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Hematologic effect of recombinant human granulocyte colony-stimulating factor in patients receiving myelosuppressive chemotherapy.

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*The changes of hematologic parameters in recombinant human granulocyte colong-stimulating factor (rhG-CSF) in prophylactic patients receiving myelosuppressive chemotherapy have been studied on 8 cases using flow cytochemistry blood autoanalyser (Technicon^R H*1). Our study demonstrated slightly decreased red blood count (RBC) and hemoglobin (Hb) which peaked on 7th day and decreased platelet count which peaked on the 6th day. No severe neutropenia (absolute neutrophil count, ANC <0.50x10^9/L) was noticed in 6 rhG-CSF primary prophylactic patients, but severe neutropenia was noticed in 2 rhG-CSF secondary prophylactic patients for periods of less than 1 week. There is no increasing of neutrophil during leukocytosis within 24 hours after starting rhG-CSF prophylaxis, and decreasing occurred within 24 hours after the end of rhG-CSF prophylaxis. There were slight lymphocytosis, monocytosis, and basophilia in some cases.*

*We concluded that rhG-CSF has no effect on anemia and thrombocytopenia, side-effect of chemotherapy regimens, however on WBC, it possesses the leukocytosis effect, especially on neutrophil. These findings demonstrate the valuable clinical use of rhG-CSF in patients receiving myelosuppressive chemotherapy. We also concluded that the information obtained from automated blood cell analyser, Technicon ^{R} H*1, could be very useful for monitoring rhG-CSF prophylactic patients receiving myelosuppressive chemotherapy.*

Key words: *Hematologic change, Granulocyte-clony stimulating factor.*

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นวพรรณ จารุรักษ์, ปราณี ไกรลาศศิริ, นรินทร์ วรวุฒิ, นุชรา นิธิไพจิตร์, ณรงค์ ศรีสิงห์, นงลักษณ์ แดงจีน. ผลของ รีคอมบิแน้นท์ ฮิวแมน กรานูโลไซต์-โคโลนี สติมูเลติ้ง แฟคเตอร์ (อาร์เอชจี-ซีเอสเอฟ) ในผู้ป่วยที่ได้รับเคมีบำบัด ต่อเซลล์เม็ดเลือด. จุฬาลงกรณ์เวชสาร 2537 กันยายน; 38(9): 515-527

ผู้รายงานได้ทำการศึกษาการเปลี่ยนแปลงของเซลล์เม็ดเลือดในผู้ป่วยที่ได้รับ Recombinant human granulocyte colony-stimulating factor (rhG-CSF) หลังได้รับเคมีบำบัดในผู้ป่วยมะเร็ง จำนวน 8 รายแบ่งเป็นผู้ป่วยที่ได้รับ rhG-CSF เพื่อเป็น Primary prophylaxis จำนวน 6 ราย และผู้ป่วยที่ได้รับ rhG-CSF เพื่อเป็น secondary prophylaxis จำนวน 2 ราย มีการเปลี่ยนแปลงของ Hb อย่างมีนัยสำคัญทางสถิติ และพบว่าลดต่ำลงมากที่สุดในวันที่ 7 ส่วนค่าดัชนีพบว่ามีการเปลี่ยนแปลงเพียงเล็กน้อย และมีการลดลงของเกร็ดเลือดอย่างชัดเจนโดยพบการลดลงต่ำสุดในวันที่ 6 หลังจากผู้ป่วยได้รับเคมีบำบัด ส่วนจำนวนเม็ดเลือดขาวและเม็ดเลือดขาวชนิด neutrophil มีการลดลงในช่วงระยะเวลาสั้น ๆ แล้วกลับสูงขึ้น ไม่พบการลดลงอย่างรุนแรง (<0.50 x 10^9 / L) ในผู้ป่วยกลุ่มที่ได้รับ rhG-CSF เพื่อเป็น primary prophylaxis ส่วนในกลุ่มที่ได้รับ rhG-CSF เพื่อเป็น secondary prophylaxis มีการลดลง อย่างรุนแรงในช่วงสั้นไม่ถึงสัปดาห์ ไม่พบว่ามีการติดเชื้อเกิดขึ้นในผู้ป่วยทั้ง 8 ราย การให้ rhG-CSF ทำให้ จำนวนเม็ดเลือดขาว และเม็ดเลือดขาวชนิด neutrophil มีการเพิ่มขึ้นภายใน 24 ชั่วโมง และลดลงภายใน 24 ชั่วโมงหลังจากการหยุดให้ ในผู้ป่วยบางรายพบว่าสูงขึ้นถึง 15 เท่า นอกจากนี้ยังพบการเพิ่มขึ้น ของเซลล์เม็ดเลือดขาวชนิด lymphocyte, monocyte, และ basophil บ้างเล็กน้อย

