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Comparison of the Efficacy of Biosimilar G-CSF Molecules in the Prevention of Chemotherapy-Induced Neutropenia in Breast Cancer Patients Receiving Adjuvant Docetaxel-Cyclophosphamide Combination Treatment

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ABSTRACT

Objective: Adjuvant chemotherapy is one of the most crucial factors in reducing recurrence risk in early-stage breast cancer. The docetaxel-cyclophosphamide (TC) protocol is among the most frequently used regimens in adjuvant therapy. With a risk of febrile neutropenia exceeding 20% during this treatment, guidelines recommend the prophylactic use of granulocyte stimulating factors (G-CSF). Zarzio® and Fraven®, both hematopoietic growth factors, are currently available in the market, with Zarzio® being the first biosimilar approved by the Food and Drug Administration, while Fraven® is used exclusively in our country.

Material and Methods: In our study, we aimed to investigate whether there are differences between these two biosimilars, Zarzio® and Fraven®, in terms of efficacy and tolerability in patients with breast cancer who received adjuvant TC protocol chemotherapy. Patients diagnosed with early-stage breast cancer who underwent adjuvant TC combination therapy were included in the study. Data on the G-CSF molecules used by patients and their demographic information were acquired retrospectively through the hospital database system. Outcome measures included the presence of post-treatment neutropenic fever and the incidence of dose reduction or delay due to neutropenia. Patients aged between 18-70 years were included in the study, while those with prior chemotherapy history, those not receiving G-CSF prophylaxis, or those with known chronic hematologic diseases were excluded.

Results: Of the 66 patients included in our study, a total of 264 cycles of G-CSF treatment were administered, with 85 cycles (33%) using Zarzio® (median 5 doses, range: 3-5) and 179 cycles (67%) using Fraven® (median 5 doses, range: 3-7). Among patients using Fraven®, dose delays occurred in 5 cases due to neutropenia, whereas among patients using Zarzio®, 3 cases experienced dose delays (p=0.106). There were five cases of neutropenic fever in our study, with four occurring in patients prophylactically using Fraven® and one in a patient using Zarzio® (p=0.347).

Conclusion: Severe neutropenia is one of the most feared side effects of adjuvant chemotherapy in early-stage breast cancer. Our study is noteworthy as it is the first to investigate the efficacy and tolerability of the biosimilars Zarzio® and Fraven®, and we found no significant differences between the two biosimilars in terms of neutropenia development, incidence of neutropenic fever, or dose reduction or delay due to neutropenia.

Keywords: Febrile neutropenia; filgrastim; biosimilar; breast cancer

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INTRODUCTION

Neutropenia and febrile neutropenia are serious complications of cytotoxic chemotherapy that increase patient morbidity and mortality as well as treatment costs. They are also significant dose-limiting toxicities particularly in patients undergoing curative treatment. Because of these risks, prophylaxis with granulocyte stimulating factors (G-CSF) is recommended in regimens with over 20% risk of febrile neutropenia or in regimens with 10-20% risk of febrile neutropenia and having other risk factors for neutropenia, which is prevented by neutropenia by mobilizing peripheral blood progenitor cells.[1] Docetaxel-cyclophosphamide (TC) is a common adjuvant treatment regimen for early stage human epithelial growth factor 2 (HER2) negative breast cancer, which requires prophylactic G-CSF use due to the high risk of febrile neutropenia.[2,3]

After the patent for the reference molecule expired, biosimilar molecules were approved to increase the availability of recombinant human G-CSF. Biosimilar drugs are not identical to the reference molecule and might differ in properties that affect the final form of proteins such as amino acid sequence and glycosylation; however, they are highly similar to the reference biological product and have the same biological activity, efficacy, and safety.[4] Filgrastim-sdnz (Zarzio®) became the first biosimilar approved by the Food and Drug Administration in the United States in 2015. Since then, many biosimilars have become available in numerous countries, and another biosimilar, Fraven®, which is only available in Türkiye, was approved in 2020 after structural similarities to the reference molecule were demonstrated in a study.[5] However, there is no published study evaluating the effectiveness of Fraven® in cancer patients.

The aim of this study was to evaluate the effectiveness of Zarzio and Fraven treatments in the patient group using the TC protocol in the adjuvant treatment of breast cancer. The primary aim of the study was to evaluate the effect of both biosimilars on the incidence of neutropenic fever. The secondary aims of the study were dose reductions, dose delays, and relative dose intensity (RDI).

