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# A comparison of the effects of every day and every other day administration of Granulocyte - colony stimulating factor (G-CSF) on the number of leukocyte, platelets, hemoglobin, and pain in patients with breast cancer



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## ABSTRACTS

**Background:** Prophylaxis fever and neutropenia using G-CSF are recommended in most chemotherapy regimens in women with breast cancer. Among common side effects of G-CSF injection, one can refer to skeletal pains. The present study was carried out in order to examine the level of pain and changes in blood cells in two methods of every day and every other day administration of G-CSF.

**Methods:** In the present clinical trial, 186 patients (93 in each group) were considered as the study sample. Ninety-three patients with breast cancer were given G-CSF on a daily basis, and then every other day in the next phase of their chemotherapy, the effect of these two methods on the number of WBC, Hb, PLT, and pain level in the patients were compared.

**Results:** There was no significant difference between the two administration methods regarding the number of white blood cells and platelet of the patients. The mean score of pain in every other day administration of G-CSF was 5.6 while it was 6.6 in the group with a daily administration, and this difference was significantly meaningful ( $p = 0.016$ ). In patients with breast cancer, every other day compared to daily administration of G-CSF did not lead to any difference in the number of white blood cells and platelets.

**Conclusion:** There was no significant difference between the groups received G-CSF on an everyday basis and the one on an every-other-day basis in terms of leukocytopenia. It is recommended that G-CSF is administered on an every-other-day basis

**Keywords:** G-CSF, Prophylaxis, breast, cancer

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## INTRODUCTION

Breast cancer is the most common cancer among women (33% of cases) and the main cause of death from cancer in women of 40-44 years old (20% of cases). By 1985, breast cancer had been the main cause of death among women, surpassed by lung cancer after that year. Over the last few decades, 5-year survival rate of patients with breast cancer has increased 15% and reached about 70%. The rate of cancer incidence differs as many as ten times in different countries. England and Wales have the highest rate of death from breast cancer while South Korea the least. The incidence rate in unindustrialized countries is lower than industrialized countries (except for Japan).<sup>1</sup> The more a woman lives without breast cancer, the lower the risk of developing cancer in her will be. Therefore, the risk of developing breast cancer in a 50-year-old woman is 11% and in a 70-year-old woman is 7%.<sup>1</sup>

The most common site of metastasis include the bones, lung, liver, chest, and brain although there are reports which state that metastatic breast cancer can exist in almost all body organs. Most

women with metastatic disease that are primarily diagnosed with breast cancer and definitely treated usually experience metastatic recurrence. In the USA, about 10% of the patients who had recently been diagnosed with breast cancer pretended to have metastasis.<sup>2</sup>

A common side effect of chemotherapy is a decrease in the number of white blood cells (WBC), which leads to an increase in the risk of developing an infection.<sup>3</sup> In most patients, WBCs retain their initial count immediately after chemotherapy, and there is no need to inject G-CSF. However, in some types of chemotherapy like those with high dose, WBCs take more time to retain their initial count, and using G-CSF can shorten this time and accelerate the increase in the number of WBCs. Therefore, prophylaxis of fever and neutropenia using G-CSF are recommended in most chemotherapy regimens in women with breast cancer.

Pain caused by cancer is an important reason for the low quality of life and resistance against accepting conventional therapies. Recent studies indicate

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that some hematopoietic factors like GM-CSF and G-CFS can alleviate post-operational pain and inflammatory pains through interactions of nerves associated with the tumor, and is one of the most important laboratory mechanisms relevant with applying the effects through metalloproteinases such as MMP9 and TNF $\alpha$ .<sup>4</sup> The aim of breast metastatic cancer treatment is similar to palliative treatments, while a certain cure is an aim at the beginning of the treatment. In both cases, the most effective chemotherapy regimen needs to be used.<sup>5</sup>

Chemotherapy is widely utilized in breast cancer, and it has been indicated that it can improve the patients' survival. On the one hand, chemotherapy due to some side effects leads to a mandatory decrease in the chemotherapy dose received by the patient, and on the other hand, the interval between two chemotherapies rises. Therefore, its palliative or therapeutic effect of the treatment drops.<sup>5</sup>

G-CFS leads to a proliferation of neutrophil cell line and potentially alleviates bone marrow suppression. Thus it can enhance the effectiveness of the therapy. In general, when patients with cancer receive intense and heavy chemotherapy regimens, G-CFS can lead to a decrease in febrile neutropenia and the time of neutropenia.<sup>6</sup> G-CSF is the main regulator of granulopoiesis process, is widely given to patients who undergo chemotherapy, and boosts immature granulocytic cells and reduces the period of neutropenia.

The present study was aimed to compare the effect of G-CFS on the number of WBCs and the level of pain among patients with breast cancer in two methods of every day and every other day administration.