*การศึกษานี้สรุปว่า rhG-CSF ไม่มีผลต่อการเกิดภาวะซีดและการลดลงของเกร็ดเลือดซึ่งเป็นผลจากการได้รับเคมีบำบัด และพบว่า rhG-CSF มีผลต่อการเพิ่มขึ้นของจำนวนเม็ดเลือดขาวโดยเฉพาะชนิด neutrophil และพบว่าเครื่องตรวจวิเคราะห์เลือดอัตโนมัติ (Technicon^R H*1) สามารถนำมาใช้ติดตามการรักษาผู้ป่วยดังกล่าวได้อย่างมีประสิทธิภาพ*

The advent of high-dose chemotherapy has been a recent important step in cancer treatment. The consequence of such therapy is its myelosuppressive effect, typically neutropenia, which usually associates with morbidity and mortality.[1] As the development of blood cells is regulated by variety of glycoprotein growth factors (GFs), the clinical use of these hemopoietins may be of value in reducing the myelosuppressive related complications. The large-scale production of various GFs has been made possible by recombinant DNA technology and these are now available for clinical studies.[2] Among these GFs, recombinant human growth colony-stimulating factor (rhG-CSF) has been widely used to reduce neutropenia and thus lead to improvement in the treatment of cancer patients.[3] This study deals with hematologic changes in rhG-CSF prophylactic patients receiving myelosuppressive chemotherapy. We have used the information obtained from the routine use of automated hematology instrument (Technicon^R H*1,Tarrytown NY,USA.) to study the peripheral blood changes of three basic blood cell types; erythrocyte, thrombocyte, and leukocyte.

Table 1 Patient characteristics.

Case No.	Clinical diagnosis	Age (years)	Sex	Chemotherapy	Chlinical use of rh G-CSF
1	Small cell lung Cancer	49	M	CP,VP-16	For primary prophylaxis Lenograstim 100 ug SC x3 days.
2	Liposarcoma	62	M	IFX,VP-16	For primary prophylaxis Filgrastim 300 ug SC x8 days.
3	Small cell lung cancer	61	M	CP,VP-16	For secondary prophylaxis Filgrastim 300 ug SC x9 days.
4	Small cell lung cancer	62	M	DDP,IFX,VP-16	For primary prophylaxis Filgrastim 300 ug SC x10 days.
5	Small cell lung cancer	66	F	CP,VP-16	For primary prophylaxis Filgrastim 300 ug SC x10 days.
6	Small cell lung cancer	77	F	CP,VP-16	For primary prophylaxis Filgrastim 300 ug SC x3 days.
7	Small cell lung cancer	74	M	Paclitaxel	For secondary prophylaxis Filgrastim 300 ug SC x7 days.
8	Non-small cell lung cancer	57	M	DDP,VP-16	For primary prophylaxis Lenograstim 120 ug SC x3 days.

M =male F =female SC =subcutaneous injection
CP =Carboplatin DDP =Cisplatin
IFX =Ifosfamide VP-16 =Etoposide

Material and Method

We followed up complete blood count (CBC) in 8 patients receiving myelosuppressive chemotherapy. Only 2 patients received rhG-CSF as a secondary prophylaxis,[2] the others received rhG-CSF as a primary prophylaxis.[2] The details of the patients are shown in table 1. The first peripheral blood samples of all of the patients were drawn before starting rhG-CSF prophylaxis, the second samples were collected within 24 hour after starting rhG-CSF, the samples were gotten once a day. All samples were collected in EDTA tubes and sent to the Hematology Unit, Department of Laboratory Medicine, Chulalongkorn Hospital for analysis.

All blood samples were analysed by use of a Technicon^R H*1(H*1, Technicon Instrument Corp., Tarrytown, NY, USA.). The Technicon^R H*1 is a new hematology analyser that performs a CBC and white cell differential count on whole blood samples using both cytochemistry and light scattering (laser) technology. For red blood cell (RBC) analysis, whole blood hemoglobin concentration (Hb) is determined by using the cyamethemoglobin method, with a spectrometer set at 540 nm. RBC enumeration, volume, morphology, HB, and indicies (mean cell volume=MCV, Mean cell Hb=MCH, mean cell Hb concentration=MCHC) are analysed by a helium-neon laser, light scatter is measured at two nonoverlapping intervals (2.5° to 3.5°, narrow angle; and 5° to 15°, wide angle) to give a two-dimensional RBC cytogram. The enumeration of platelets and the determination of the size distribution are accurately measured by scattered laser light at the same two angles as RBC. There are two channels that determine the differential count, and these are called the peroxidase and basophil/lobularity (B/L) channel. The manufactural reference values and reference values from a previous study in 1005 healthy Thai subjects (Krailadsiri P,et al.) in 1994[4] are show in table 2.