MATERIAL AND METHODS

Between January and December 2023, the study included patients receiving chemotherapy at Ankara Etlik City Hospital's medical oncology outpatient clinics. The Ankara Etlik City Hospital Ethical Committee approved the study (approval number: AEŞH-EK1-2023-776, date: 10.01.2024). The study was conducted according to the Helsinki Declaration principles. The study included HER2-negative breast cancer patients who received an adjuvant TC regimen and were given Zarzio® or Fraven® as primary prophylaxis for chemotherapy-induced neutropenia. Patients aged 18 to 70 were included in the study. The exclusion criteria included being older than 70 years, prior chemotherapy exposure, including neoadjuvant therapy, kidney and/or liver failure, septicemia, and a secondary hematological disease. The primary end point of the study was neutropenic fever and the secondary endpoints were dose reductions, dose delays and RDI.

Docetaxel was administered at 75 mg/m^2 and cyclophosphamide at 600 mg/m^2, both in 21-day cycles, in accordance with the standard TC protocol. Patients who had completed four cycles of TC combination therapy were included in the study. G-CSF biosimilars were administered on the second day of each chemotherapy cycle. In our cancer center, patients weighing less than 60 kilograms received 30 mU, while those weighing more than 60 kilograms received 48 mU. The study team obtained patients' information retrospectively from the hospital database system, including the prescribed G-CSF biosimilar, neutropenia rate, febrile neutropenia incidence, planned and received doses of each chemotherapy drug, dose reductions, and delays. At the conclusion of all planned chemotherapy cycles, the RDI was calculated by dividing the administered dose of each chemotherapy drug by the scheduled dose.

Statistical Analysis

Statistical analyses were performed using SPSS version 24 after the completion of normality tests. Categorical variables were evaluated using chi-square and Fisher's exact tests, and continuous variables were evaluated using the Mann-Whitney U test. P-values <0.05 were considered statistically significant.

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RESULTS

The study enrolled 66 patients (65 female) who had received 264 cycles of docetaxel and cyclophosphamide. Fifty-nine (88.4%) of the patients were under the age of 65. All patients had positive estrogen receptors, while 10 (or 15.2%) had negative progesterone receptors. The patient demographics are shown in Table 1.

The patients received a total of 264 cycles of G-CSF treatment: 85 (33%) were Zarzio (median 5 cycles, minimum-maximum: 3-5), and 179 (67%) were Fraven (median 5 cycles, minimum-maximum: 3-7). Dose delays were used in eight (3%) patients, due to neutropenia, three (3.5%) in the Zarzio group and five (2.7%) in the Fraven group (p=0.106). Five patients experienced febrile neutropenia, one 1.17% in the Zarzio

group and four 2.2% in the Fraven group (p=0.347). In the Zarzio group, the only patient who experienced febrile neutropenia encountered the incident after the fourth cycle with the use of 48 mU for 3 days. In the Fraven group, one patient experienced febrile neutropenia in the second cycle with the use of 30 mU for 3 days, and a second patient experienced febrile neutropenia in the third cycle with the use of 30 mU for 3 days. In the other two patients, febrile neutropenia occurred in the fourth cycle, one with the use of 30 mU for 3 days and the other one with 48 mU for 3 days. All patients were hospitalized for the treatment of febrile neutropenia, and no deaths occurred.

Cyclophosphamide doses were reduced in three patients (median RDI 100%, range: 80-100%), while docetaxel doses were reduced in seven patients (median RDI 100%, range: 75-100%). There was no statistically significant difference between the two biosimilars in terms of febrile neutropenia, neutropenia-related dose delays, or neutropenia-induced dose reductions. The incidence of febrile neutropenia and dose delays are summarized in Table 2.

DISCUSSION

To our knowledge, this is the first study to compare the clinical efficacy of the filgrastim biosimilars Fraven® and Zarzio®. Although numerically more neutropenic fever was detected in the patient group receiving Fraven® in our study, no statistically significant difference was found between Fraven® and Zarzio® (Table 3).

