

Original Article

Low Dose rhG-CSF for Prophylaxis of Chemotherapy Induced Neutropenia in Non-Hodgkin's Lymphoma

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Abstract: Background: In the treatment of non-Hodgkin's lymphoma, the use of standard dose granulocyte-colony stimulating factors (rhG-CSF) at 5 $\mu\text{g}/\text{kg}/\text{day}$ for chemotherapy induced neutropenia has shown strong evidence of clinical benefits. However, the efficacy of low-dose rhG-CSF in non-Hodgkin's lymphoma patients undergoing standard CHOP chemotherapy has not been evaluated.

Method: This was a randomized, prospective trial of low dose granulocyte-colony stimulating factor (lenograstim at 50 μg , 100 μg) in intermediate-grade non-Hodgkin's lymphoma patients with severe chemotherapy-induced neutropenia. Patients were evaluated for efficacy of low-dose therapy on the prevention and recovery from neutropenia. **Results:** Patients were randomized to receive 50 μg of rhG-CSF (12 patients) and 100 μg of rhG-CSF (16 patients). The two groups had similar backgrounds. The nadir neutrophil counts were significantly higher ($p < 0.05$) compared to observation period without rhG-CSF for both groups. The duration of neutropenic days was also significantly reduced by 43% for the 50 μg and 100 μg groups. **Conclusion:** Low dose rhG-CSF is very effective in improving chemotherapy-induced neutropenia in intermediate-grade non-Hodgkin's lymphoma patients. This trial has shown that low dose therapy may deliver cost-effective therapy without compromising standard care.

Key Words : ● Lenograstim ● rhG-CSF ● Low-dose ● Non-Hodgkin's lymphoma

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In anticancer chemotherapy, myelosuppression, especially neutropenia, is by far the most common dose limiting toxicity, and infection during neutropenic state remains one of the most common causes of treatment related mortality in cancer patients, leading to the delay in chemotherapy and thus the decrease in therapeutic efficacy.

Granulocyte colony stimulating factor (rhG-CSF) is a hematopoietic growth factor which acts upon the granulocyte-macrophage progenitor cells to simulate proliferation, differentiation of neutrophils and to enhance neutrophil function.^{1,2} With the use of rhG-CSF, it is possible to ameliorate and prevent chemotherapy induced neutropenia allowing delivery of optimal dose intensities of cytotoxic agents.^{3,4} The usual dose of rhG-CSF used in the western countries has been 5 $\mu\text{g}/\text{kg}/\text{day}$ (filgrastim). Lenograstim is a recombinant-glycosylated G-CSF produced in culture by Chinese hamster ovary cells structurally identical to the endogenous human molecules. Several comparative studies, both in vitro and in vivo, in animals and in human, have been shown that lenograstim is more active than filgrastim on a weight-by-weight basis^{5,7}. In Japan, Kohno⁸ found that low dose of rhG-CSF (2 $\mu\text{g}/\text{kg}$ or 50 $\mu\text{g}/\text{m}^2$ of lenograstim) enables the efficient collection of peripheral blood stem cells after disease-oriented conventional dose chemotherapy in breast cancer patients. In another study by Toner⁹, a randomized, crossover comparison of low versus standard dose lenograstim prophylaxis after chemotherapy demonstrated no sig-

nificant difference in measures of neutropenia, hospitalization and other clinical outcomes.

The primary purpose of the present study was to examine the effectiveness of applying low doses of rhG-CSF in reducing the severity and duration of neutropenia in adult patients with NHL who received CHOP chemotherapy.

Patients and Methods

Twenty eight patients with intermediate grade NHL who were scheduled to receive at least two cycles of CHOP chemotherapy and who developed leukopenia with WBC 2,000/ mm^3 or less or neutropenia (ANC < 1,000/ mm^3) after CHOP chemotherapy were enrolled in the study. The eligibility criteria included a performance status of less than 3, age between 15 and 80 years, not receiving radiotherapy within 4 weeks of the start of study, no evidence of myelosuppression due to marked bone marrow infiltration with malignant lymphoma prior to the initiation of the study, normal hepatic and renal functions. Exclusion criteria included 1) patients with impairment of hepatic, renal, or cardiovascular function whose clinical condition makes participation in the study inappropriate as judged by the investigators; 2) patients with thrombocytopenia difficult to control; 3) patients with overt infections; 4) patients showing abnormal results in blood coagulation tests who therefore may have hemorrhagic diathesis; 5) pregnant patients or nursing women and patients with childbearing potential; 6) patients who are idiosyncratic to drugs analogous to rhG-CSF; 7) patients show-

ing an anaphylactic reaction on skin testing with rhG-CSF; 8) patients with granulocytopenia apparently due to immunologic abnormality. Informed consent was obtained from every patient in the study.

