Efficacy and Safety of In-Asia-Manufactured rhG-CSF 300 mcg As Primary Prophylaxis for Prevention of CHOP Chemotherapy-induced Severe Neutropenia in Elderly Patients with Lymphoma Non-Hodgkin

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ABSTRACT

We conducted open label, non-comparative trial in patients aged > 60 with advanced and intermediate-grade Non-Hodgkin Lymphoma (NHL) (stadium II, III, IV) to evaluate the efficacy and safety of In-Asia-manufactured rhG-CSF 300 mcg for prevention of CHOP (cyclophosphamide, doxorubicin, vincristine) chemotherapy-induced severe neutropenia. Primary prophylaxis with this in-Asia-manufactured rhG-CSF 300 mcg could reduce median duration of grade 4 neutropenia in cycle 1 and cycle 2 to three days and of grade 3 neutropenia in cycle 1 to two days and in cycle 2 to two half days from four and five days median duration of grade 4 and 3 neutropenia without rhG-CSF respectively. Febrile neutropenia was occurred in seven patients who received in-Asia-manufactured rhG-CSF 300 mcg (24.1%), lower than if rhG-CSF was not given (31.3-34% FN). Three patients (10.3 %) who received in-Asia-manufactured rhG-CSF 300 mcg were hospitalized due to febrile neutropenia, lower than if rhG-CSF was not given (24-28% hospitalized due to febrile neutropenia). Mostly reported adverse events were nausea and vomiting which were occurred in nine patients (31.0%). In conclusion, the use of in-Asia-manufactured rhG-CSF 300 mcg for primary prophylaxis in elderly patients with non-Hodgkin lymphoma receiving CHOP chemotherapy could reduce the duration of neutropenia, reduce the rate of febrile neutropenia (FN) and febrile neutropenia hospitalization (FNH).

ABSTRAK

Penelitian *open-label,* non-komparatif ini dilakukan untuk mengevaluasi efektivitas dan keamanan *recombinant human G-CSF* produksi Asia sebagai profilaksis primer dalam pencegahan neutropenia derajat berat pada pasien usia lanjut (>60 tahun) dengan limfoma non-Hodgkin (LNH) derajat sedang dan lanjut (stadium II,III,IV) yang mendapat terapi CHOP (siklofosfamid, doksorubisin, vinkristin). Profilaksis primer *recombinant human G-CSF (rhG-CSF)* produksi Asia dapat mengurangi median durasi neutropenia derajat 4 pada siklus sitostatistika ke-1 dan ke-2 menjadi tiga hari, sementara median durasi neutropenia derajat 3 pada siklus sitostistika ke-1 menjadi dua hari dan pada siklus sitostatistika ke-2 menjadi dua setengah hari, dari median durasi neutropenia grade 4 dan grade 3 tanpa G-CSF, yaitu empat dan lima hari berurutan. *Febrile neutropenia* ditemukan pada 7 pasien yang mendapat *rhG-CSF* produksi Asia (24.1%), lebih rendah jika dibandingkan studi tanpa *rhG-CFS* (31.3-34% FN). Tiga pasien mendapat *rhG-CSF* produksi Asia (10,3%) dirawat inap akibat *febrile neutropenia,* lebih rendah jika dibandingkan rawat inap pada studi tanpa *rhG-CSF* (24-28%). Kejadian yang tidak diinginkan terbanyak adalah mual dan muntah yang terjadi pada 9 (31%) pasien. Sebagai kesimpulan, penggunaan rhG-CSF produksi Asia untuk profilaksis primer pada pasien LNH usia lanjut yang mendapat regimen CHOP dapat mengurangi durasi neutropenia, mengurangi kejadian febrile neutropenia, dan angka rawat inap akibat *febrile neutropenia.*

