EFFECT OF G-CSF ON ANC LEVEL IN ALL (Acute Lymphoblastic Leukemia) PATIENT WITH NEUTROPENIA AND FEBRILE NEUTROPENIA DURING CHEMOTHERAPY

Siti Nur Asiyah[1], Bambang Permono[2], Yulistiani, Mariyatul Qibtiyah[3]
[1]Department of Child Health, Dr. Soetomo Hospital, Surabaya
[2]Department of Clinical Pharmacy, Faculty of Pharmacy, Universitas Airlangga
[3]Pharmacy Unit, Dr. Soetomo Hospital, Surabaya

ABSTRAK

Leukemia limfoblastik akut (LLA) adalah kanker yang paling umum pada anak-anak. Chemotherapy-induced neutropenia (CIN) adalah salah satu efek samping serius yang dapat menyebabkan komplikasi seperti febrile neutropenia. Kadar neutrofil meningkat menggunakan G-CSF, yang efektivitasnya berdasarkan ANC (jumlah neutrofil absolut) pra dan pasca terapi G-CSF masih belum diketahui. Penelitian ini untuk menganalisis perubahan kadar ANC pra dan pasca terapi G-CSF pada pasien neutropenia dan febrile neutropenia dengan protokol kemoterapi risiko standar dan risiko tinggi. Penelitian ini adalah penelitian retrospektif-observasional dari Januari 2010 sampai Desember 2013. Kadar ANC pra-terapi dicatat sebelum menerima terapi G-CSF. Kadar ANC Pasca terapi dicatat antara hari 1 sampai 7 setelah terapi dihentikan. Data dianalisis dengan menggunakan paired t-test untuk menentukan perubahan kadar ANC sebelum dan sesudah terapi. Rentang dosis G-CSF pasien neutropenia vs febrile neutropenia dengan terapi protokol SR adalah 9,172 ± 1,5646 vs 9,079 ± 1,646 mg/kgBB, dan untuk protokol HR 9,909 ± 1,1229 vs 9,114 ± 1,8551 mg/kgBB/hari. Simpulan, G-CSF dalam dosis 5-10 mg/kgBB per hari dapat meningkatkan kadar ANC secara signifikan pada pasien LLA dengan neutropenia pada protokol risiko tinggi dan standar serta pasien LLA dengan febrile neutropenia pada protokol risiko standar. Namun, peningkatan kadar ANC tidak signifikan pada semua pasien dengan febrile neutropenia pada protokol risiko tinggi. ***(FMI 2014;50:179-186)***

Kata kunci: *chemotherapy induced neutropenia, leukemia limfoblastik akut, anak, G-CSF*

ABSTRACT

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children. Chemotherapy-induced neutropenia (CIN) is one of the serious adverse events that may cause complication such as febrile neutropenia. Neutrophils level is increased using G-CSF, whose effectiveness based on ANC (absolute neutrophil counts) pre and post G-CSF therapy level remains unknown. This study was to analyze the ANC level changes pre and post G-CSF therapy in neutropenia and febrile neutropenia patients with standard risk and high risk chemotherapy protocol. This was a retrospective-observational study from January 2010 to December 2013. Pre-therapy ANC level had been collected before receiving G-CSF therapy. Post-therapy ANC level was collected between day 1 to 7 after therapy discontinuation. Data were analyzed using paired t-test to determine ANC level changes pre- and post-therapy. Range of G-CSF dose of neutropenia vs febrile neutropenia patient with SR protocols therapy was 9.172 ± 1.5646 vs 9.079 ± 1.646 µg/kgBW, and for HR protocols 9.909 ± 1.1229 vs 9.114 ± 1.8551 µg/kgBW/day. In conclusion, G-CSF in a dose of 5-10 µg/kgBW per day increases ANC level significantly in ALL patients with neutropenia under high risk and standard risk protocol and in ALL patients with febrile neutropenia under standard risk protocol. However, the increase of ANC level is not significant in ALL patients with febrile neutropenia under high risk protocol. ***(FMI 2014;50:179-186)***

Keywords*: chemotherapy induced neutropenia, acute lymphoblastic leukemia, pediatric, G-CSF*

Correspondence: Siti Nur Asiyah, Department of Child Health, Dr. Soetomo Hospital, Surabaya, Indonesia.