All blood samples were also smeaered and stained with routine Wright's stain for confirming the results obtained from the automated analyzer.

Table 2. The manufactural reference ranges and reference ranges in 1005 healthy Thai subjects. (modified from Krailadsiri P,et al., 1994)

Parameters	Kriladsiri P, et al.		The manufactuer	
	Percent	x10 E 9/L	Percent	x10 E 9/L
WBC (x10 E 9/L)	-	3.6-9.8	-	4.8-10.8
Neutrophil	36.4-68.9	1.31-6.75	40.0-47.0	1.92-7.99
Lymphocyte	20.4-49.0	0.73-1.47	19.0-48.0	0.91-5.18
Monocyte	2.5-8.1	0.09-0.80	3.4-9.0	0.16-0.97
Eosinophil	0-8.4	0.00-0.82	0-7.0	0.00-0.76
Basophil	0-2.5	0.00-0.24	0.1.5	0.00-0.16
Large unstained cell	0-9.5	0.00-0.93	0-4.0	0.00-1.03

Results

Figures 1 through 4 show the changes in peripheral blood of our study begining from before rhG-CSF prophylaxis through the course of rhG-CSF prophylaxis. Table 3 demonstrates mean and standard deviations of hematologic parameters of our study.

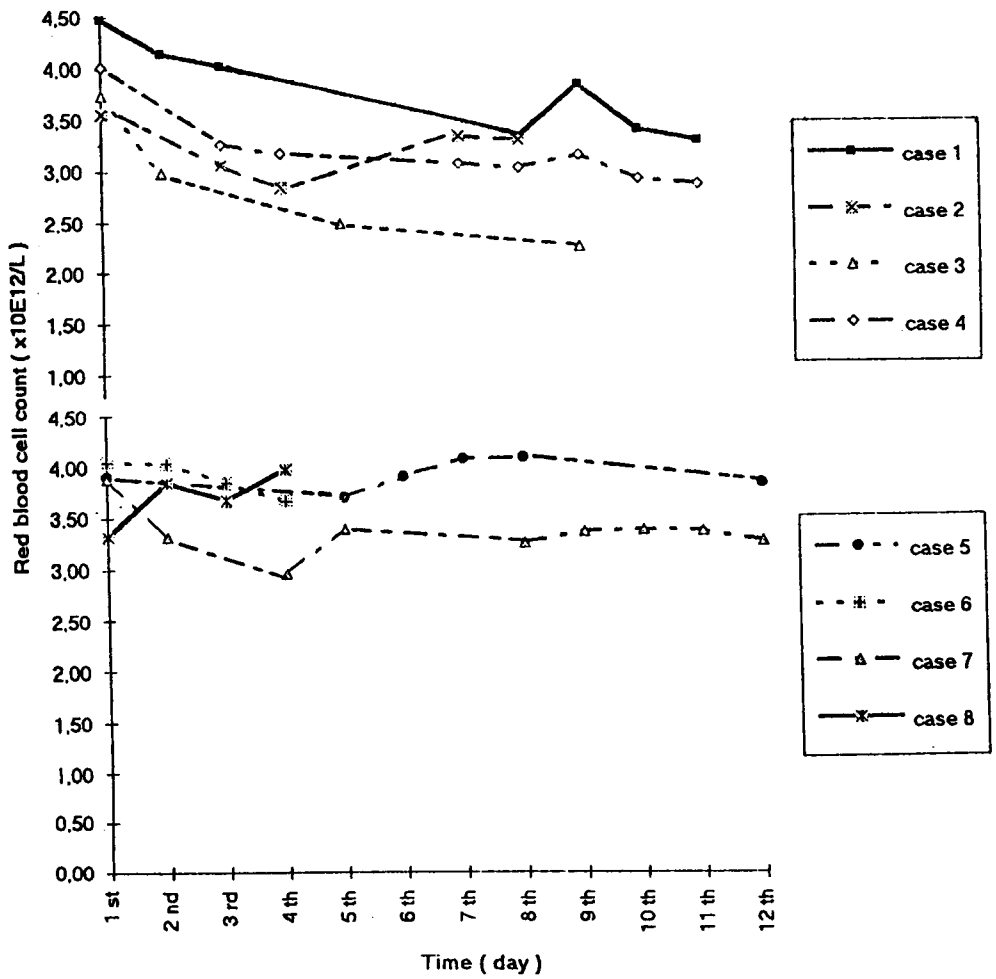

Figure 1. Effect of rhG-CSF on RBC in patients receiving myelosuppressive chemotherapy.

