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An analysis of the cost-effectiveness of filgrastim versus lenograstim in colorectal cancer patients with FOLFOX chemotherapy regimen

Jainuri Erik Pratama*, Viren Ramadhan, Saharuddin, Ridlo Pahlavi

Instalasi Farmasi, RS Kariadi Semarang
Corresponding author: erik.rsdk@gmail.com

Abstract

Background: Granulocyte colony-stimulating factor (GCSF) is a primary regulator of the granulopoiesis process, which mobilizes stem cells from the bone marrow to the blood vessels. Filgrastim and lenograstim are the types of GCSF that have been widely used.

Objective: This research aims to study the comparative therapeutic outcomes and cost-effectiveness of filgrastim and lenograstim therapies in colorectal cancer patients undergoing chemotherapy with the FOLFOX regimen.

Method: This research was conducted at the pharmacy installation of the Dr. Kariadi Central General Hospital (RSUP Dr. Kariadi) from December 2023 to January 2024. It is observational research with a retrospective pre-posttest cohort study design that evaluates the comparative effectiveness and costs of filgrastim and lenograstim therapies in patients with neutropenia based on an increase in white blood cells (WBC) and absolute neutrophil count (ANC) scores of patients. The data was analyzed using the unpaired comparative analysis method and using the cost-effectiveness analysis (CEA) method to determine the cost-effectiveness. The observations were carried out twice, before and after administering the GCSF therapy. The samples consisted of 25 patients divided into two treatment groups.

Results: The average scores of WBC and ANC levels in 15 patients who received filgrastim therapy were 2000 cells/mm^3 and 666 cells/mm^3. At the same time, the WBC and ANC levels in 10 patients who received lenograstim therapy were 1980 cells/mm^3 and 449 cells/mm^3. After administering the GCSF therapy, there was a significant increase in WBC and ANC levels ($p<0.05$) in each group. Still, there was no significant difference in the increase in WBC and ANC between the groups receiving filgrastim and lenograstim ($p>0.05$). The CEA analysis results showed that an increase of 1 cell/ml of WBC score cost Rp24.2 for filgrastim and Rp347 for lenograstim. In contrast, an increase of 1 cell/ml of ANC score cost Rp111.8 for filgrastim and Rp1572.5 for lenograstim.

Conclusion: This research concludes that filgrastim is as effective as lenograstim, yet filgrastim is considered more cost-effective than lenograstim.

Keywords: GCSF, filgrastim, lenograstim, neutropenia, cost-effectiveness analysis

1. Introduction

Chemotherapy is one of the cancer treatments. It can cause various side effects, even unexpected toxic effects. As many as 5–15% of deaths occur due to the toxic effects of chemotherapy. One of the common toxic effects of cancer chemotherapy is bone marrow suppression, which causes myelosuppressive effects (Bracci *et al*., 2014).

Neutropenia is a condition in which the number of neutrophils in the blood decreases, less than 500 cells/mm^3 or less than 1000 cells/mm^3. Neutropenia can occur due to impaired formation and shift of neutrophils to tissue, as well as increased destruction of neutrophils in the circulation. Disruption of neutrophil formation can occur due to infiltration of malignant cells and the myelosuppressive effects of chemotherapy drugs (Pilatova *et al.*, 2018). The severity of neutropenia depends on the Absolute Neutrophil Count (ANC), a measure of the

number of neutrophils in the blood. Severe neutropenia occurs when ANC <500 cells/mm^3 (American Academy of Allergy, 2023).

Neutropenia can occur in cases of hematological malignancies and solid cancers. Around 20-40% of neutropenia occurs in solid cancers. The majority of neutropenic episodes occur in the first cycle of chemotherapy in breast cancer as much as 71%, lymphoma cancer as much as 70%, colorectal cancer 53%, ovarian cancer as much as 46%, and lung cancer as much as 60% (Smith *et al*., 2015). The hematopoietic growth stimulating factor is a cytokine that regulates the proliferation, differentiation, and function of hematopoietic cells. There are two forms of hematopoietic growth-stimulating factors: granulocyte colony-stimulating factor (GCSF) and granulocyte-macrophage colony-stimulating factor (GMCSF). Examples of GCSF are lenograstim, filgrastim, and pegylated filgrastim. In contrast, an example of GM-CSF is sargramostim. Both types have been widely studied in cancer patients at risk of neutropenia as prevention or therapy for febrile neutropenia (Pilatova *et al*., 2018).