## MATERIALS AND METHODS

In the present clinical trial, 186 patients (93 in each group) were considered as the study sample. Ninety-three patients with breast cancer were given G-CFS on a daily basis, and then every other day

in the next phase of their chemotherapy, the effect of these two methods on the number of WBC, Hb, PLT, and pain level in the patients were compared with chemotherapy, 93 patients with breast cancer were given G-CFS once on a daily basis and once every other day, and the effects of these two methods on the count of WBC, Hb, and PLT and the level of pain among the patients were examined. It should be noted that the level of pain was scored from 0 to 5 based on a McGill questionnaire.

### Inclusion and exclusion criteria:

Patients with breast cancer undergoing chemotherapy and willing to participate in the study and exclusion criteria include: Lack of the patient's tendency to continue the study, Sensitivity to G-CFS, and Causing any type of infection in the patient due to the effect of the administration on the level of leukocytes, hemoglobin, and platelet.

### The method of calculating the sample size and the method of sampling

According to what said above and took into account the dependence of the two groups, the sample size was calculated as 93 individuals based on proportion difference formula in the two dependent groups based on PASS Software.

### Statistical analysis methods

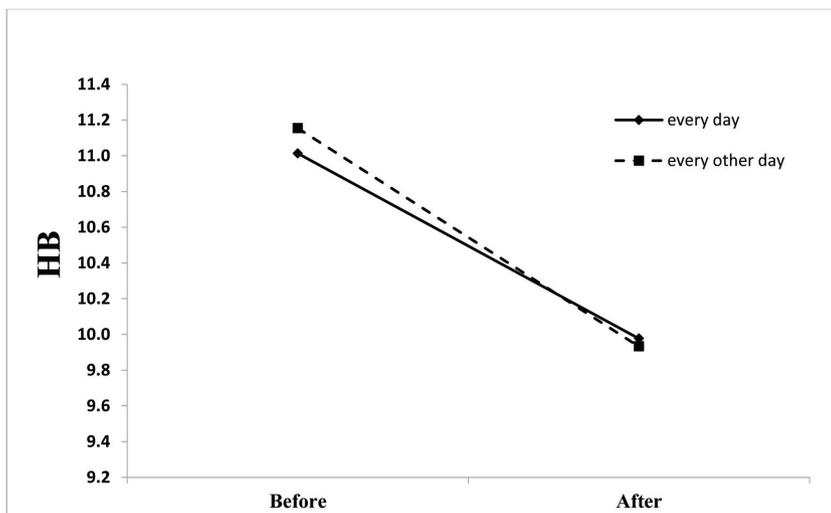
In order to describe the collected data, mean and standard deviation were used for quantitative variables and frequency and percentage for qualitative variables. Data analysis was carried out using methods that deal with the dependence among the data (i.e., paired samples t-test, GEE, mixed model, etc.). All of the analyses were carried out using SPSS Software.

## RESULTS

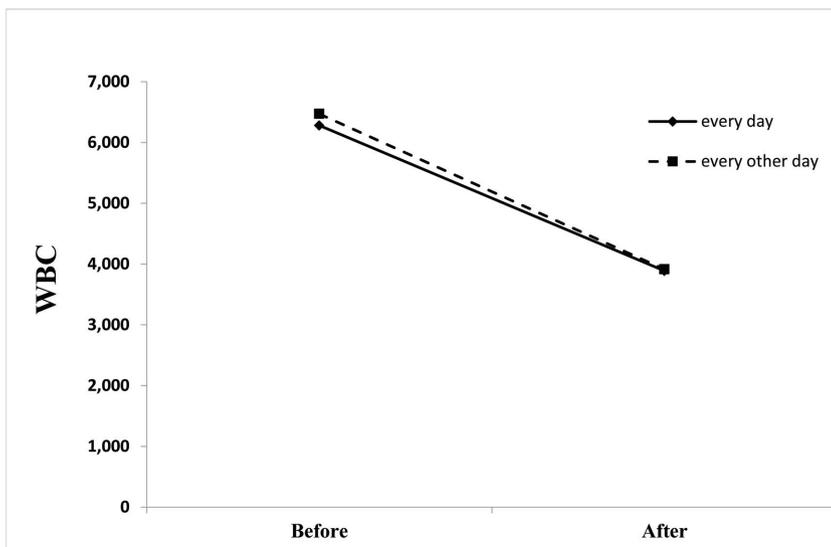
In the present study that was a clinical trial, 186 patients (93 patients in each group) who had