Study Design

Patients receiving standard CHOP chemotherapy which consisted of cyclophosphamide 750 mg/m² intravenously day 1, doxorubicin 50 mg/m² intravenously day 1, vincristine 1.4 mg/m² intravenously day 1 (maximum 2 mg) and prednisolone 60 mg/day orally day 1-5. The first cycle was used as the observation period. Only patients with a neutrophil count of less than 1,000/mm³ were entered in the second period. In the subsequent cycles of chemotherapy at the same dosages, the patients were randomized to receive rhG-CSF (lenograstim) either 50 or 100

μg/day subcutaneously for 14 days beginning on day 3 of chemotherapy. Complete blood counts were done every other day for 14 days. The evaluation of each patient with regard to the effect of rhG-CSF on the prevention of and recovery from neutropenia was performed by comparing with findings during the observation period (first cycle); that is the reduction in the duration of neutropenia (less than 1,000/mm³), reduction in the recovery time to neutrophil counts of more than 1,500/mm³, and the nadir neutrophil count.

Results

The characteristics of the patients in the two groups are shown in table 1. Twelve patients received 50 μg of lenograstim while sixteen patients received 100 μg. The median age and the male to female ration were similar in both groups. Table 2 shows the nadir neutrophil

Table 1 Patients' characteristics

Patient profile	50 μg	100 μg
number of patients	12	16
median age	54 (19-76)	51(25-75)
male/female ratio	7/5	9/7
avg. female weight	55.3 kg	54.6 kg
avg. male weight	54.6 kg	46.5 kg
avg. weight m/f	55 kg	50.5 kg

Table 2 Nadir neutrophil counts

Dose	Nadir neutrophil count		
	Control	With rhG-CSF	p value
50 μg	709±507	1,458±876	0.05
100 μg	517±432	1,777±1,243	0.015

Table 3 Duration of neutropenia

Dose	Number of days with ANC<1000		
	Control	With rhG-CSF	p value
50 μ g	7	3	0.008
100 μ g	7	3	0.0004

counts during control period and with rhG-CSF in both groups. During the study period with rhG-CSF, the nadir neutrophil counts were statistically higher than during observation period without rhG-CSF in both dosage groups. The duration of neutropenia (ANC less than 1,000/mm³) during treatment period was also less than during the observation period in both 50 μ g and 100 μ g groups (table 3).

Discussion

Granulocyte colony stimulating factors have been vital in the field of oncology since its development and has dramatically changed the practice of giving chemotherapy. It has played a significant role in mitigating neutropenia, reducing infections, reducing days of hospitalization, and improving overall morbidity for chemotherapy patients with secondary myelosuppression.¹⁰⁻¹³ However, most of the published studies used rhG-CSF: in recommended dose of 5 μ g/kg/d and higher. Recently, there has been interest in the effect of low dose rhG-CSF. This, of course, would be not without merit particularly in cost savings for the patient. Although there are currently a few published papers in this area, there has not been a study to evaluate the clinical effects of low dose rhG-CSF in

myelosuppressed patients with non-Hodgkin's lymphoma.

In the literature, there has already been data revealing the significant impact of using colony stimulating factor in treatment of non-Hodgkin's lymphoma as part of the chemotherapy protocol. Bergman et al¹⁴ have shown in their pilot study the significant reduction of neutropenia and duration of neutropenia in the group that received colony stimulating factor for 35 patients with high grade NHL after chemotherapy. The dose of colony stimulating factor given in this study was 5 μ g/kg/d.

There has also been published data that showed low dose rhG-CSF can have dramatic effects on the bone marrow milieu. Recently published literature by Pedrazzoli et al¹⁵ has shown interesting data that lenograstim demonstrated greater capacity to stimulate the growth of CD34+ peripheral blood cells compared to filgrastim. This concurs with the accumulating evidence that glycosylated rhG-CSF (lenograstim) is better than the non-glycosylated rhG-CSF (filgrastim) in the overall stimulation of the bone marrow.¹⁶⁻¹⁷ The data also showed interesting results that stimulation by lenograstim was evident especially at low doses. This data, although obtained in in-vitro analysis, may be pertinent

in the kinetics of lenograstim revealing significant stimulation of granulocytes at low doses.

Another very interesting study conducted by Shimazaki et al¹⁸ from Japan previously demonstrated that low dose rhG-CSF (50 $\mu\text{g}/\text{m}^2$) delivered subcutaneously, accelerated neutrophil recovery in autologous blood stem cell transplant patients. Pharmacokinetic data showed that the half-life of elimination of rhG-CSF ($t_{1/2}$) exceeded 15 hours during severe neutropenia but decreased during the recovery of neutrophils. These observations suggested that neutrophils provided a negative feedback mechanism for clearing rhG-CSF from the circulation. More importantly, pre-dose levels of rhG-CSF in patients receiving 50 $\mu\text{g}/\text{m}^2$ rhG-CSF reached 10 ng/mL, equivalent to the concentrations used in clonogenic assay in vitro to stimulate myeloid progenitor cells.

These studies as well as the study by Kohno and Toner confirmed that low dose lenograstim have a significant effect on the bone marrow as a growth factor despite the dose being lower than that used in clinical practice at this time. It has clearly shown that stimulation, maturation, and activation of granulocytes are significantly affected by low dose growth factors. There has not been a study prior to ours to evaluate low dose rhG-CSF and its clinical outcomes in non-Hodgkin's lymphoma patients.