Table 3. Hematologic changes in rhG-CSF prophylaxis patients receiving myelosuppressive chemotherapy.

Parameters	Before rhG-CSF administration mean (± SD)	During rhG-CSF administration mean(± SD)	After rhG-CSF administration mean(± SD)
Primary prophylaxis (n=6, duration of rhG-CSF administration =5.7 ± 3.4 days)			
RBC (x10E9/L)	3.95(± 0.44)	3.49(± 0.63)	3.71(± 0.57)
HB (g/dl)	11.11(± 1.32)	10.51(± 0.95)	10.53(± 1.02)
Platelet count(x10E9/L)	264(± 168)	143(± 104)	156(± 70)
WBC (x10E9/L)	7.87(± 3.22)	8.47(± 6.21)	9.78(± 7.05)
Neutrophil (x10E9/L)	5.97(± 3.42)	7.22(± 6.03)	7.98(± 5.89)
Lymphocyte(x10E9/L)	1.29(± 0.77)	1.09(± 0.78)	1.29(± 1.07)
Monocyte(x10E9/L)	0.20(± 0.15)	0.15(± 0.10)	0.19(± 0.10)
Eosinophil(x10E9/L)	0.20(± 0.20)	0.16(± 0.12)	0.07(± 0.06)
Basophil(x10E9/L)	0.05(± 0.02)	0.06(± 0.05)	0.07(± 0.05)
Large unstained cell (x10E9/L)	0.16(± 0.15)	0.19(± 0.16)	0.21(± 0.17)
Secondary prophylaxis (n=2, duration of rhG-CSF administration = 7.7 ± 1.2 days)			
RBC(x10E9/L)	3.72(±0.54)	3.44(± 0.63)	3.55(± 0.80)
HB(g/dl)	12.20(± 0.52)	9.33(± 0.90)	9.57(± 0.40)
Platelet count(x10E9/L)	1.10(± 70)	73(± 58)	1.08(± 57)
WBC(x10E9/L)	3.86(± 2.12)	20.64(±10.64)	46.71(±32.31)
Neutrophil(x10E9/L)	2.64(± 2.22)	21.08(±10.85)	42.83(±30.41)
Lymphocyte(x10E9/L)	0.89(± 0.27)	0.60(± 0.22)	0.83(± 0.32)
Monocyte(x10E9/L)	0.06(± 0.03)	0.54(± 0.10)	1.18(± 0.94)
Eosinophil(x10E9/L)	0.12(± 0.07)	0.18(± 0.16)	0.08(± 0.06)
Basophil(x10E9/L)	0.02(± 0.02)	0.10(± 0.10)	0.13(± 0.07)
Large unstained cell (x10E9/L)	0.08(± 0.02)	0.28(± 0.28)	0.60(± 0.10)

Figure 1 shows the effect of rhG-CSF on RBC in patients receiving myelosuppressive chemotherapy, and the results demonstrated no significant change on RBC numbers both in primary and secondary prophylactic patients, which is also presented in table 3. Figure 2 shows the effect of rhG-CSF on Hb. Figure 2 and table 3 demonstrate significant anemia, especially in secondary prophylactic patients. We noticed slight immediate decreasing on both numbers and Hb after the completion of the myelosuppressive chemotherapy course (the begining of rhG-CSF prophylactic course), and improvement occurred within 4-5 days. Table 3 demonstrates that there were increases of WBC and neutrophil during and after rhG-CSF administrations. Table 4 demonstrates nonsignificant change of RBC indicies. Figure 3 presents the effect of rhG-CSF on platelet which was similar to the RBC. The platelet number decreased after the completion of myelosuppressive chemotherapy. It hit its peak on the 4th day. Figures 4 and 5, demonstrate the WBC changes during rhG-CSF prophylaxis. Figures 4a and 4b showed the changes in total white blood cells (WBC). In cases 2,5, 6, and 8 WBC<$3.6 \times 10^9/L$[4] were not noticed during rhG-CSF prophylaxis. In cases 1,3,4,