**Table 1** Mixed model analysis results

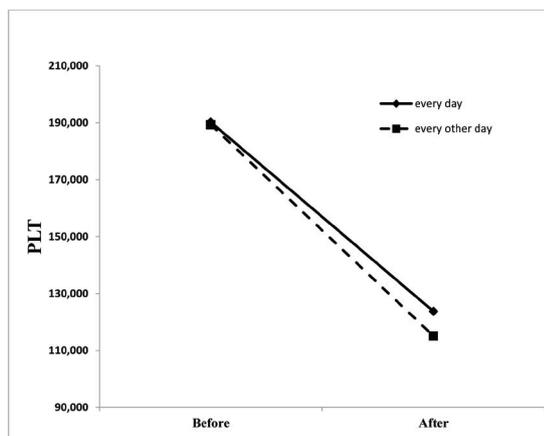
Variables	pain			PLT			WBC			HB		
	p-Value	SE	Coefficient	p-Value	SE	Coefficient	p-Value	SE	Coefficient	p-Value	SE	Coefficient
Constant	<0.001	0.217	7.269	<0.001	6484.304	-62326.9	<0.001	343.934	-2309.62	<0.001	0.124	-1.087
Every other day vs. Every day	0.016	0.315	-0.759	0.058	9410.919	-17843.3	0.823	499.164	-111.662	0.006	0.181	-0.499
Period effect	<0.001	0.315	-1.376	0.353	9410.919	-8736.91	0.722	499.164	-177.619	0.558	0.181	0.106
Carryover effect	0.594	0.578	-0.308	0.178	14895.02	20060.94	0.917	789.855	-81.873	0.058	0.308	0.585



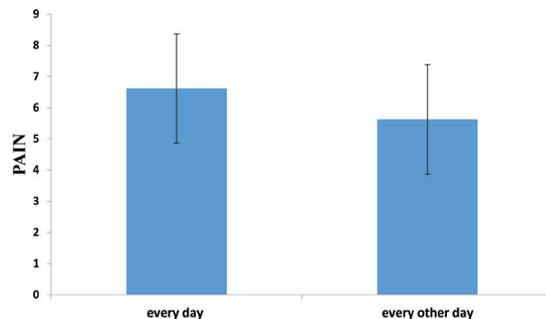
**Figure 1** The average patient hemoglobin (Hb) in every other day administration method compared to the everyday group



**Figure 2** The average patient WBC in every other day administration method compared to the everyday group



**Figure 3** The average patient PLT in every other day administration method compared to the everyday group



**Figure 4** The mean score of pain in every other day administration method compared to the everyday group

the study inclusion criteria were considered as the study sample, and the following results were obtained. The mean age of the study subjects was  $47.2 \pm 6.4$  years."

The results of the present study showed that patients in the every other day administration method experienced a higher level of decrease in average hemoglobin (Hb) compared to the everyday group, such that hemoglobin decreased 1.22% in the every other day group while 1.04% in the everyday group and this difference was statistically significant ( $p = 0.006$ ) (Figure 1).

The results of the present clinical trial showed that a decrease in mean WBC was 2557 and 2394 in the every other day and everyday groups, respectively, and this difference was not statistically significant ( $p = 0.82$ ) (Figure 2).

In this clinical trial, it was indicated that the mean PLT decreased 74222 and 66474 in the every other day group and the everyday group, respectively, and the two groups were not quite significantly different in this regard, but their difference is marginally significant ( $p = 0.058$ ) (Figure 3).

The mean score of pain was 5.6 and 6.6 in the every other day and the everyday groups, respectively. As seen, the patients in the every other day group experienced significantly less pain than the everyday group ( $p = 0.016$ ) (Figure 4).

## DISCUSSION

The present clinical trial study was mainly aimed at comparing the effect of G-CFS on the number of leukocytes, hemoglobin, platelets and the level of pain among 186 patients (93 patients in each group) with breast cancer who had undergone chemotherapy by two methods of every day (ED) and every other day (EOD) G-CFS administration.

The results of the present clinical trial showed that compared to every other day administration, everyday administration of G-CFS did not have a significant effect on the number of leukocytes in the

two groups, such that decrease in mean WBC was 2557 and 2394 in the every other day and everyday groups, respectively ( $p = 0.82$ ). This shows that everyday administration of G-CFS in these patients is not as effective as its every-other-day administration and cannot remarkably prevent a drop in WBC or increase it. This finding is in line with the results of other studies.<sup>7,8,9</sup>

A study was carried out by Ronald de Wit et al. over 1993-1995 on 36 patients with metastatic cancer or Stage IIIA and Stage IIIB who were given a treatment regimen including doxorubicin of 75 mg/m<sup>2</sup> and cyclophosphamide of 1000 mg/m<sup>2</sup> once in 3 weeks. Eighteen patients received G-CFS before and after chemotherapy, and the other 18 patients received it only after chemotherapy. One of the groups that subcutaneously received 5 µg/kg G-CFS before chemotherapy received it after chemotherapy, too. The results showed that occurrence of 4<sup>th</sup>-grade neutropenia and leukocytes in the group that received G-CFS before and after chemotherapy was 74% while it was 66% in the group that received it only after chemotherapy. This difference; however, was not significant ( $p = 0.21$ ).<sup>10</sup>