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is defined as clonally malignant disorder of stem cell which is marked by excessive proliferation of lymphoid cells and differentiation disorder in many stages of maturation process as well as apoptosis inability (Randolph 2004). Annual incidence of this malignancy in United States is reported around 3.7-4.9 cases in every 100,000 children aged 0-14 years old with 2 years old as the peak (Ribera & Oriol 2009), while in Jakarta ALL was the most common malignancy disease in children who were taken care in Pediatric Department of FKUI/RSCM in 2009 with 60-70 new patients per year. Meanwhile, Dr. Soetomo Surabaya Hospital encountered 70 children leukemia cases in 2002 (Permono et al 2008).

Because of high incident and prevalence of ALL, many efforts have been done, including curative and supportive treatment. Supportive treatment includes the treatment of other diseases accompanying leukemia and also the complication. Chemotherapy can be given as

curative/specific treatment to treat the leukemia (Permono et al 2008). Chemotherapy is the essential treatment for ALL patients, but this drug also has many side-effects, even the toxic one. Chemotherapy suppresses hematopoietic system and leads to seriously hematological toxicity as neutropenia (Crawford et al 2004). The decrease of neutrophil is often occurred in chemotherapy treatment which is dose-limiting toxicity (Lyman et al 2005). Chemotherapy applied as ALL treatment in Dr. Soetomo Surabaya Hospital follows Indonesian ALL chemotherapy protocol 2006 which comprises of chemotherapy protocol for standard and high risks. For standard risk, regimen treatment given includes of induction, consolidation, re-induction, and maintenance phases (Permono et al 2008).

Neutrophil is a phagocyte which has prominent function to protect cells from bacterial infection. Neutrophil eats and kills bacteria, releases cytotoxic and chemotactic inflammatory mediator in the inflammation site (Panopoulos & Watowich 2008). Neutrophil disturbance will cause the body easily infected. If neutropenia occurs, chemotherapy should be delayed because chemotherapy in neutropenia will lead to increasing infection risk and even septic condition which threatens life (Crawford et al 2004, Padilla & Ropka 2005, Fortner et al 2006).

Chemotherapy induced neutropenia (CIN) is neutropenia caused by chemotherapy application. CIN can be treated by either decreasing dose of chemotherapy or delaying chemotherapy application to reduce incident and modify dose given. Decreasing dose of chemotherapy and delaying chemotherapy applicat-ion will give a suboptimal effect of cytotoxic delivery to the target organ which will lead to a decrease in survival rate. Besides, CIN can also be dealt by giving colony-stimulating factors (CSFs), which will stimulate proliferation and maturation of bone marrow progenitor cells.

G-CSF application in patients will increase amount of circulated neutrophil, but it is dose-dependent. GM-CSF application will stimulate granulocyte, macrophage, and eosinophil colony growth (Rosary 2010). G-CSF dose recommendation for neutropenic patients is 5 μg/kg BW/day, but this dose can be increased according to the duration and severity of neutropenia (Lacy et al 2010). Meanwhile, recommended dose for neutropenic fever patients is higher, that is 12 μg/kg BW/day (Anderson et al 2002). Other literature also recommends G-CSF dose 5 μg/kg BW/day with duration of application is about 5-7 days (Schwartzberg 2008, Rosary 2010).

The benefit of G-CSF treatment for neutropenic patients is controversial. In Dr. Soetomo Hospital, G-CSF is given as “neutropenic treatment”. G-CSF treatment as neutropenic prophylaxis is still difficult to be applied on because of the expensive price for developing countries. There is still no written protocol about G-CSF application for ALL patients who suffers neutropenia. Considering that, it is important to conduct an advance study related to G-CSF application for neutropenic treatment towards ANC value target in ALL patients, so that G-CSF can be used more effectively and efficiently. This study was focused on the G-CSF application in ALL patients with neutropenia and neutropenic fever during chemotherapy treatment.

MATERIALS AND METHODS

This was an observational study with longitudinal retrospective data collection. In this study, we did no intervention towards patients’ neutropenia or neutron-penic fever treatment in Pediatric ward of Dr. Soetomo Surabaya Hospital. Site of study took place at Pediatric ward of Dr. Soetomo Surabaya Hospital from January 2010–December 2013. The inclusion criteria of this study were all patients aged ≤ 18 years old (children) who got chemotherapy, ANC value < 1000/mm3 and/or WBC value < 4000/mm3, ALL patients with neutron-penia and neutropenic fever, and patients obtained G-CSF treatment. The exclusion criteria of this study were ALL patients who gained G-CSF only as neutropenic prophylaxis, new ALL patients who had gained G-CSF before endured chemotherapy induction, and ALL patients who have an allergy to G-CSF. Samples were obtained by time limited sampling method, which was every patient fulfilling the inclusion criteria during January 2010–December 2013 period was collected as this study’s sample.