and 7 WBC<3.6x10^9/L were noticed for durations of 6,7,6, and 4 days respectively. For the changes in ANC, cases 1,2,4,5,6,and 8 did not experience the severe neutropenia (ANC <0.50x10^9/L),[5] only cases 3,and 7 had severe neutropenia for 6, and 2 days respectively. Cases 2, 5, and 8 did not experience the moderate neutropenia (ANC<1.00x10^9/L),[5] cases 1,3,4,6, and 7 had ANC<1.00x10^9/L for 2,6,1,1, and 2 days respectively. These results indicated that the durations of neutropenia associated with infection were shorter than 1 week. And even if the WBC in some patients were lower than reference values[4] the neutropenia did not occur. The increase in ANC was observed within 24 hours of rhG-CSF administration, except in two febrile neutropenic cases (cases3, and 7). In 5 subjects (cases 1,2,6,7, and 8), the ANC were reported to decrease within 24 hours of the end of rhG-CSF prophylaxis. In the others, the ANC were noticed to decrease between 24 hours of the end of rhG-CSF prophylaxis. Cases 3, and7 hadrhG-CSF for secondary prophylaxis and during our study they experienced severe neutropenia for 6 and 2 days respectively. In case 3, the patient had rhG-CSF prophylaxis for 9 days and ANC began to increase on the 5th day and reached the normal values[4] on the 7th day of whole course of rhG-CSF prophylaxis. In case 7, the patient had rhG-CSF prophylaxis for 7 days and had severe neutropenia for 2 days, on the 4th day and 5th day. On the 9th day, ANC increased 15-fold over the begining and began to drop on the 10th day at 1-fold rate of the peak through the 12th day. For the patients who received rhG-CSF as primary prophylaxis, they did not have sever neutorpenia. Only cases 1,4, and 6 had moderate neutropenia which they retained for a few days. For the changes in lymphocytes monocytes, eosinophil, basophil, and large unstained cell (LUC) in cases 5 and 6 there were lymphocytosis (>1.47x10^9/L),[4] case 7 was noticed for monocytosis (>0.80 x10^9/L)[4] and basophilia (>0.24x10^9/L).[4] Eosinophilia (>0.82x10^9/L)[18] and increasing of LUC (>0.93x10^9/L)[7] were not noticed. Cases 5 and 6 had only a 1 1/2 to 2-fold increase in lymphocytes during rhG-CSF prophylaxis. The lymphocytosis occurred at the same time of leukocytosis. Case 7 had a 3-fold increase in monocytes and a 1/2-fold increasein basophil for a few days at the same time that leukocytosis occurred.

Table 4. Change of RBC indicies during rhG-CSF prophylaxis in patients receiving myelosuppressive chemotherapy.

Case No.	mean(± SD) MCV fL	MCH pg	MCHC g/dl
1	79.6(± 2.3)	26.0(± 0.8)	32.7(± 0.9)
2	94.1(± 0.9)	31.1(± 0.2)	33.1(± 0.5)
3	102.2(± 1.3)	35.4(± 0.8)	34.6(± 1.1)
4	91.3(± 1.7)	31.9(± 0.9)	34.9(± 1.1)
5	96.7(± 0.6)	30.6(± 1.0)	31.7(± 1.0)
6	93.6(± 1.1)	30.7(± 0.3)	32.8(± 0.7)
7	98.0(± 3.8)	30.5(± 0.7)	31.1(± 1.5)
8	84.6(± 1.4)	27.3(± 0.6)	32.2(± 0.6)

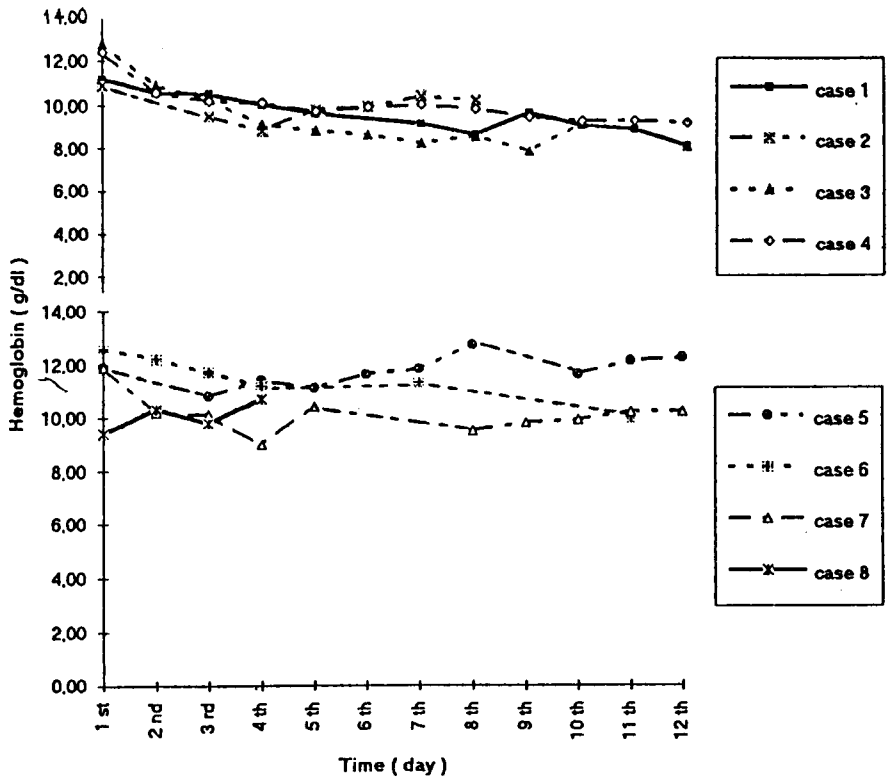

Figure 2. Effect of rhG-CSF on Hb in patientes receiving myelosuppressivechemotherapy.