Systematic review and meta-analysis studies state that mortality is reduced in patients who receive GCSF after chemotherapy. However, in these studies, GCSF (filgrastim) was not used as a therapy for neutropenia but was used as primary prophylaxis (Mitchell *et al*., 2016). According to ESMO (European Society for Medical Oncology) patients with neutropenia can be treated with GCSF, which can increase neutrophils, reduce the incidence of febrile neutropenia, duration of neutropenia, length of treatment, reduce the number of morbidity and mortality rates in cancer patients (Klastersky *et al.*, 2016).

Several previous studies have shown different results, making the use of GCSF as a therapy still controversial. In addition, Wang *et al.*'s study found that the use of long-acting GCSF agents was more cost-effective than short-acting GCSF agents (Wang *et al*., 2023). However, the widespread use of GCSF agents is still limited because it is associated with high costs or prices (Klastersky *et al*., 2016). This research aims to compare the outcomes of WBC and ANC increases and the cost effectiveness of using filgrastim and lenograstim in colorectal cancer patients with neutropenia who would undergo FOLFOX chemotherapy.

2. Method

2.1. Research design and sampling techniques

This research is a retrospective cohort pre-posttest study in which WBC and ANC observations in each group were carried out twice, i.e., baseline data and post-GCSF therapy data.

This research has been approved by the research ethics committee of Dr. Kariadi Central General Hospital (RSUP Dr. Kariadi), with the number 16139/EC/KEPK-RSDK/2024.

This research was conducted at the pharmacy installation of RSUP Dr. Kariadi during the research period from December 2023 to January 2024. The sampling in this research was carried out using the proportionate stratified random sampling technique, where each treatment group sample was selected randomly based on a simple lottery. The number of samples in this research was determined using the total sampling method. The sample criteria in this research are as follows:

1. Inclusion criteria
   a. Adult patients aged 17–60 years.
   b. Patients diagnosed with colorectal cancer and undergoing FOLFOX chemotherapy regimen.
   c. Patients having neutropenia (WBC levels <4000 cells/mm^3 and ANC <1500 cells/mm^3)
2. Exclusion criteria
   Patients having infections that would affect WBC and ANC scores.
3. Drop-out criteria
   a. Patients having hypersensitivity reactions to filgrastim or lenograstim.
   b. Patients who died during the research period.
   c. Patients who returned home at their request without any blood tests after filgrastim or lenograstim therapy.

2.2. Data analysis

To determine the effectiveness of therapy, a comparative hypothesis test was conducted on the patient's WBC and ANC profiles before and after GCSF therapy was administered to each treatment group. The comparative test used was the paired t-test if the data distribution was normal ($p>0.05$). However, the Wilcoxon test was used if the data distribution was abnormal ($p<0.05$).

An unpaired comparative hypothesis test (independent t-test) was conducted to determine whether there was a difference between changes in the patient's WBC and ANC profiles after GCSF therapy was administered between the filgrastim and lenograstim groups. The comparative test used was the independent t-test if the data distribution was normal ($p>0.05$). Still, the Wilcoxon test was used if the data distribution was abnormal ($p<0.05$) (Dahlan, 2009).

Furthermore, to compare cost-effectiveness, a CEA—ACER (average cost-effectiveness ratio) analysis was carried out by measuring the average direct costs, i.e., the total cost of GCSF, compared to the average outcome of increasing WBC and ANC cell levels per mm^3.

3. Results and discussion

During the data collection period from December 2023 to January 2024, at RSUP Dr. Kariadi, 25 patients met the inclusion criteria. Of the 25 samples, 15 patients received filgrastim therapy, and 10 patients received lenograstim therapy. **Table 1** showed a picture of patients having neutropenia based on sex, where the percentage of female patients is more dominant, namely 14 patients (54.94%) compared to 11 male patients (47.06%). Of the 25 patients, there are 19 patients (76%) aged 18–59 years, while six patients (24%) were >60 years old, and no patients are <18 years old.