Data obtained from this study were demographical data, namely: patients’ identities (age, body weight, and gender); clinical examinations; and laboratorial exam-ination (ANC and WBC value) of patients fulfilled inclusion criteria. Data displays were including display of patients’ demographical data based on age, gender, ALL type and display of ANC and WBC value, consisting of analysis of ANC and WBC value of ALL patients with neutropenia and neutropenic fever who got G-CSF treatment during chemotherapy (using either SR or HR protocol), and analysis of G-CSF dose regimentation used as neutropenic and neutropenic fever treatment.

Effect of G-CSF treatment can be evaluated from the comparison data between before and after treatment, using paired t-test for normal distribution and Wilcoxon test for the other one. Besides, this study also evaluated both the tendency of increasing WBC and ANC value in

patients who got G-CSF treatment and G-CSF treatment target achievement.

RESULTS

The results were obtained for patients receiving G-CSF therapy during the years 2010 to 2013 that met the inclusion criteria by 65 patients. From 65 total samples, there were 4 patients who had relapse (protocol change from SR to HR) and included HR protocol. From Table 3 it can be seen that the average dose received in febrile neutropenic patients the same magnitude when compared with neutropenic patients (p = 1.867), ranging between (9.079 ± 1.646) mg/kg/day vs. (9.172 ± 1.5646) mg/kg/day. From Table 4 it can be seen that the average dose received in febrile neutropenic patients at HR when compared with neutropenic patients (p = 4.534), ranging between (9.909 ± 1.1229) mg/kg/day vs. (9.114 ± 1.8551) μg/kg/day. At Dr. Soetomo Hospital there was no standard procedure on the granting of G-CSF in patients with neutropenia and febrile neutropenia. G-CSF. Recommended dose of G-CSF in neutropenic patients is 5 mg/kg/day, and the dose can be increased based on the duration and severity of neutropenia (Lacy et al 2010). In patients with febrile neutropenia are recommended higher doses, ie 12 mg/kg/day (Anderson et al 2002). From Table 5 and 6 above it can be concluded that the administration of G-CSF therapy in patients with neutropenia and febrile neutropenia LLA during protocol chemotherapy with Standard Risk or High Risk able to raise the value of the ANC and WBC.

Table 1. Characteristics of patients who receive G-CSF therapy in Pediatric Department, Dr. Soetomo Teaching Hospital from January 2010-Desember 2013

Cemotherapy Protocol Sample Protocol		SR Number of Patient (N = 32)		HR Number of Patient (N = 33)	
		n	%	n	%
Gender					
	Boy	23	71.9 %	23	69.7 %
	Girl	9	28.1 %	10	30.3 %
Age					
	< 2 th	1	3.1 %	1	3.0 %
	2-10 th	31	96.9 %	26	78.8 %
	> 10 th	0	0%	6	18.2 %
LLA type					
	L1	32	100 %	30	90.9 %
	L2	0	0 %	3	9.1 %
	L3	0	0 %	0	0 %

Table 2. Distribution of patients undergoing chemotherapy and G-CSF Receiving Therapy in Pediatric Department, Dr. Soetomo Hospital, from January 2010 - December 2013

Protocol Therapy Phases		N= (65 samples)	
		n	%
Standard Risk (32 samples)			
	Induction	25	78.1 %
	Consolidation	4	12.5 %
	Maintenance	1	3.1 %
	Remission	2	6.3 %
Neutropenia		18	56.25 %
Febrile Neutropenia		14	43.75 %
High Risk (33 samples)	Induction	13	39.4 %
	Consolidation	4	12.1 %
	Reinduction	3	9.1 %
	Maintenance	8	24.2 %
	Relapse	4	12.1 %
	Remission	1	3.0 %
Neutropenia		22	66.67 %

