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Non-glycosylated recombinant human granulocyte colony-stimulating factor (rhG-CSF) treatment for patients with febrile neutropenia following chemotherapy.

Narin Voravud* Virote Sriuranpong*
Nuchara Nithipaijit* Navapun Charuruks**

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Febrile neutropenia after chemotherapy administration in cancer patients contribute to significant morbidity and mortality. Current therapy is prompt empirical antibiotics for this condition. Prognosis depends on several factors especially severity and duration of neutropenia. rhG-CSF is a growth factor for neutrophils. Utilization of rhG-CSF to accelerate neutrophil production during neutropenia and infection may decrease severity and consequence of the afore-mentioned condition. Therefore, we studied therapeutic efficacy of rhG-CSF in combination with antibiotics and compared with antibiotics alone in cancer patients who developed febrile neutropenia after chemotherapy. It was found that rhG-CSF can reduce mortality rate from infection (32% VS 7%, p=0.004), and incidence of septic shock (36% VS 11.1%, p-0.009). However, no statistical difference between the two groups when compared duration of fever, absolute granulocyte count, duration of antibiotics and days of hospitalization. Median absolute granlocyte count nadir was not different between the two treatment groups (180/mm^3 VS 200/mm^3, p=0.630). Side effects of rhG-CSF were myalgia (22.1%) and bone pain (12.9%). The use of rhG-CSF in combination with antibiotics in the management of febrile neutropenia after chemotherapy can effectively decrease mortality rate and incidence of septic shock with only mild side effects.

Key words : *Colony stimulating factor, Antineoplastic agents, Febrile neutropenia.*

Reprint request : Voravud N., Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand.

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*Department of Medicine, Faculty of Medicine, Chulalongkorn University.

**Department of Laboratory Medicine, Faculty of Medicine, Chulalongkorn University.

นรินทร์ วรวุฒิ, วิโรจน์ ศรีอุฬารพงศ์, นุชรา นิธิไพจิตร, นวพรรณ จารุรักษ์. นอน-ไกลโคไซเลทเทต รีคอมบิเน็นท์ ฮิวแมน แกรนนูโลไซท์ โคโลนี-สติมูเลติง แฟคเตอร์ (อาร์เฮชจี-ซีเอสเอฟ) ในการรักษาผู้ป่วยที่มีไข้และภาวะเม็ดเลือดขาวต่ำหลังได้รับยาเคมีบำบัด. จุฬาลงกรณ์เวชสาร 2538 กุมภาพันธ์; 39(2): 107-118

ภาวะไข้ร่วมกับเม็ดเลือดขาวต่ำหลังได้รับยาเคมีบำบัดเป็นผลข้างเคียงที่พบบ่อยในผู้ป่วยมะเร็งซึ่งก่อให้เกิดผลแทรกซ้อนและอัตราตายสูง การรักษาที่ใช้อยู่ในปัจจุบันคือการให้ยาปฏิชีวนะเมื่อเกิดภาวะนี้ขึ้น การพยากรณ์โรคขึ้นอยู่กับปัจจัยหลายอย่างโดยเฉพาะความรุนแรง และระยะเวลาที่เม็ดเลือดขาวต่ำ rhG-CSF เป็นสารที่กระตุ้นการสร้างเม็ดเลือดขาว neutrophils การให้ rhG-CSF เพื่อเพิ่มการสร้างเม็ดเลือด neutrophils ในภาวะที่เม็ดเลือดขาวตกต่ำและมีการติดเชื้ออาจช่วยลดความรุนแรง และผลข้างเคียงของภาวะดังกล่าวได้ ดังนั้น คณะผู้วิจัยได้ศึกษาผลของการใช้ rhG-CSF ร่วมกับยาปฏิชีวนะเปรียบเทียบกับการใช้ยาปฏิชีวนะในผู้ป่วยมะเร็งที่เกิดไข้ขณะที่เม็ดเลือดขาวต่ำหลังได้ยาเคมีบำบัด พบว่า rhG-CSF สามารถลดอัตราตายจากการติดเชื้อ (32% VS 7%, p= 0.004) และภาวะช็อคจากโรคติดเชื้อ (36% VS 11.1%, p= 0.009) แต่ไม่พบความแตกต่างระหว่างทั้งสองกลุ่ม เมื่อเปรียบเทียบระยะเวลาเฉลี่ยของการมีไข้, จำนวนเม็ดเลือดขาวต่ำ, การได้ยาปฏิชีวนะ และระยะเวลาการอยู่ในโรงพยาบาล จำนวนเม็ดเลือดขาวที่ต่ำที่สุดของทั้งสองกลุ่มไม่แตกต่างกัน (180/mm^3 VS 200/mm^3, p = 0.630) ผลข้างเคียงของ rhG-CSF คืออาการปวดเมื่อยกล้ามเนื้อ (22.1%) และปวดกระดูก (12.9%) การใช้ rhG-CSF ร่วมกับยาปฏิชีวนะในการรักษาภาวะไข้ขณะที่เม็ดเลือดขาวต่ำหลังได้ยาเคมีบำบัดในผู้ป่วยมะเร็ง สามารถลดอัตราตายและภาวะช็อคจากโรคติดเชื้อได้อย่างมีประสิทธิภาพ และมีผลข้างเคียงจากยาน้อย