Kata kunci : Efektivitas, keamanan, G-CSF, LNH pada usia lanjut

INTRODUCTION

Non-Hodgkin Lymphoma (NHL) remains a deadly malignancy, primarily affecting the elderly (61% were age >60 years).[1] CHOP therapy, the standard curative treatment for NHL patients, consists of cyclophosphamide 750 mg/m^{2}, doxorubicin 50 mg/m^{2}, and vincristine 1.4 mg/m^{2} (maximum dose, 2.0 mg), was given intravenously on day 1, together with prednisone 60-100 mg/m^{2} (per oral) PO on day 1-5, administered every 21 days for 6-8 cycles.[2-5] However, standard-dose of CHOP used to treat lymphoma can cause many side effects. The most serious side effect is neutropenia. The incidence of neutropenia is higher in the elderly as reported by Morrison et al., i.e. 34% in older patients compared with 21% in below 65 years (P<.05).[6]

Studies show that the best long-term outcome was reached if patients receive the full dose of chemotherapy on time at every cycle. Most delay and reduction in the planned doses of chemotherapy were due to its side effect. Several retrospective studies on NHL chemotherapy showed that dose reductions of 20% to 30% have been associated with lower complete response rates and/or reduced survival.[7-11] Chemotherapy-induced neutropenia could reduce the dose intensity of CHOP therapy or delay chemotherapy schedule. Severe neutropenia can be also life threatening due to increasing risk for infection and sepsis. Studies have described a large percentage of neutropenia-related deaths within the first two cycles of therapy.[12,13]

The American Society of Clinical Oncology (ASCO) recommends the prophylactic use of G-CSF for patients receiving standard doses of chemotherapy as primary and secondary prophylaxis of febrile neutropenia to ensure that they can receive chemotherapy treatment at the planned dose and schedule. Primary prophylaxis of human recombinant G-CSF refers to the use of the growth factor before any occurrence of neutropenia. Secondary prophylaxis refers to its use in subsequent chemotherapy cycles after the occurrence of neutropenia in at least one of the preceding cycles.[14,15] Primary prophylaxis is recommended for the prevention of febrile neutropenia in patients with high risk of febrile neutropenia based on age, medical history, disease characteristics and myelotoxicity of chemotherapy regimen or special circumstances, such as patients who receive relative non-myelosuppressive chemotherapy but have potential risk factors for febrile neutropenia or infection due to bone marrow compromise or co-morbidity.

Even though recombinant human G-CSF preparation is already available in Indonesia, but its use is limited due to the high-price and low affordability of the most population. However, rapid progress of biotechnology in Asian country makes such biotechnology products are now also produced in a more affordable price. The aim of this study was to evaluate the efficacy and safety of rhG-CSF 300 mcg manufactured in Asia for prevention of severe neutropenia resulted from CHOP chemotherapy in elderly patients with non-Hodgkin lymphoma. We also monitored adverse events occurred during this in-Asia-manufactured rhG-CSF 300 mcg therapy.

MATERI AND METHOD

Patients Characteristics

We conducted an open label, non-comparative trial from July 2003 to September 2004. Patients who were eligible for the trial were patients, aged more than 60, with advanced-stage and intermediate-grade NHL (stadium II, III, IV) determined by histology and cytology examination, which have baseline leukocyte count >3,000/µl or neutrophil count >1,500/µl, thrombocytes >100,000/µl, performance status ECOG <2, life survival ≥6 months, and received standard CHOP regiment. Patients, who were contraindicated for rhG-CSF, had received autologous/allogeneic stem cells, were pregnant and lactating, were excluded from the study.

Methods

In-Asia-manufactured rhG-CSF 300 mcg was given on the second day post-chemotherapy cycle 1 and 2 with the dose of 5 µg/kg BW once daily for 14 days. Concomitant therapy was paracetamol 500 mg three times daily and methylprednisolone 4 mg twice daily (08.00 AM and 08.00 PM).

Laboratory examination was done everyday during In-Asia-manufactured rhG-CSF 300 mcg therapy including hemoglobin, hematocrit, leucocyte count, neutrophil count, thrombocyte count, and white blood cell. C-reactive protein and thorax X-ray were examined if there was suspicion of infection (Table 1).

Adverse event, such as bone pain, nausea, vomiting, abdominal pain, rash, thrombocytopenia, and other adverse events were closely monitored and documented during study period. Physical and vital sign examinations were also done routinely during In-Asia-manufactured rhG-CSF 300 mcg therapy in order to detect any change in patient condition and any sign of focal infection.