Table 3. Doses between patients with and febrile neutropenia neutropenia SR

Number Patient SR	Patient's body weight (Dose G-CSF)	Dose (µg/kg BW)		Information
		*FN	**N	
1.	16 kg (160 µg)		10	+
2.	10 kg (100 µg)	10		-
3.	14 kg (70 µg)	5		-
4.	14 kg (100 µg)	7.1		-
5.	29 kg (200 µg)		6.8	+
6.	20 kg (200 µg)		10	+
7.	12 kg (120 µg)		10	+
8.	14 kg (100 µg)		7.1	+
9.	13.5 kg (120 µg)		8.9	+
10.	14 kg (160 µg)		11.4	-
11.	13.5 kg (130 µg)		9.6	+
12.	10 kg (100 µg)		10	+
13.	38 kg (300 µg)	7.9		-
14.	16 kg (150 µg)		9.4	+
15.	10.6 kg (100 µg)		9.4	+
16.	40 kg (300 µg)		7.5	+
17.	15 kg (150 µg)	10		-
18.	18 kg (140 µg)	7.8		-
19.	15 kg (150 µg)	10		-
20.	11 kg (110 µg)		10	+
21.	13.5 kg (150 µg)	11.1		-
22.	15 kg (150 µg)		10	+
23.	15 kg (150 µg)	10		-
24.	11 kg (110 µg)	10		-
25.	24.5 kg (200 µg)	8.2		-
26.	16 kg (160 µg)		10	+
27.	30 kg (300 µg)	10		-
28.	22 kg (110 µg)		5	+
29.	16 kg (160 µg)	10		-
30.	10 kg (100 µg)		10	+
31.	20 kg (200 µg)		10	+
32.	4 kg (40 µg)	10		-
	x±SD	9.079 ± 1.646	9.172 ± 1.5646	(+) = 17 (53.12%) (-) = 15 (46.88 %)

DISCUSSION

In general, the purpose of this study was to analyze the alteration of ANC and WBC value after G-CSF application in pediatric patients with ALL who suffered neutropenia and neutropenic fever during chemotherapy treatment, while the specific purpose including analyzing either dose regimentation of G-CSF used as neutropenic and neutropenic fever treatment or neutropenic parameter (WBC and ANC) alteration in pediatric patients with ALL who endured standard or high risk chemotherapy protocol. From the observation conducted from January 2010 until December 2013, we obtained 65 patients who got G-CSF treatment. From the patients fulfilled inclusion criteria, there were 23 boys (71.9%) and 9 girls (28.1%) who got SR protocol, while the other 23 boys (69.7%) and 10 girls (30.3%) got HR protocol. Permono et al (2008) reported that ratio ALL patients between boys and girls is 1.15. According to the age, there were 96.9% patients age between 2-10 years old in SR protocol, while 78.8% in HR protocol. There were more patients with final diagnose ALL type L1 than type L2 with ratio 10:1 for HR, while 100% patients in SR protocol were ALL type L1. A journal reported that about 70-80% ALL cases in pediatric were type L1 (Wirawan 2002). These data are displayed at Table 1.

Table 4. Dose G-CSF Patient HR Neutropenia and Febrile Neutropenia

Number of Patient HR	Patient BW (Dose G-CSF)	Dose (µg/kg BW)		Information
		*FN	**N	
1.	20 kg (230 µg)		11.5	-
2.	14 kg (150 µg)		10.7	-
3.	32 kg (300 µg)		10	+
4.	16 kg (150 µg)		9.4	+
5.	15 kg (150 µg)	10		-
6.	11 kg (110 µg)	10		-
7.	32 kg (300 µg)		9.4	+
8.	17 kg (170 µg)		10	+
9.	12 kg (120 µg)	10		-
10.	44 kg (300 µg)	6.8		-
11.	35 kg (350 µg)	10		-
12.	40 kg (400 µg)		10	+
13.	17 kg (170 µg)		10	+
14.	29 kg (150 µg)		5.2	+
15.	21.5 kg (200 µg)		9.3	+
16.	19 kg (190 µg)		10	+
17.	19.8 kg (200 µg)	10.1		-
18.	14 kg (140 µg)	10		-
19.	14 kg (150 µg)	10.7		-
20.	28 kg (280 µg)	10		-
21.	41 kg (430 µg)		10.5	-
22.	47 kg (300 µg)		6.4	+
23.	15 kg (150 µg)		10	+
24.	12 kg (120 µg)		10	+
25.	22 kg (200 µg)	9.1		-
26.	47 kg (300 µg)		6.4	+
27.	10 kg (100 µg)		10	+
28.	13 kg (65 µg)		5	+
29.	15 kg (150 µg)		10	+
30.	6 kg (40 µg)		6.7	+
31.	12 kg (120 µg)	10		-
32.	21 kg (220 µg)		10.5	-
33.	8.4 kg (80 µg)		9.5	+
	X ± SD	9.909 ± 1.1229	9.114 ± 1.8551	(+) = 18 (54.55%) (-) = 15 (45.45%)