Recently, considerable progress has been made in the management of cancer, including the use of new antineoplastic agents and regimens. The development of intensive antitumor regimens with potential cure for some malignancies has led to severe and prolonged chemotherapy-induced cytopenia. With increasing dose intensity of chemotherapy, neutropenia becomes the most common dose-limiting toxicity of cytotoxic regimens. Consequently, the risk of infection following chemotherapy-induced neutropenia increases proportionally to the depth and duration of neutropenia.[1] Infection in the neutropenic cancer patient presents a number of problems including high morbidity and mortality rates from such sequelae. Death from infection in a setting of granulocytopenia is not infrequent and the morbidity and economic cost associated with non-fatal infection is usually substantial. Moreover, it is frequently necessary to reduce the dosage of chemotherapy and to delay the next treatment until after the patient recovers from the febrile neutropenia. The compromising effects of dose reduction and delay of chemotherapy on the therapeutic outcome are enormous. In vitro and in vivo studies in a wide range of malignant diseases have supported the importance of the dose intensity of chemotherapy as a major determinant of tumor response which will contribute to better response rate and survival rate.[2] Therefore, an inability to deliver a proper dose of chemotherapy on schedule owing to the development of febrile neutropenia may substantially compromise the response and survival of cancer patients.

Because of the magnitude of this problem, prompt diagnosis and empirical antibacterial therapy in the febrile, neutropenic patient with neoplastic disease has become standard. In spite of the initiation of broad-spectrum intravenous antibiotics, death from sepsis ranges from 5-20%.[3] The most important factor in determing the outcome of infection in the febrile, neutropenic patients is the severity and duration of neutropenia. If the nadir absolute granulocyte count (AGC) falls below 1000, 500 and 100/mm^3, the frequency of life-threatening infection rises steeply from 10% to 19% and 28%, respectively. Patients with severe neutropenia which had persisted for longer than 3 weeks had a 60% chance of developing severe infection[1]. Therefore, one therapeutic approach to decrease the morbidity and mortality from chemotherapy-induced febrile neutropenia is to administer a growth factor that can accerelate the production of polymorphonuclear cells from the bone marrow.

Granulocyte colony-stimulating factor (G-CSF) is a human glycoprotein which acts primarily to stimulate proliferation, differentiation, maturation, and function of neutrophils. Recombinant human granulocyte colony-stimulating factor (rhG-CSF) has been produced by introducing a cDNA encoding the human gene into Escherichia coli. It consists of 175 amino acids and differs from the endogenous protein in two respects. Firstly, it has methionine as a terminal amino acid. Secondly, it is not glycosylated secondary to being expressed in E. coli. Nevertheless, its activities are similar to the natural glycosylated G-CSF.[4] In vitro and in vivo data showed that rhG-CSF leads to the increase in absolute neutrophil count (ANC) in peripheral blood of normal volunteers and cancer patients who received myelosuppressive agents. The rhG-CSF has a beneficial effect to reduce the incidence of febrile neutropenia from 57 to 28%

when used as primary prophylaxis of chemotherapy-induced neutropenia.[5]

Despite the effectiveness of rhG-CSF in the prevention of chemotherapy-induced febrile neutropenia, the therapeutic efficacy of rhG-CSF in the treatment of febrile neutropenia is unclear. Therefore, we conducted a prospective open-labelled phase II study of rhG-CSF in the management of chemotherapy-induced febrile neutropenia. The objectives of the study were to evaluate (1) the efficacy of rhG-CSF in the treat-ment of infection in cancer patients with chemotherapy-induced neutropenia, and (2) the toxicity of rhG-CSF given in this fashion.