Statistical Analysis

This non-comparative trial was using descriptive method. Baseline characteristics, the incidence of neutropenia (in percentage), severity (day of nadir absolute neutrophil count [ANC]) and duration of neutropenia (in days) were presented in numbers and graphics. The percentage of each grade neutropenia,

febrile neutropenia hospitalization rate, clinical infection rate, adverse event rate were also described.

RESULTS

Patient Characteristics

Between November 2003 and October 2005, 38 patients with non-Hodgkin lymphoma were screened and recruited to the study. Of these 38 patients, six patients were excluded from the study. Data from a total 32 patients were available for baseline analysis. Three patients were dropped out at the beginning of the study and left out for main analysis of cycle 1 since they could not contribute for outcome analysis. Another three patients dropped out during cycle 1 and six patients did not start cycle 2, leaving 20 patients available for analysis at cycle 2.

The proportion of male (53.1%) is slightly higher than female (46.9%). Patients were between 60 to 75 years-old (mean: 67.1 years). The majority had body mass index (BMI), calculated as weight in kilograms divided by the square of height in meters, ranged between normal to underweight (96.6% with BMI below 24.9) which is a characteristic for cancer patients. Baseline demographic characteristics of the study participants are described in table 2.

Table 1: Treatment and test schedule

	Week-1	Week-2	Week-3	Week-4	Week-5
S					
C	X rhG-CSF 300 mcg Treatment		STOP	X rhG-CSF 300 mcgTreatment	
R					
E	Laboratory Examination		STOP	Laboratory Examination	
E					
N					
I	Anamnesis & Physical Monitoring				
N	CRP & thorax X-ray if any focal infection suspected				
G	Adverse event monitoring				

Screening: Histology and cytology examination, performance status, anamnesis & physical examination, laboratory examination, pregnancy test
X   : Chemotherapy
Lab Exam: Hemoglobin, Hematocrit, Leucocyte count, Differential count, Neutrophil, Thrombocyte

Table 2: Baseline demographic characteristic of study participants

Male, N (%)	17 (53.1)
Age, mean, years	67.1
Weight, mean (SD), kg	49.2 (9.7)
Height, mean (SD), cm	156.1 (8.2)
BMI, mean (SD), kg/m^2	20.2 (2.9)
Underweight, N (%)	11 (51.7)
With significant comorbidity, N (%)	7 (21.9)

Duration of Neutropenia

The median duration of grade 4 neutropenia in cycle 1 and cycle 2 was three days. The median duration of grade 3 neutropenia in cycle 1 was two days and in cycle 2 was two half days (Table 3). Changes of absolute neutrophil count (ANC) day-by-day throughout the study showed a marked variation between patients. Figure 1 shows example of representative individual graph during CHOP and In-Asia-manufactured rhG-CSF 300 mcg therapy from 4 patients

Among 29 patients who received this In-Asia-manufactured rhG-CSF 300 mcg, 3 (10.3 %) required hospitalization due to febrile neutropenia. Among those 3 patients, 1 patient had septicemia and died due to

Table 3: Duration and percentage of neutropenia in cycle 1 and cycle 2

Grade of neutropenia in Cycle 1	N	% of Total N	Mean	Standard Deviation	Median	Minimum	Maximum
0	4	13.8 %	0.00	0.000	0.00	0	0
1	2	6.9%	1.00	0.000	1.00	1	1
2	1	3.4%	2.00	-	2.00	2	2
3	1	3.4%	2.00	-	2.00	2	2
4	21	72.4%	3.48	0.281	3.00	2	7
Total	29	100.0%	2.72	0.317	3.00	0	7

Grade of neutropenia in Cycle	N	% of Total N	Mean	Standard Deviation	Median	Minimum	Maximum
0	4	20.0 %	0.00	0.000	0.00	0	0
2	2	10.0%	2.00	0.000	2.00	2	2
3	2	10.0%	2.50	0.707	2.50	2	3
4	12	60.0%	3.25	1.138	3.00	1	6
Total	20	100.0%	2.40	1.569	3.00	0	6