Table 5. Statistical Analysis The increase in WBC and ANC in patients with SR-HR

Parameter	Standard Risk		High Risk	
	N	FN	N	FN
WBC	3417.22 ± 989.62 (p=0.005)	752.86 ± 1593.17 (p=0.100)	1929.09 ± 2031.94 (p=0.00)	1700.00 ± 1440.29 (p=0.003)
ANC	962.67 ± 1158.85 (p=0.003)	443.93 ± 645.02 (p=0.026)	1081.27 ± 1066.43 (p=0.00)	799.55 ± 1472.96 (p=0.102)

Table 6. Percentage increase in WBC and ANC on Patient SR - HR

Parameter	Standard Risk		High Risk	
	N	FN	N	FN
WBC	203.74 %	38.38 %	107.61 %	161.07 %
ANC	601.67 %	275.61 %	423.11 %	477.10 %

G-CSF is recommended by ASCO (2006) to be given at least 24-72 hours after chemotherapy is given until ANC value increase at least 2-3 x 109/L. Other reference reported that G-CSF application should be stopped if ANC post-nadir around 1500-2000/υL (Anderson et al 2002). Either security or effectiveness of G-CSF given together with cytotoxic chemotherapy is still not known precisely (McEvoy 2008).

Table 3 displays the dose average obtained by patients. In SR protocol, the dose gained by neutropenic fever patients is the same as by neutropenic patients ($p = 1.867$), about (9.079 ± 1.646) μg/kg BW/day vs (9.172 ± 1.5646) μg/kg BW/day respectively. In HR protocol, the dose given for neutropenic fever patients is also the same as for neutropenic patients ($p = 4.534$), respectively around (9.909 ± 1.1228) μg/kg BW/day vs (9.114 ± 1.8551) μg/kg BW/day (displayed by Table 5). These data tell that G-CSF dose for both SR and HR patients in Dr. Soetomo Hospital Surabaya. Hospital is the same for either neutropenic patients or neutropenic fever patients ($p < 0.05$). The same dose of G-CSF treatment given for 3 days to neutropenic patients and neutropenic fever patients either for SR or HR protocol can increase WBC and ANC value.

A reference tells that usually dose of G-CSF given is 1-20 μg/kg BW/day. Generally, initial dose given for myelosuppressive chemotherapy patients is 5 μg/kg BW/day. Application G-CSF daily for 14-21 days or more may be needed to overcome neutropenia in patients enduring intensive myelosuppressive cancer chemotherapy (Kaushansky & Kipps 2006). A literature reported that there is a different dose given between in neutropenic fever patients and in non neutropenic fever patients. For neutropenic fever patients, the dose of G-CSF recommended is higher, namely 12 μg/kg BW/day (Anderson et al 2002). The increase of neutrophil as a respond for G-CSF application is dose-dependent. A literature recommends 5 μg/kg BW/day as an adequate dose for neutropenia (Lacy et al 2002), while 12 μg/kg BW/day for neutropenic fever (Anderson et al 2002).

From 32 samples with SR protocol, there were 18 patients suffered from neutropenia and 14 patients suffered from neutropenic fever. Patients suffered from neutropenia in SR protocol showed significant difference between before and after G-CSF application for either WBC value ($p = 0.005$) or ANC value ($p = 0.003$), while in patients with neutropenic fever, there were no significant difference between before and after G-CSF application both in ANC value ($p = 0.026$) and WBC value ($p = 0.100$). G-CSF works only in granulocyte cells, so it does not increase either proliferation or differentiation of the whole leukocyte cells. WBC consists of both lymphocyte (T- and B-lymphocyte) and phagocyte (monocyte and granulocyte), while granulocyte itself consists of three types of cells: neutrophil, eosinophil, and basophil. Lymphocyte is part of WBC which about 20-50%, while monocyte takes part 2-8% of total WBC value (Theml et al 2004). Neutrophil consists of 0-4% band and 50-70% segment, while eosinophil 1-4%, and basophil 0-1% of total WBC value. Band neutrophil is the precursor of segment cell which roles as immune respond for bacteria. Segment neutrophil is beneficial in immune system by migrating to the infected tissues to eliminate bacteria by phagocyte mechanism. These variable WBC components cause the increase of ANC value is not always in line with the increase of WBC value (Theml et al 2004).

Generally, acute leukemia has high risk of fever and neutropenic incidents at induction and consolidation phase, also high risk for infection that needing supportive treatment, including blood/ thrombocyte transfusion, granulocyte-increasing drugs, antifungal, antibiotic, antiviral, also good nutrition and psychosocial assessment (Permono et al 2008).