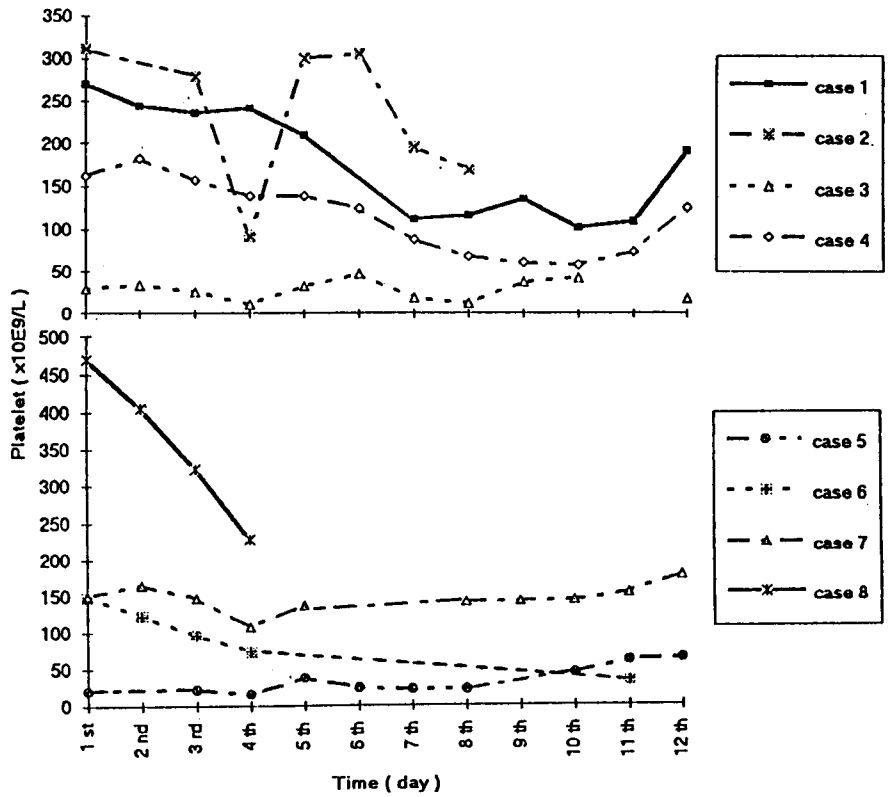

Figure 3. Effect of rhG-CSF on platelet in patients receiving myelosuppressive chemotherapy.