Table 4: Incidence of clinical infection

Clinical infection	N (%)
Febrile neutropenia	7 (24.1)
Respiratory tract symptoms, cough	3 (10.3)
GI tract symptoms, diarrhea	2 (6.9)
Septicemia	1 (3.5)

Table 5: adverse events occurred during cycle 1 and cycle 2 of CHOP treatment

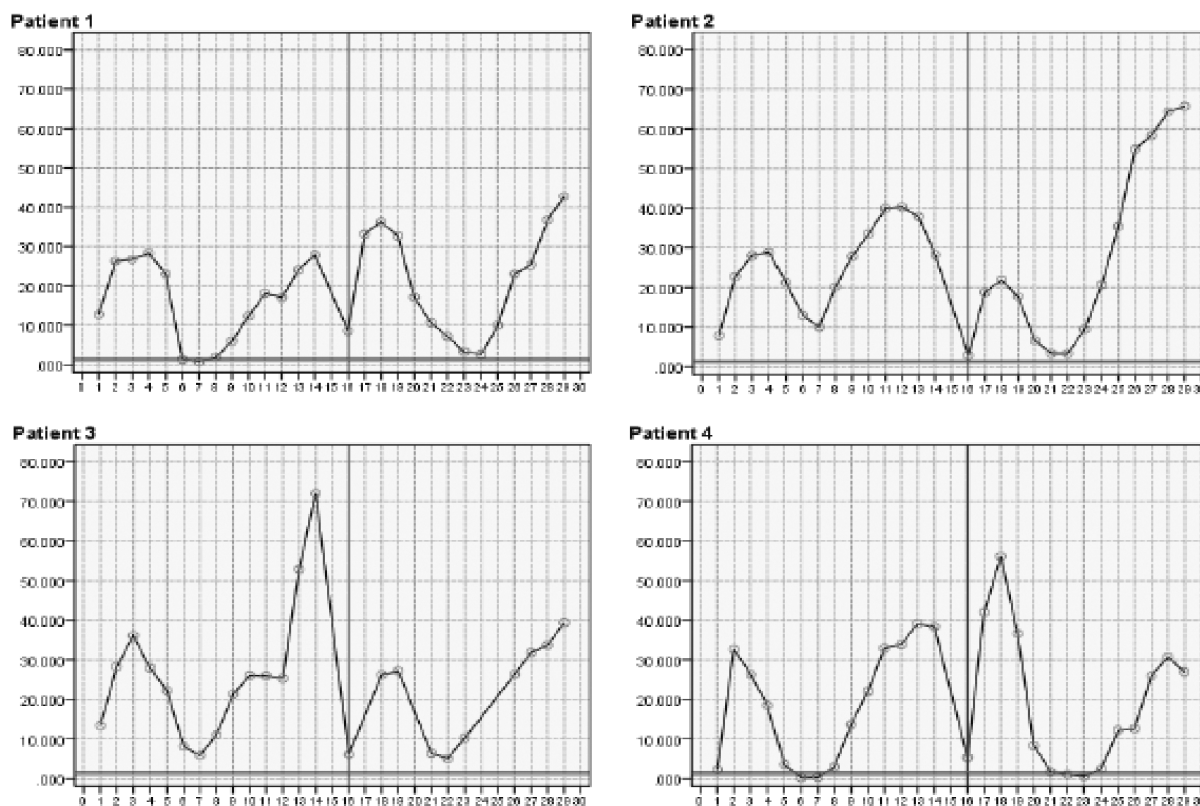| Non-hematological symptoms	N(%)
Nausea or vomiting	9 (31.0)
Dyspepsia	5 (17.2)
Asthenia or weakness	6 (20.7)
Neuropathy	3 (10.3)
Bone pain	2 (6.9)
Constipation	1 (3.5)

Figure 1: Individual Absolute Neutrophil Count Graphic During CHOP and rhG-CSF 300 mcg Therapy

septic shock. Clinical infection observed during CHOP and this In-Asia-manufactured rhG-CSF 300 mcg therapy were reported in Table 4.

