (7,14,17). Initially, there was considerable concern that concomittant administration of this agent with chemotherapy might result in the depletion of progenitor cells stimulated by CSF that enter the cell cycle but subsequently are destroyed after interaction with the chemotherapeutic drugs (7,17). However several recent studies suggested that parallel administration of G-CSF and chemotherapy in patients with AML and ALL is not harmfull and does not increase the incidence and duration of neutropenia (27-29). On the contrary, it has been shown that the duration of chemotherapy related neutropenia is markedly shortened (27,28). Based on these studies, we administered G-CSF and chemotherapy concurrently.

Compared with control group, G-CSF treated patients had a significantly faster neutrophil recovery. The median neutrophil recovery time was reduced by about 4 days after MOPP megimen. Clinical results of previous studies included patients with HD (23,35), NHL (21,22) and acute leukemia (20,28) which administered G-CSF and GM-CSF after chemotherapy were similar to ours. Therefore, our results demonstrate that simultaneous administration of G-CSF and chemotherapy are feasible without prolonged chemotherapy induced neutropenia.

Most randomized and nonrandomized trials documented that either G-CSF or GM-CSF decrease the degree and duration of granulocytopenia when given with chemotherapy. Whether this will translate into a decrease in morbidity related neutropenia including febrile episode, documented infection, IV antibiotic use, and hospitalization has not yet been established. In patients with small-cell lung cancer treated with G-CSF, Crawford et al. (18) showed a shorter duration of granulocytopenia, a lower incidence of fever with neutropenia and culture-confirmed infections. In patients with NHL, similar data reported by Silvestri et al. (22). In another study by Ohno et al. (20) suggested that G-CSF significantly reduced the duration of neutropenia and the incidence of documented infection, but little difference in the incidence of febrile episodes and the number of days taking of antibiotics. In our study, the group of patients receiving G-CSF had a shorter duration of neutropenia, a lower incidence of febrile episodes, and parenteral antibiotic use, however, no difference was seen in the incidence of documented infections. Similar data have been reported by Pettengel et al. (21) in patients with NHL. While the duration of granulocytopenia was reduced by G-CSF therapy, this did not translate into a lower incidence of documented infections. These results may be due to a better follow-up for study patients or a carefull laboratory culture techniques study in our hospital.

In most studies an important outcome was reported that the use of G-CSF enabled more patients to complete therapy and allow delivery of the planned dose on time (21,22,27,36,37). In this study, full doses of chemotherapy within the scheduled time could be given to 26/26 (%100) of G-CSF patients, but to only 18/24 (%75) of controls ($p<0.01$). However, Riccardi, et al. (24) reported that the use of GM-CSF after

MOPP/ ABY/CAD chemotherapy in patients with HD was not effective in improving the drug scheduling.

In conclusion, the use of G-CSF concomittant with MOPP chemotherapy in patients with HD was well tolerated and appeared to have a significant role in decreasing the incidence, duration, and severity of neutropenia, febrile episode and the total number of days on iv antibiotics, and in maintaining chemotherapy schedules. G-CSF therapy was not capable of reducing the incidence of documented infections but reduced their severity. Althought our data provides good evidence for benefical effects of G-CSF, the impact of this treatment on neutropenia-related morbidity and dose intensity must be addressed by other randomized trials.

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