In this research, all patients (100%) experience neutropenia with a WBC score <4000 cells/ml, while 13 patients (52%) experience severe neutropenia with an ANC score <500 cells/ml, and 12 patients (48%) experienced mild-moderate neutropenia.

Table 1. Patient characteristics

Patient characteristics		Total	Percentage
Sex	Male	11	44
	Female	14	56
Age	< 18 years old	0	0
	18–59 years old	19	76
	> 59 years old	6	24
Total WBC	> 4000 cells/ml	0	0
	< 4000 cells/ml	25	100
Total ANC	Mild (1000–1500 cells/ml)	3	12
	Moderate (500–1000 cells/ml)	9	36
	Severe (<500 cells/ml)	13	52
Colorectal cancer stages	Stadium II	0	0
	Stadium III	8	32
	Stadium IVa	10	40
	Stadium IVb	7	28
	Stadium IV c	0	0
FOLFOX Chemotherapy Cycle	Cycle 1	0	0
	Cycle 2	1	4
	Cycle 3	1	4
	Cycle 4	5	20
	Cycle 5	3	12
	Cycle 6	2	8
	Cycle 7	3	12
	Cycle 8	2	8
	Cycle 9	1	4
	Cycle 10	1	4
	Cycle 11	3	12

Patient characteristics		Total	Percentage
	Cycle 12	3	12
Nutritional Status	Normal	22	88
	Malnutrition	3	12

Table 2 showed the WBC and ANC scores in the group of patients receiving filgrastim therapy. Before the filgrastim therapy, all groups of patients (100%) had WBC scores <4000 cells/ml, while based on the ANC score, there were seven patients (47%) with ANC scores <500 cells/ml, five patients (33%) with ANC scores of 500–1000 cells/ml, and three patients (20%) with ANC scores of 1000–1500 cells/ml. The WBC and ANC scores of patients after receiving the filgrastim therapy all had increased, but there were six patients whose ANC scores were still below the normal score after the lenograstim therapy.

Table 2 WBC and ANC score profile of patients with filgrastim therapy

Before the therapy						After the therapy					
WBC Score	Σ	%	ANC Score	Σ	%	WBC Score	Σ	%	ANC Score	Σ	%
< 4000	15	100	> 1500	0	0	< 4000	4	27	> 1500	9	60
			1000–1500	3	20				1000–1500	4	28
			500–1000	5	33				500–1000	1	6
> 4000	0	0				> 4000	11	73			
			< 500	7	47				< 500	1	6
Total	15	100		15	100		15	100		15	100

Table 3 showed the WBC and ANC scores in the group of patients receiving lenograstim therapy. Before the lenograstim therapy, there were ten patients (100%) with a WBC score of <4000 cells/ml, while based on the ANC score, there were six patients (60%) with an ANC score of <500 cells/ml, four patients (40%) with an ANC value of 500–1000 cells/ml, and no patients with an ANC score of 1000–1500 cells/ml or more than 1500 cells/ml. The WBC and ANC scores of patients after receiving the lenograstim therapy were all above the normal score. However, there were four patients whose ANC scores were still below the normal score after the lenograstim therapy.

In general, both groups of patients with filgrastim and lenograstim therapies experienced an increase in WBC and ANC scores after the therapy was administered. The data obtained were tested for data normality first using the Shapiro–Wilk method and obtained a test of WBC and ANC data distribution in each normal group. To determine whether there was a difference between changes in WBC and ANC scores in each treatment group after receiving the therapy, a statistical test was carried out using the Paired T-test. **Table 4** below showed the analysis results of the two parameters.

Table 3 WBC and ANC scores profile of patients with lenograstim therapy.

Before the therapy						After the therapy					
WBC Score	Σ	%	ANC Score	Σ	%	WBC Score	Σ	%	ANC Score	Σ	%
< 4000	10	100	> 1500	0	0	< 4000	2	20	> 1500	6	60
			1000–1500	0	0				1000–1500	3	30
> 4000	0	0	500–1000	4	40	> 4000	8	80	500–1000	0	0
			< 500	6	60				< 500	1	10
Total	10	100		10	100		10	100		10	100

Table 4 Statistical analysis results of WBC and ANC parameters

Parameter	Filgrastim			Lenograstim		
	Before	After	Sig (p)	Before	After	Sig (p)
WBC Score	2000± 879.1	9553 ± 1962.7	0.002	1980 ± 1003.1	6990 ± 1410	0.003
ANC Score	666 ± 462.1	2304 ± 386	0.002	449 ± 244.8	1556.2 ± 1302.2	0.001

To determine whether there is a difference in the increase in WBC and ANC levels in patients receiving filgrastim and lenograstim therapies, a statistical analysis was conducted on changes in WBC and ANC scores using the independent t-test method. **Table 5** below showed the analysis results of changes in the scores of the two variables.