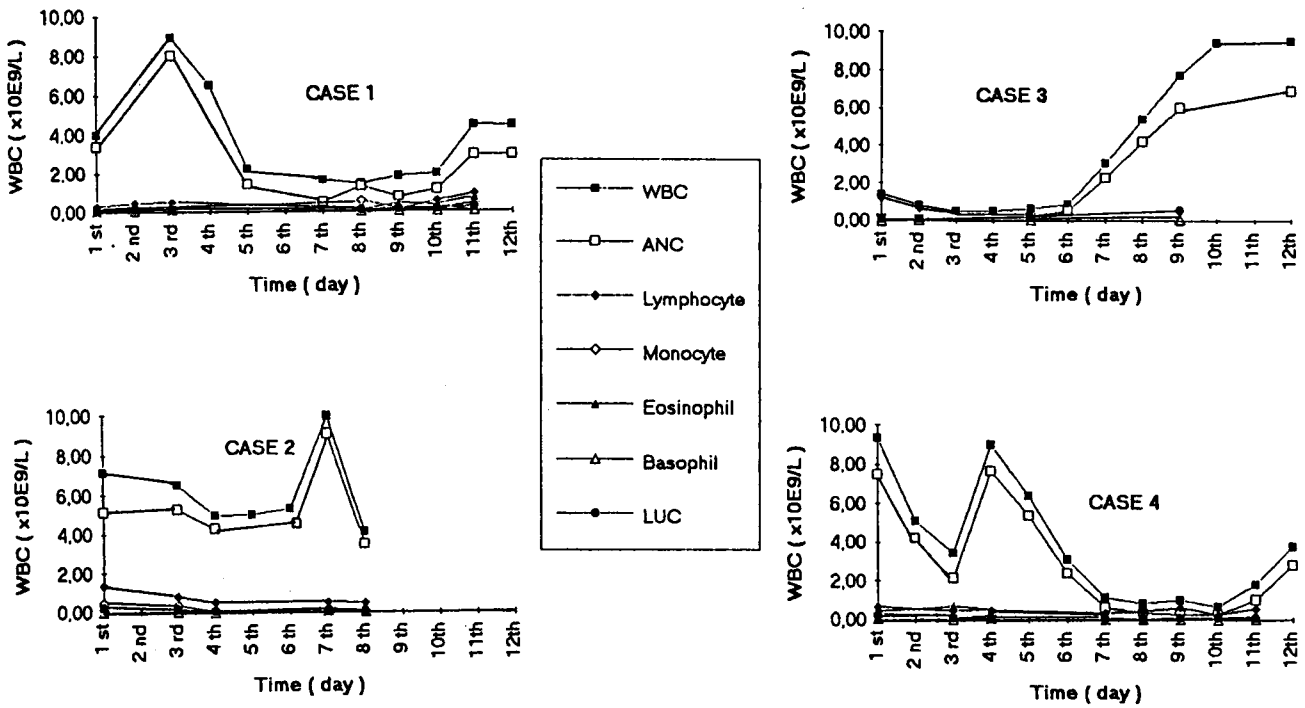

Figure 4a. Effect of rhG-CSF on WBC in patients receiving myelosuppressive chemotherapy.

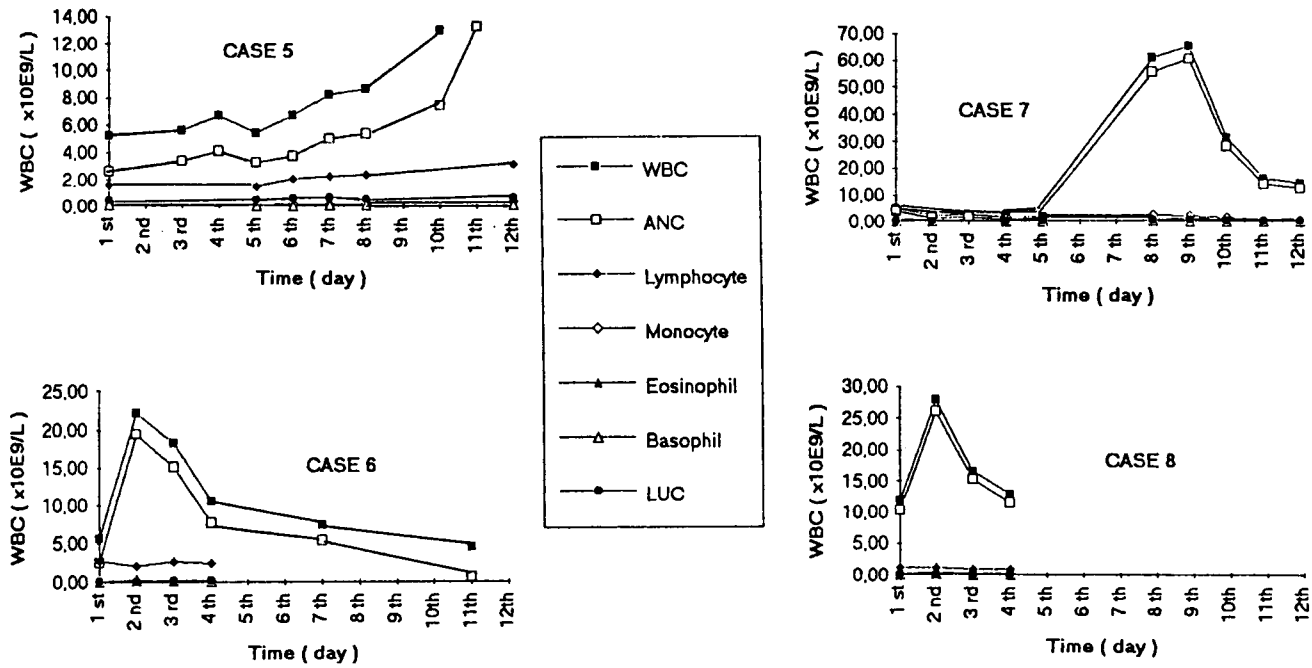

Figure 4b. Effect of rhG-CSF on WBC in patients receiving myelosuppressive chemotherapy.

Discussion

We studied the pattern of hematologic changes in rhG-CSF prophylactic patients receiving myelosuppressive chemotherapy. We used a flow cytochemistry blood autoanalyser (Technicon^{R} H* 1) in order to evaluate the effects of rhG-CSF on three basic blood cells; erythrocytes, and leukocytes.