Adverse Events

Mostly reported side effects were nausea or vomiting which were occurred in 9 (31.0%) patients. Other non-hematological toxicities were dyspepsia or heartburn, asthenia or weakness, neuropathy, skeletal pain, and constipation (Table 5).

DISCUSSION

In this study, we found that this In-Asia-manufactured rhG-CSF 300 mcg could shorten the median duration of grade 3 and 4 neutropenia. In similar study conducted by Hartman et al.,[17] patients receiving standard chemotherapy without *rh*G-CSF had grade 4 and 3 neutropenia with median duration of four and five days, respectively. Whereas patients receiving standard chemotherapy with *rh*G-CSF had grade 4 and 3 neutropenia with median duration two days and three days, respectively. Primary prophylaxis with this In-Asia-manufactured rhG-CSF 300 mcg has reduced median duration of grade 4 neutropenia in cycle 1 and cycle 2 to three days and of grade 3 neutropenia in cycle 1 to two days and in cycle 2 to two

half days.

As a preventive treatment adjunct to chemotherapy, *rh*G-CSF has been shown to shorten the neutropenic period and to reduce the incidence of febrile neutropenia in high-risk patients.[18-20] Several risk factors associated with development of chemotherapy-induced neutropenia including age,[21] performance status,[22] medical comorbidities,[23] laboratory abnormalities,[22] and tumor type.[23] Elderly patients tend to have more limited hematopoietic reserve than younger patients do, and are therefore more susceptible to chemotherapy-induced myelosuppression than younger are. This was seen in our study which had slightly longer median duration time of neutropenia in patients who were given In-Asia-manufactured rhG-CSF 300 mcg, when compared with median duration time of neutropenia in patients who were given rhG-CSF in study conducted by Hartman et al[17]. The explanation for this result is because our study only included subject above 65 years, 51.7% were underweight, and 21.9% had significant comorbidity whereas in Hartman study included patients above 21 years and 81% were in 0-1 (fully functional to good) peformance score.

rhG-CSF has more clinical benefit if given as prophylaxis as shown in eight randomized, controlled

trials (RCTs) on GM-CSF,[24-28] G-CSF,[29,30] or both[31] as treatment in febrile patients with chemotherapy-induced neutropenia. The largest was an Australian multi-center trial of 218 patients receiving rhG-CSF (12 μg/kg/day, by continuous subcutaneous infusion) or placebo, along with intravenous antibiotics. In this Australian trial, treatment of febrile neutropenia patients with rhG-CSF could reduced duration of neutropenia by one day, but the duration of fever, duration of antibiotic therapy, and median period of hospitalization were not affected, despite continuous infusion of rhG-CSF at a dose more than twice that routinely used in practice.[29]

In our study, with in-Asia-manufactured rhG-CSF 300 mcg primary prophylaxis, there were only 10.3% patients who were hospitalized due to febrile neutropenia. This was in accordance with Hartman et al. and other study which showed 10-15% hospitalization for febrile neutropenia.[35,36] In study done by Chrischilles,[33] the effect of full-dose CHOP in intermediate NHL patients without rhG-CSF, causing febrile neutropenia hospitalization (FNH) in 28% of patients 65 years of age or greater. In the Oncology Practice Patterns (OPP) study analyzing patterns of CHOP or CNOP (cyclophospamide, Novantrone, vincristine) chemotherapy in 492 patients with intermediate NHL showed 24% patients without rhG-CSF were hospitalized for febrile neutropenia.[34]

The OPP study showed that primary prophylactic of rhG-CSF was associated with a significant reduction in the incidence of hospitalizations for febrile neutropenia (FN) in all patients receiving appropriate chemotherapeutic dose intensity. The risk of hospitalization of FN in the study was significantly associated with the following characteristics: age 65 years or older, serum albumin level at presentation less than or equal to 3.5 g/dL, planned average relative dose intensity greater than or equal to 80%, baseline absolute neutrophil count less than 1500/mm^3, and the presence of hepatic disease.[32]