Table 5 Statistical analysis results of changes in WBC and ANC scores

Parameter	Filgrastim	Lenograstim	Sig (p)
Δ WBC	7553.3 ± 2040.8	5010	0.359
Δ ANC	1637 ± 439.5	1107.2 ± 230	0.365

A total of 15 patients with neutropenia received the filgrastim therapy. Before receiving the filgrastim therapy, the baseline WBC and ANC values of all patients are below normal scores. After the filgrastim therapy, there is a significant increase in WBC and ANC levels ($p<0.05$).

Neutrophils are the main target of GCSF. Exogenous GCSF increases the number of peripheral blood neutrophils in humans by stimulating the expansion of neutrophil precursors and increasing the maturation rate and release of neutrophils into the circulation. GCSF stimulates neutrophil production and mobilizes bone marrow neutrophils and stem cells into the blood. GCSF has also improved the cellular functions of mature neutrophils, including adhesion and phagocytosis (Scotte *et al*., 2024). GCSF can reduce the duration of treatment due to neutropenia. According to study conducted by Utomo *et al*., that the duration of treatment for cancer patients due to febrile neutropenia who were given GCSF decreased by 3 days compared to placebo, namely 5 days (Utomo *et al*., 2020).

Filgrastim is a GCSF analog that works by stimulating proliferation and differentiation by interacting specifically with receptors found on various myeloid stem cells, which will develop into neutrophils. In addition, filgrastim also activates the phagocytic process of mature

neutrophils, prolongs the duration of neutrophils in the blood and directs hematopoietic stem cells to increase their concentration in the peripheral circulation (Scotte *et al.*, 2024).

GCSF consists of a non-glycosylated recombinant form synthesized from *Escherichia coli* (filgrastim) and a glycosylated form synthesized from Chinese hamster ovary cells (lenograstim). The glycosylation process on filgrastim compounds causes modification of chemical properties, such as molecular rigidity, pH, temperature, and higher elastase, resulting in a longer plasma half-life. In addition, the glycosylation process will reduce aggregate formation and increase receptor affinity, leading to increased bioavailability and molecular activity (Ria *et al*., 2010).

A total of 10 neutropenia patients in this study received the lenograstim therapy. Before receiving the lenograstim therapy, the baseline WBC and ANC scores of all patients were below normal values. After undergoing the lenograstim therapy for two days, there was a significant increase in WBC and ANC levels ($p<0.05$).

Various studies have been conducted to prove the effectiveness of lenograstim in patients experiencing febrile neutropenia. These studies show that lenograstim is excellent at reducing the incidence of febrile neutropenia (Cooper *et al.*, 2011). In line with previous studies, the administration of lenograstim in this research showed a significant increase in WBC and neutrophil levels.

Another factor that affects neutropenia is nutritional deficiency (Budiana & Febiani, 2017). Based on the results of the nutritionist assessment, patients having neutropenia after receiving the lenograstim therapy were deficient. Malignancy patients will have nutritional deficiencies caused by several factors, such as lack of food intake due to the influence of side effects of chemotherapy drugs and malabsorption of nutrients in the gastrointestinal tract. A study showed that chemotherapy patients would experience several nutritional deficiencies, such as vitamin A and retinol, vitamin E, vitamin C, beta carotene, selenium, zinc, and B vitamins (Garófolo, 2013).