From our study, the erythrocytes slightly decreased in both number and Hb during the first few days of rhG-CSF prophylaxis, as did the platelet number. The antineoplastic agents directly suppress the bone marrow causing anemia and thrombocytopenia which frequently accompany neutropenia which usually occurs within 7 to 10 days.[6] In contrast, the side-effect of myelosuppressive agents has more effect on platelets than on RBC because the life span of RBC (120 days) is longer than for platelets (10 days).[7] Erythropoiesis is suppressed in mice following prolonged treatment with rhG-CSF.[8] In the first few days of treatment (4 to 5 days) the deficiency is seen only in marrow differential counts and radioactive iron incorporation into the bone marrow, but this short fall of RBC production is off set by the increased erythropoietic activity noted in the spleen.[8-9] In splenectomized mice, however, protracted administration of rhG-CSF resulted in anemia. This anemia was present in splenectomized animals not only after doses of 250 ug/kg/day, but also in mice treated with 10 ug/kg/day, a dose in routing clinical use. However, the mouse differs in several important areas of hemopoietic role from humens; firstly, extramedullary hemopoiesis is rare, although splenomegaly has been reported in patients with congenital agranulocytosis receiving rhG-CSF for up to 13 months.[10] Secondly, in humans there are restricted skeletal sites of red-cell production. there were no individual reports where investigators found that thrombocytopenia was definitely related to rhG-CSF therapy and might be due to the fact that patients treated with chemotherapy and rhG-CSF received almost twice as many chemotherapy cycles. We concluded that rhG-CSF does not appear to have an adverse effect on RBC and platelets in most clinical seetings.

From our study we found that rhG-CSF produced increased neutrophil counts in the peripheral blood. In some cases there was more than a 10-fold increase of neutrophils while the other white cells had no or little increas. This demonstrates the specificity of rhG-CSF to stimulate proliferative and functional activation of the neutrophil lineage. Souza, et al., 1986[11] and Welte, et al., 1987[12] observed the selectively stimulated neutrophil production. In reality, the purpose of rhG-CSF prophylactic therapy is the prevention of severe neutrophi or to minimize the neutopenic risk associated with infection. This means the increasing of ANC should be controlled carefully to avoid unnecessary waste and the adverse effect of over use. Furthermore, the study about pharmakokinetics doses and duration of rhG-CSF prophylaxis in Thai patients should be evaluaed to get the best benefit. However, there were little lymphocytosis, monocytosis, and basophilia in some case previous studies of Bronchud, et al.,1987[13] and Molineux, et al., 1990 a[8] reported that the production of lymphocytosis in vivo is largely unaffected by the administration of rhG-CSF in humans and mice, however lymphocytosis has been reported in cats treated with rhG-CSF.[14] It is possible that these effects are due to a direct stimulatory effect of rhG-CSF on

lymphoid precursor cells; however, there have been reports of indirect stimulation of pre-B cells by G-CSF in combination with other growth factors.[15] Interestingly, the kinetics of monocyte production are also affected during rhG-CSF administration in mice.[16] It is noteworthy that Metcalf, 1991[17] has shown rhG-CSF to be a growth stimulus for macrophages progenitors indicating that this effect may well be a direct stimulation of monocyte growth. for basophilia, the mechanism may not involve with rhG-CSF administration, and further study should give more information about that.

Information obtained from the automated blood analyzer (Technicon^{R} H*1) have been readily accepted for precision and accuracy. It is also convenient to use and easy to calibrate.[18] We found that data from it proved very useful to follow-up the rhG-CSF prophylactic patient receiving myelosuppressive chemotherapy. Whatever the case, with the ability to follow-up large populations with automated blood cell analysis prospective studies should be done to evaluate the activity of neutrophils.

Summary

Chemotherapy destroys young, rapidly multiplying cells, and malignant tumor cells possess these characteristice; however, some normal body cells also have short life spans and rapid cell proliferation. The majority of these cells are located in the bone marrow. The effect of cytotoxic drugs on bone marrow is referred to as "myelosuppression". The degree to which a patient experiences bone-marrow-function suppression after chemotherapy depends on the agents used, dose, schedule, route of administration, previous antineoplastic treatment, concomitant adjuvant therapy, and other factors such as age, nutritional status, tumor type, and stage of tumor development. Infection is a major cause of morbidity and mortality in patients who receive cytotoxic chemotherapy, but prevention of neutropenia could reduce such risk. The goal of monitoring patients receiving chemotherapy is to prevent infection.[19] The rhG-CSF can reduce cancer treatment morbidity and mortality with decreased myelosuppression and decreased incidence of febrile neutropenia as well as improvement in adherence to the chemotherapy regimen with improved dosing and scheduling. The most important finding is the increasing of neutrophil which can be achieved with daily rhG-CSF administration over a long period.

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This work could not have been carried out without the accomodation of the patients.

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