In their study, Paola Papaldo et al. focused on 506 patients with breast cancer stages I and II over 1991-1994. In that study, the occurrence rate of neutropenia grade 3 and 4 and febrile neutropenia were significantly higher in the control group (without receiving G-CFS) than the G-CFS ( $P$ -value was 0.00001 and 0.004, respectively). However, there was no significant difference between the 5 therapeutic groups in terms of supportive effects of G-CFS on bone marrow.<sup>5</sup>

These results indicate this fact that G-CFS leads to prevention of leukocytopenia. However, its higher doses compared to lower doses cannot lead to a significant increase in the level of WBC in the patients under chemotherapy.

In the present study, it was indicated that decrease in mean hemoglobin (Hb) was higher in the method of G-CFS administration on EOD basis than ED basis. The average decrease in Hb was 1.22 in EOD method and 1.04 in ED method, and this difference was statistically significant ( $p = 0.006$ ). This finding is in contrast with those of other studies.

In the study carried out by Ronald et al., there was no significant difference between Hb means in the group that had received G-CFS before and after chemotherapy and the group that had received it only after chemotherapy.<sup>10</sup>

Research results show that GSCF promotes erythropoiesis.<sup>11</sup> It also enhances the effect of erythropoietin. In patients with cancer, it has been indicated that G-CFS does not lead to a negative effect

on the level of hemoglobin during and after chemotherapy.<sup>12</sup> On the other hand, the results of some studies have indicated that a high dose of G-CFS leads to inhibition of iridoid cell line.<sup>6</sup> Therefore, it can be concluded that the effect of G-CFS on the level of Hb depends on its dose, and in normal doses, it can lead to hematopoiesis process and prevent Hb decrease. This effect is obvious in clinical trials, and on the other hand, a decrease in Hb in the group receiving G-CFS on EOD basis can also be attributed to chemotherapy although this effect of G-CFS requires more comprehensive evaluations. On the other hand, higher doses of G-CFS can lead to inhibition of erythropoiesis, which is reported in the study carried out by Papaldo et al.,<sup>7</sup>

During the current clinical trial, it was concluded that the level of platelets in the ED group was higher than the EOD group, although this difference was not quite significant, it was marginally significant ( $p = 0.058$ ). This finding is in line with those of other studies. A study by Ronald et al. reported that the occurrence rate of thrombocytopenia in the group receiving G-CFS before and after chemotherapy was much higher than the group that received G-CFS only after chemotherapy (54% vs. 6%,  $p < 0.0001$ ). In explaining this phenomenon, Ronald et al. stated that administration of G-CFS during chemotherapy led to an intensification of the myelotoxic effect of therapeutic chemicals in platelet production process.<sup>10</sup> Papaldo et al. also explained that occurrence rate of thrombocytopenia in the group receiving G-CFS was higher than the control group, but this difference was not statistically significant (11% vs. 7%,  $p = 0.0112$ ).<sup>5</sup>

Therefore, as it was specified, these studies and the present study, G-CFS led to a decrease in the number of platelets in individuals who had undergone chemotherapy. On the one hand, this phenomenon can be as a result of the intensification of myelotoxic effect on the production process of platelets, and on the other hand, it can be caused by the neutrophil inductive effect of G-CFS. Although this effect in the present study and the study carried out by Papado et al., had a larger sample than the study conducted by Ronald et al., this difference was not statistically significant.

The results of the present clinical trial showed that the patients received G-CFS on an everyday basis experienced a higher level of skeletal pain than those receiving it on an every-other-day basis, and this difference was significant ( $p = 0.016$ ). This finding was in agreement with those of similar studies. As was seen in Paolo Papaldo et al., the occurrence rate of skeletal pain was higher in the ED group (therapeutic programs 1 and 3) than the therapeutic G-CFS group 5 (53% vs. 26%,  $p = 0.0101$ ).<sup>7</sup> As it was

concluded, skeletal pain as the side effect of G-CFS caused by stimulation of bone marrow to produce in the therapeutic groups that received more G-CFS was remarkably significant.

## CONCLUSION

The results of the present study showed that there was no significant difference between the group received G-CFS on an everyday basis and the one on an every-other-day basis in terms of leukocytopenia. On the other hand, thrombocytopenia in the EOD group occurred more, but it was not statistically significant. The effects of G-CFS and the effect of everyday administration of G-CFS on the level of hemoglobin requires further and more comprehensive studies. In addition, everyday G-CFS administration is accompanied with more skeletal pains, and it is recommended that G-CFS is administered on an every-other-day basis.

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