Patients and Methods

All of the cancer patients in this prospective study developed febrile neutropenia after receiving cytotoxic chemotherapy. Febrile neutropenia was defined as a body temperature of 38.5°C or greater, presumed or proved to have infection, and an absolute neutrophil count of less than 1,000 /mm^3 following myelosuppressive chemotherapy.

Preparation of recombinant human granulocyte colony-stimulating factor(rhG-CSF)

The study drug, non glycosylated rhG-CSF (Neupogen^R), is a human glycoprotein produced in Escherichia coli by recombinant-DNA technology. It has 175 amino acids with a molecular weight of 18,800 and is non-glycosylated. The product is a clear, colorless, sterile solution with a concentration of 300 ug of protein per milliliter. The specific activity of the recombinant protein is $1x10^8$ per milligram of protein. Production of the medication was partly supported by the Roche Pharmaceutical Co, Thailand.

Eligibility

Patients were eligible for enrollment in the study if they had histological or cytological proven non-hematologic malignancies. All eligible patients developed fever of over 38.5°C and had absolute neutrophil counts of less than 1,000/mm^3 following myelosuppressive antineoplastic agents. All patients had normal renal and hepatic functions, no other serious medical illness that precluded participation, and no history of autoimmune disease.

Study Design

This study was designed as an open-lable phase II study of both the safety and efficacy of rhG-CSF in the treatment of cancer patients with fever and neutropenia. All of the patients enrolled in the study had to be admitted to the hospital. After microbiologic study, the patients received 5 ug/kg/day of rhG-CSF given subcutancously once daily until ANC over 10,000 /mm^3 and beyond nadir period. Empirical antibiotics consisting of 25 mg/kg/doses of ceftazidime given intravenously every 8 hours and 7.5 mg/kg/doses of amikacin given intravenously every 12 hours were given at the onset of febrile neutropenia after the diagnosis of microbiologic studies. The patients with positive culture or specific sites of infection received antibiotics according to the clinical evidence of infection depending on the physician's judgement.

The initial assessments included complete history and physical examination. Pretreatment laboratory investigations consisted of a complete blood count with differential and platelet count, liver and renalfunction studies. Physical examinations were performed regularly throughout the study period. Complete blood counts were

obtained daily during the neutropenic period and then at least thrice weekly after recovery from the neutropenia (neutropenia was defined as an absolute neutrophil count of 1,000/mm^3 or less). Toxicities were monitored daily throughout the study period.

The therapeutic efficacy of rhG-CSF in the treatment of febrile neutropenia was assessed by determining the duration and severity of the fever and neutropenia, the duration of rhG-CSF therapy and antibiotic use, the duration of hospitalization due to the febrile neutropenia, and the incidence of septic shock and death from sepsis. Our results were compared to cancer patients with fever and neutropenia following chemotherapy who were treated with antibiotics but without rhG-CSF. The toxicities of rhG-CSF were assessed accor-ding to the WHO grading for therapy-induced toxicities.[6]

Statistical Analysis

Statistical analysis was performed by the Pearson chi-square test for difference of mortality and septic shock. The difference of other parameters between the rhG-CSF group and a control group was evaluated by the Mann-Whitney U test, using the SPSS for windows (version 6.0) statistical program.

Results

The clinical characteristics of the study patients are shown in Table 1. Sixty-two patients developed febrile neutropenia following chemotherapy. Forty patients (54 episodes) received non-glycosylated rhG-CSF treatment and antibiotics whereas twenty-two patients (25 episodes) did not receive rhG-CSF administration and served as controls. The median ages of both groups were comparable, 55 versus 50 years. Six episodes (11.1%) received chemotherapy concomittently with radiation in the rhG-CSF group whereas 2 episodes (8%) of the control group received chemoradiation. The median absolute granulocyte count at the onset of febrile neutropenia was 215/mm^3 (range 26-960) and 350/mm^3 (range 100-960), respectively. The diagnosis and myelosuppressive regimens are depicted in Table 2.

Table 1. Patient Characteristics.

			rhG-CSF used	No rhG-CSF
Total No. of patients			40	22
Total episodes of febrile neutropenia			54	25
Sex				
Male : Female			19:21	9:13
Median age			55	50
rang			40-76	19-77
Performance status(Zubord) (episodes)				
1			12(22%)	3(12%)
2			24(45%)	10(40%)
3			18(33%)	12(48%)
Diagnosis (number of patients)				
head and neck cancer			6	-
lung cancer	:	non small cell	8	4
	:	small cell	3	2
breast cancer			6	3
digestive	:	hepatocellular carcinoma	2	1
	:	cholangio carcinoma	-	1
gastrointestinal cancer	:	stomach	1	1
	:	colorectal	5	4
genitoururinary	:	bladder	1	1
germ cell tumor			-	3
ovary			1	-
sarcoma			5	2
unknown primary			2	-
concomitant chemoradiation			6	2
Mean hematologic prestudy value (per mm^3)				
total WBC			850	1,020
absolute neutrophil count			215(26-960)	350(100-960)

Table 2. Malignancy and Chemotherapy regimens.