In this study, we critically evaluated non-Hodgkin's lymphoma patients undergoing standard CHOP chemotherapy regimen and the effects of low dose rhG-CSF (lenograstim 50 μg ,

100 μg). The nadir neutrophil count for the control vs. rhG-CSF group revealed a statistically significant difference for the 50 μg ($p = 0.05$) and 100 μg ($p = 0.015$) compared to the group that did not receive any rhG-CSF. The mean nadir neutrophil count for control was $581/\text{mm}^3$, compared to the mean for of $1,458/\text{mm}^3$ in the 50 μg group and $1,666/\text{mm}^3$ in the 100 μg group.

The number of days of neutropenia defined as absolute neutrophil count (ANC) less than $1,000/\text{mm}^3$ was also shown to be statistically significant. The number of days was reduced 43% from a mean of 7 days for control to only 3 days for the μg that received rhG-CSF at both doses. (50 μg , $p = 0.008$; 100 μg , $p = 0.0004$).

This is the first study of its kind to evaluate low dose rhG-CSF in a clinical study of patients with intermediate grade non-Hodgkin's lymphoma. It has shown that low doses of lenograstim has a significant effect in reducing the days of neutropenia and increasing the nadir neutrophil count in patients with secondary myelosuppression. However, there was no difference in the 50 μg vs. 100 μg dose group in the mean days of neutropenia and only a very small insignificant difference was seen in the mean nadir neutrophil count.

The benefits of low dose rhG-CSF is clear. The patient will save money. In these days of cost containment with rapidly increasing costs for hospitalization, decreasing the total usage of rhG-CSF will save the patient a significant amount of money. There have been numerous

literature on cost analysis of using colony stimulating factors and of its overall cost benefit.¹⁹ In one study by Lawless²⁰ where the impact of rhG-CSF on recovery from autologous bone marrow transplantation (ABMT) was evaluated, the health insurance company determined that, as a result of rhG-CSF therapy along with peripheral blood stem cell transplantation (PBSCT), bone marrow transplantation costs to the company dropped by more than 50% since 1990.

There is a limitation of this study that deserves discussion. The fact that Thai people may be of smaller size than an average westerner needs to be considered in light of the significant effects we have observed in this study. The average weight for females in this study was 55 kg and for male 51 kg, far lower than the medically touted average of 70 kg in the western world. This confounding factor may have biased our study and perhaps further studies are needed.

The objective of this study was to evaluate the clinical efficacy of rhG-CSF (lenograstim) in reducing the severity and duration of neutropenia associated with chemotherapy in patients with intermediate grade non-Hodgkin's lymphoma. Our data has shown that low dose regimen of rhG-CSF in doses of 50 μg and 100 μg is effective in improving these outcomes with no greater benefit in using 100 μg of lenograstim. We recommend continued clinical trials in using low dose lenograstim to evaluate outcomes so that it may benefit patients by saving cost without compromising standard patient care.

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บทคัดย่อ: ในการรักษาผู้ป่วยมะเร็งต่อมน้ำเหลืองด้วยยาเคมีบำบัด เมื่อเกิดภาวะเม็ดเลือดขาวต่ำ การใช้ยากระตุ้นเม็ดเลือดขาวในขนาด 5 $\mu\text{g}/\text{kg}/\text{วัน}$ ทำให้ได้ผลเป็นที่น่าพอใจ แต่ยังไม่มีการศึกษาการใช้ยากระตุ้นเม็ดเลือดขาวในขนาดต่ำในผู้ป่วยเหล่านี้ การศึกษาเป็นการศึกษาไปข้างหน้า โดยศึกษาผู้ป่วยที่เป็นมะเร็งต่อมน้ำเหลืองชนิดที่ไม่ใช่ฮอดคินที่เกิดภาวะเม็ดเลือดขาวต่ำมากจากการได้เคมีบำบัด โดยแบ่งเป็นสองกลุ่ม กลุ่มแรกได้ยา lenograstim 50 $\mu\text{g}/\text{วัน}$ (12 คน) และกลุ่มที่ 2 ได้ lenograstim 100 $\mu\text{g}/\text{วัน}$ (16 คน) พบว่าค่าต่ำสุดของ neutrophil ในผู้ป่วยทั้ง 2 กลุ่ม สูงกว่าในระยะเวลาที่ไม่ได้รับยา lenograstim ($p < 0.05$) และระยะเวลาที่มีเม็ดเลือดขาวต่ำกว่าลดลงร้อยละ 43 ทั้ง 2 กลุ่ม โดยสรุป lenograstim ในขนาดต่ำได้ผลดี ป้องกันภาวะเม็ดเลือดขาวต่ำในผู้ป่วยที่เป็นมะเร็งต่อมน้ำเหลืองชนิดที่ไม่ใช่ฮอดคินที่ได้รับยาเคมีบำบัดได้

Key Words : ● Lenograstim ● rhG-CSF ● Low-dose ● Non-Hodgkin's lymphoma

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