From 33 samples with HR protocol, there were 22 patients suffered from neutropenia and 11 patients suffered from neutropenic fever. Paired t-test is used to evaluate whether G-CSF application in ALL patients with neutropenia could increase WBC and ANC value significantly. From that analysis, it is known that G-CSF treatment in neutropenic patients with HR protocol gave significant difference in WBC ($p = 0.000$) and ANC value ($p = 0.000$) between before and after application of G-CSF, while there was no significant difference in WBC ($p = 0.003$) and ANC value ($p = 0.102$) of neutropenic fever patients. Dose and duration of G-CSF application should be considered well in patients with neutropenic fever. A reference recommended higher dose for neutropenic fever patients than only neutropenic patients, with duration of treatment depends on the severity of neutropenia (Anderson et al 2002).

Besides chemotherapy treatment, disease progressivity can also affect the severity of neutropenia. Disease progressivity itself can be affected by prognostic factors. Initial amount of leukocyte > 50,000 cell/mm3 has bad prognosis, and either early age < 18 months old or late age > 10 years old also has worse prognosis than they who ages between those. Infant < 1 year old or baby < 6 months old has the worst prognosis. Immunological phenotype of lymphoblast when diagnose is conducted can also become a prognosis factor. Leukemia type L3 with κ- and λ-antibody on the surface of blast cells has bad prognosis. Most of studies

concluded that girls have better prognosis than boys, because boys can also suffer from testicular relapse, hyperleukocytosis, organomegaly, and mediatinum period (Permono et al 2008).

Normally, the level of G-CSF in plasma is difficult to be detected because its concentration is less than 10 pg/cc. In other conditions, like aplastic anemia, neutropenia, infection, and maternity complication, G-CSF concentration is tend to be higher than normal and can reach 100,000 pg/cc (Morstyn et al 2004). G-CSF production is induced by stimulation of inflammatory mediators, such as interleukin-1β (IL-1 β), tumor necrosis factor-α (TNF- α), and lipopolysacharide (LPS), which then can increase rapidly during infection. Therefore, pathogens mediating immune system activation which is detected by the receptor from the increase of LPS, microbe, and cytokine released as the respond of infection, can induce the increase of G-CSF in circulation. This stimulates both neutrophil production in bone marrow and neutrophil mobilization to the peripheral circulation (Panopoulos & Watowich 2008).

In the other hand, a theory about CIN states that patients' bone marrows have bad respond towards cytokine and colony stimulating activity if they had been exposed by chemotherapy drugs before, because colony forming unit granulocyte macrophage (CFU-GM) produced was less than normal. The amount of stem cells available to respond growth factors are also less than normal or there was a final failure of organelle system which led to the characteristic alteration of stem cells and made it more resistant or less responsive towards either cytokine or growth factor stimulus (Gardner 1999).

According to that explanation, it can be concluded that although there is a high level of endogenous growth factor in the neutropenic patients – moreover in the state of infection (neutropenic fever patients) – but in the other hand, a decrease of stem cell respond towards growth factor also occurs. Individual amount of endogenous growth factor and individual stem cell respond will cause a different and also individual effect of G-CSF treatment among patients.

Effectiveness monitoring of G-CSF application was also affected by the time when ANC level was measured after G-CSF had been given. Onset of action of G-CSF is 24 hour (Anderson et al 2002, Lacy et al 2010). Another reference states that ANC value will decrease below the baseline 5-60 minutes after G-CSF is injected subcutaneously or intravenously, and in 1-4 hours later ANC value will increase rapidly in 24 hour after the injection. The decrease of ANC value in 1-4 hours after G-CSF injection is caused by neutrophil margination to the wall of blood vessel and later followed by the increase of ANC level which was a result of demargination and mobilization of mature neutrophil from bone marrow or other tissues (McEvoy 2008).

From this study, can be concluded that G-CSF treatment for neutropenic and neutropenic fever ALL patients during chemotherapy with either standard risk or high risk protocol can increase ANC value significantly, while G-CSF treatment in neutropenic fever ALL patients with high risk protocol cannot increase ANC value significantly.

CONCLUSIONS

G-CSF in a dose of 5-10 µg/kgBW per day increases ANC level significantly in ALL patients with neutropenia under high risk and standard risk protocol and in ALL patients with febrile neutropenia under standard risk protocol. However, the increase of ANC level is not significant in ALL patients with febrile neutropenia under high risk protocol.

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