Malignancy	Chemotherapy regimens	rhG-CSF used (episodes)	No rhG-CSF (episodes)
Lung	Carboplatin, Etoposide	5	5
	Epriubicin, Cyclophosphamide, Etoposide	1	1
	Cisplatin, Mitomycin C, Vincristine	3	1
	Cisplatin, Etoposide	1	1
	Paclitaxel	3	-
	Etoposide	2	1
Head and Neck	Cisplatin, Epirubicin	2	-
	Cisplatin, Epirubicin, Bleomycin	3	-
	Ifosfamide	2	-
Breast	5FU, Cyclophosphamide, Epirubicin	3	-
	5FU, Cyclophosphamide, Methotrexate	2	2
	5FU, Carboplatin,	1	-
	Ifosfamide, Mitoxantone	1	1
Hepatoma and Cholangio carcinoma	Epirubicin	1	2
	Chemoembolization (5FU, Mitomycin C)	1	-
Stomach	5FU, Etoposide, Leucovorin	2	1
	5FU, Cisplatin, Epirubicin, Leucovorin	1	-
Colorectal	5FU, Interferon	3	2
	5FU, Leucovorin	1	2
	Cisplatin, 5FU	1	-
Germ cell	Cisplatin, Etoposide, Bleomycin	-	1
	Doxorubicin, Vincristine, Cyclophosphamide, Bleomycin, Cisplatin	-	2
Sarcoma	Ifosfamide, Etoposide	6	-
	Ifosfamide, Epirubicin	2	1
	Ifosfamide, Doxorubicin, Vincristine, Cisplatin	1	-
	Ifosfamide, Epirubicin, Vincristine	-	1
	Methotrexate (high dose)	1	-
Ovary	Ifosfamide	1	-
Bladder	Cisplatin, 5FU, Interferon	1	-
	5FU, Interferon	1	1
Unknown Primary	Paclitaxel	3	-

The therapeutic efficacy of rhG-CSF in the management of chemotherapy-induced febrile neutropenia is show in Table 3. Septic shock as a severe complication of febrile neutropenia developed in 6 of 54 episodes (11.1%) in the rhG-CSF treated group and 9 of 25 episodes (36%) of control group (p=0.009). This sequele contributed to a mortality rate of 7% and 32%, respectively (p=0.004). The duration of neutropenia was expressed as the number of days of absolute granulocyte count below 1,000/mm.^{3} There was no difference in the median duration of neutropenia (p = 0.16), fever (p = 0.33), antibiotic treatment (p = 0.22), and hospitalization (p = 0.52) between the rhG-CSF and control groups. The shorter than expected duration of these parameters which was observed in the control group may be related to the higher mortality rate of this group. The median absolute nadir granulocyte count was 180/mm^3 (range 20-950) in the rhG-CSF treated group versus 200/mm^3 (range 10-900) in the control group (p = 0.63).

Table 3. Result of treatment.

	rhG-CSF used	No rhG-CSF	P value
Septic shock (episodes)	6(11.1%)	9(36%)	0.009*
Dead from sepsis(episodes)	4(7.4%)	8(32%)	0.004*
Median Duration of : (days)			
: fever	4.5(1-49)	5(1-30)	0.332
: neutropenia (AGC<1,000/mm3)	4(1-13)	4(1-10)	0.159
: neutropenia (AGC <500/mm3)	2(0-13)	3(0-14)	0.049*
: antibiotics treatment	8(2-32)	7.5(1-18)	0.218
: rhG-CSF treatment	5(1-18)	-	-
: hospitalization	10(2-35)	11(3-19)	0.519
AGC nadir (per mm^3)	180(20-950)	200(10-600)	0.630

*Statistical significant.

Etiology of infection was found in 19 episodes (24%) of febrile neutropenia; twelve episodes (22.2%) in the rhG-CSF group and 7 episodes (28%) of the control group, as shown in Table 4. The majority of infections were gram negative bacilli. Pseudomonas aeruginosa was an uncommon organism seen in only 2 cases only, 1 in the rhG-CSF and 1 in the control group.