Clinical infection that mostly occurred in this study was febrile neutropenia (24.1%), whereas Morrison et al. reported that the incidence of FN without rhG-CSF prophylaxis was 34%.[37] In OPP study the rate of febrile neutropenia without rhG-CSF prophylaxis was 31.3%.[36] The prophylactic rhG-CSF would be clinically effective when the risk of febrile neutropenia is 20%. A major change in the 2006 ASCO guidelines for white-cell growth factors is to recommend use of rhG-CSF or granulocyte-macrophage colony-stimulating factor (GM-CSF) when the risk of FN is approximately 20%, rather than 40% as in the 1996, 1997, and 2000 guidelines.[42] The National Comprehensive Cancer Center Network (NCCN) also recently revised their own guidelines in favor of a 20% FN threshold for a definite indication of granulocyte colony-stimulating factor (G-CSF) prophylaxis and a 10% to 20%

FN threshold range indicating optional rhG-CSF prophylaxis.[39] This change is based largely on two new phase III clinical trials that show rhG-CSFs are effective when the risk of FN is approximately 20%.[40,41] In the first study, Vogel et al. compared patients with breast cancer treated with docetaxel 100 mg/m^2 with or without pegylated rhG-CSF; the risk of FN was reduced from 17% without rhG-CSF to 1% with rhG-CSF, and the risk of hospitalization for FN was reduced from 14% without rhG-CSF to 1% with rhGCSF.[40] A second study by Timmer-Bonte et al. showed that the risk of FN in small-cell lung cancer (SCLC) patients at high risk of FN could be reduced from 24% to 10% in cycle 1 by adding rhG-CSF.[41] Although this regimen is not widely used in the United States, the SCLC and breast cancer trials showed that rhG-CSFs reduce the risk of FN, even when that risk is relatively low.

As noted in the NCCN guidelines, when costs are considered, the economic impact of FN becomes greater, and the cost-saving benefits of rhG-CSF are more apparent. Economic analysis from Timmer-Bonte et al. confirms the NCCN assessments of rhG-CSF use. Adding rhG-CSF to antibiotic prophylaxis increased per-patient cost in the European setting by $650 (US) in the first cycle and $5,000 overall.[41] However, prophylactic regimens and reduced toxicity appear more cost effective in the United States, where costs of each episode of FN can be four times greater than in Europe because of markedly greater healthcare and hospital expenditures.[42] In addition, the indirect costs of FN can be substantial. It is entirely possible that, in the United States, rhG-CSF use for primary prophylaxis in the setting of cancer chemotherapies associated with a 20% rate of FN may be both clinically effective and also cost effective. Based on this economic analysis, this In-Asia-manufactured rhG-CSF 300 mcg would be more cost effective for the patients and this product has also shown comparable clinical benefit as other preparations of rhG-CSF.

Most adverse events in the use of rhG-CSF were attributed to the underlying malignancy or cytotoxic chemotherapy. In the study to evaluate the efficacy and safety of Filgrastrim, these adverse events occurred at rates between 2% to 57% included nausea/vomiting, skeletal pain, alopecia, diarrhoea, neutropenic fever, mucositis, fever, fatigue, anorexia, dyspnea, headache, cough, skin rash, chest pain, chest pain, generalized weakness, sore throat, stomatitis, constipation and unspecified pain. The highest rate of adverse event was nausea/vomiting, the lowest rate adverse event was unspecified pain. In our study, the highest rate of adverse event was also nausea or vomiting (31%), whereas bone pain only occurred in 6.9% patients. In the meta-analysis of prophylactic rhG-CFS, the mean frequency of bone

pain among patients receiving this growth factor was 21% (17-25%).[43]

In conclusion, the use of In-Asia-manufactured rhG-CSF 300 mcg for primary prophylaxis in patients with CHOP therapy could reduce the duration of neutropenia, reduce the rate of febrile neutropenia event and febrile neutropenia hospitalization, which were in accordance with other trial using rhG-CSF. The lack of this study was the study designed as open label and non-comparative. Therefore, a trial with higher level of evidence based medicine such as RCT design needs to be done in the next future. ❖

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