Analysis of changes in WBC and ANC values was carried out in each treatment group to assess the comparative achievement of filgrastim and lenograstim therapies. The results of statistical tests using the independent t-test test showed no significant difference ($p>0.05$) between changes in WBC values ($p = 0.359$) and ANC ($p = 0.365$) in the group of patients receiving the filgrastim therapy and the group of patients receiving the lenogastim therapy. The results in this research are different from the results of a study by Orciuolo *et al.* in 2011, which stated that episodes of febrile neutropenia were lower in the group of patients who received the lenograstim therapy when compared with the filgrastim. However, a study by Uddin *et al*. (2015)

found that filgrastim biosimilar was as effective as lenograstim for HSCT (hematopoietic stem-cell transplant) in patients with lymphoma. However, mobilization with filgrastim biosimilar was superior to lenograstim in younger MM (multiple myeloma) patients (Uddin *et al*., 2015).

Glycosylation in GCSF will cause changes in its pharmacokinetic profile, thereby increasing its bioavailability and molecular activity. Other studies have shown that glycosylation in GCSF causes inactivation of the elastase enzyme, thereby prolonging the duration of action of GCSF and increasing its effectiveness (Ria *et al.*, 2010). In addition, there was experimental evidence that the bond between sugar and protein (glycosylation) plays a critical role in the activity of neutrophils. Neutrophils mobilized by lenograstim show more mature expression in terms of recognition, adhesion, phagocytosis, and interaction with immunoglobulins (Ria *et al.*, 2010).

The similarity in therapeutic achievement in the filgrastim and lenograstim groups can be caused by various factors, such as differences in cancer stage, chemotherapy cycles received by patients, and nutritional status of patients. Therefore, further research is needed using a larger number of samples, with the same type of disease and severity and the same chemotherapy regimen between treatment groups.

Furthermore, a CEA analysis was conducted to compare cost-effectiveness. A study conducted by Tseng *et al.* suggests that primary prophylaxis with either a short or long-acting GCSF could be considered cost-effective in patients with breast cancer receiving chemotherapies (Tseng *et al*., 2024). A study conducted by Wang *et al.* found that the use of long-acting GCSF agents is more cost-effective than short-acting GCSF agents (Wang *et al*., 2023). However, the widespread use of GCSF agents is still limited because it is associated with high costs or prices (Klastersky *et al*., 2016).

The results of the cost-effectiveness analysis of the two regimens are shown in **Table 6** below. A cost effectiveness analysis was conducted on the total cost components of GCSF given to each treatment group compared to the increase in WBC and ANC parameter values. The analysis method used was CEA because it aims to compare two drugs used for the same indication but with different costs and effectiveness. Assessment of CEA using the ACER method aims to compare the total costs of a program or alternative treatments with clinical outcomes to produce a comparison that represents the costs of each clinical outcome. According to this comparison, we can choose an alternative treatment with lower costs (Lorensia & Doddy, 2016). The ACER value is the cost that needed to increase 1 unit efficacy of the treatment (Citraningtyas

et al., 2018). The cost data used in this research was the total administration of GCSF until the WBC and ANC scores reached normal values (WBC> 4000 cells/ml, ANC> 1500 cells/ml).

The analysis results showed that the use of the filgrastim regimen was considered more cost-effective than the lenograstim. The ACER calculation results in **Table 6** show that, for an increase of 1 cell/ml of WBC value, a cost of Rp24.2 is required for the filgrastim and Rp347 for the lenograstim regimen. Then, for an increase of 1 cell/ml ANC value, it costs Rp111.8 for the filgrastim and Rp1572.5 for the lenograstim regimen. The lower value of ACER and the higher effectiveness mean more cost effective the therapy (Nalang *et al*., 2018). The ICER (incremental cost-effectiveness ratio) calculation was not carried out because the filgrastim and lenograstim regimens were considered equally effective in increasing the patient's WBC and ANC scores.

Table 6 Cost-effectiveness analysis results

Parameter	Filgrastim	Lenograstim	Cost value / outcome (ACER)	
			Filgrastim	Lenograstim
Average total Cost of GCSF	Rp183,143	Rp1,741,051		
Δ WBC	7553.3	5010	Rp24.2	Rp347
Δ ANC	1637	1107.2	Rp111.8	Rp1572.5

This research's limitation is that no baseline data test was conducted because it is preliminary and has a limited number of samples.

4. Conclusion

The results showed that filgrastim and lenograstim therapies were equally effective in increasing patients' WBC and ANC values. However, based on a cost-effectiveness analysis, filgrastim therapy was considered more cost-effective.

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