Table 4. Etiology of infection from positive hemoculture.

	rhG-CSF used (episodes)	No rhG-CSF (episodes)
Not found	42	18
Klebseilla spp.	3	2
Staphylococcus aureus	4	1
Staphylococcus epidermidis	-	1
Pseudomonas aeruginosa.	1	1
Salmonella spp.	1	-
Escherichia coli	2	1
Enterobacter spp.	-	1
Aeromonas hydrophilla	1	-

The toxicity of the rhG-CSF treatment was mild and well tolerated. The most common side effects were myalgia (22.1%) and bone pain (12.9%), as shown in Table 5.

Table 5. Toxicities of rhG-CSF.

Toxicities	Grade I* (episodes)	Grade II* (episodes)
Myalgia	9 (16.6%)	3(5.5%)
Bone pain	5 (9.2%)	2(3.7%)

* according to WHO grading for therapy-induced toxicity
Grade I : minimal
Grade II : moderate
Grade III : severe
Grade IV : life threatening

Discussion

Empirical, broad-spectrum antibiotic therapy has been the connerstone of the initial management of fever in patients with neutropenia.[7] Organisms in patients with neutropenia and life-threatening infections were predominately gram-negative aerobic bacteria.[8] For adequate coverage against these potential pathogens, combination therapies with two or three drugs were essential to provide additive or synergistic therapy.[9] Even with combination regimens, several clinical events were associated with high mortality rates.[10] rhG-CSF given in conjunction with intravenous antibiotics after the

onset of febrile neutropenia may shorten the duration of neutropenia, and enhance neutrophil function with consequent reductions in infectious morbidity and mortality.

In our study, a significant reduction in infectious mortality was observed in the rhG-CSF treated group when compared to the control group (7% versus 32%m p = .004). Although the reduction of mortality supported the use of rhG-CSF as an adjunct to antibiotic therapy, other clinical parameters of neutrophil recovery (fever duration, time on antibiotics, duration of hospitalization) were not significantly shortened with the rhG-CSF treatment. Two randomized controlled trials have evaluated rhG-CSF as an adjunctive therapy for patients with chemotherapy-induced neutropenia. The rhG-CSF increased recovery from neutropenia in both trials,[11,12] and decreased the duration of antibiotic therapy and hospitalization in one trial.[12] The infectious mortality rate was low in both the G-CSF treated and placebo groups and the mortality rate was unaffected by rhG-CSf treatment. Conversely, our study revealed a high mortality rate of 32% in the control group. When rhG-CSF was given as an adjunct to antibiotics it significantly decreased infectious mortality (Table 6). While there is variability in the outcomes among the studies, these discrepancies seem to arise from differences in study design, malignancy types and antineoplastic regimens. Recent studies suggested that patients with protracted neutropenia or evidence of tissue infection may have the greatest chance of benefit from the addition of CSF.[13]

The toxicity of rhG-CSF given to patients with febrile neutropenia was mild and well tolerated. Side effects consisted of myalgia, bone pain, and malaise. No discontinuation of rhG-CSF occurred during the study.

The majority of the infectious organisms were gram negative bacilli. Only 4 episodes of the rhG-CSF group and 2 episodes of the control group were gram positive cocci including Staphylococcus aereus and Staphylococcus epidermidis. Pseudomonas aeruginosa was uncommon in our series. This may be explained by the fact that our study did not include leukemia patients who have frequently been reported to be associated with P.aeruginosa bacteremia.[14] The low incidence of gram positive bacterial infection may be related to the use of the peripheral intravenous line instead of the central venous line for chemotherapy administration in our patients.[15]

The hematopoietic colony-stimulating factor has been introduced into clinical practical practice as an additional supportive measure that can reduce the likelihood of neutropenic complication due to chemotherapy. Although clinical benefit has been shown in the prevention of chemotherapy-associated neutropenic fever or infection,[16,17] its therapeutic efficacy in the treatment of febrile neutropenia following chemotherapy is not yet well established. Moreover, the high cost of CSF has led to concern about its appropiate use. The therapeutic initiation of CSF, in addition to antibiotics at the onset of febrile neutropenia, should be reserved for patients at high risk for septic complications.[13,15,18,19] Our data suggests that the use of rhG-CSF with antibiotics for patients with febrile neutropenia following chemotherapy warrants prospective randomized double blind placebo, controlled trials to determine therapeutic efficacy, the cost-effectiveness of administration of rhG-CSF[19] and to identify clinical predictors of infectious complications that may direct its use in the management of febrile neutropenia.

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