Patients treated with the adjuvant TC protocol for early-stage breast cancer were chosen to assess the efficacy of these biologic products in a homogeneous cohort. The TC combination therapy is considered a high-risk febrile neutropenia protocol in which the guidelines recommend using filgrastim as primary prophylaxis, and the early-stage patient group is thought to be more homogeneous than the metastatic patient group.[2] In previous studies, the TC protocol reportedly had a 5% incidence of febrile neutropenia and a 51% incidence of grade 4 neutropenia.[6] A meta-analysis reported a febrile neutropenia incidence of 29% in the absence of G-CSF prophylaxis.[7] In a study conducted by Do et al.[8] on patients diagnosed with early breast cancer, the frequency of chemotherapy-related febrile neutropenia in the TC protocol was reported to be 4-69%, and G-CSF prophylaxis was found to reduce the risk of febrile neutropenia by 92.3%. In another study, the frequency of febrile neutropenia was reported to be 6.6% in patients who received primary prophylaxis with filgrastim or pegfilgrastim in the TC protocol, versus 31.3% in those who did not receive primary prophylaxis. In line with our findings, no febrile neutropenia-related deaths were observed in any patient.[9] One of the most important reasons why no deaths from febrile neutropenia were reported in our study could be that the majority of the patients were under the age of 65 and had adequate bone marrow reserve.

TABLE 1: Patient characteristics.

Group	Number (n)	%
Age		
<65	59	89.4%
>65	7	10.6%
ECOG performance status		
0	49	74.2%
1	17	25.8%
Menopause		
Premenopausal	29	44.6%
Postmenopausal	36	55.4%
Body mass index (kg/m^2)		
<25	21	32%
≥25	45	68%
Body surface area (m^2)		
1-1.5 m^2	19	29%
1.5-2 m^2	35	53%
≥2 m^2	12	18%
Stage		
1	30	45.5%
2	36	54.5%
Grade		
1	6	9.4%
2	37	57.8%
3	21	32.8%
Estrogen receptor status		
Negative	0	0%
1-10	1	1.5%
>10	65	98.5%
Progesterone receptor status		
Negative	10	15.2%
1-10	10	15.2%
>10	46	69.7%
HER2 status		
Negative	35	53%
Low	31	47%
Positive	0	0%
Number of cycles G-CSF used		
Zarzio	85	33%
Fraven	179	67%

G-CSF: Granulocyte stimulating factors; HER2: Human epidermal growth factor receptor 2; ECOG: Eastern Cooperative Oncology Group.

TABLE 2: Patient characteristics according to G-CSF cycles.						
	Total		Zarzio		Fraven	
			Number (n)	%	Number (n)	%
Age						
<65	236	89.4%	75	90%	160	89%
>65	28	10.6%	8	10%	19	11%
ECOG performance status						
0	196	74.2%	61	71%	134	75%
1	58	25.8%	24	29%	43	25%
Menopause						
Premenopausal	116	44.6%	34	40%	87	49%
Postmenopausal	148	55.4%	51	60%	92	51%
Body mass index (kg/m^2)						
<25	84	32%	19	34%	64	31%
≥25	180	68%	56	66%	123	69%
Body surface area (m^2)						
1-1.5 m^2	76	29%	17	19%	59	33%
1.5-2 m^2	140	53%	43	51%	96	54%
≥2 m^2	48	18%	25	30%	24	13%
Stage						
1	120	45.5%				
2	144	54.5%				
Grade						
1	32	9.4%	7	8%	17	15%
2	148	57.8%	49	57%	98	55%
3	84	32.8%	29	35%	54	30%
Estrogen receptor status						
Negative	0	0%	0	0%	0	0%
1-10	4	1.5%	2	2%	2	1%
>10	260	98.5%	83	98%	177	99%
Progesterone receptor status						
Negative	40	15.2%	10	12%	30	18%
1-10	40	15.2%	15	18%	24	13%
>10	184	69.7%	60	70%	123	69%

G-CSF: Granulocyte stimulating factors; ECOG: Eastern Cooperative Oncology Group.

TABLE 3: Summary of febrile neutropenia incidance and dose delays between the G-CSF biosimilars.			
	Fraven	Zarzio	p value
Number of cycles used	179 (67%)	85 (33%)	
Dose delays	5 (2.7%)	3 (3.5%)	0.106
Febrile neutropenia	4 (2.2%)	1 (1.1%)	0.347

G-CSF: Granulocyte stimulating factors.

Filgrastim biosimilars are available in Türkiye, where they are used as a primary prophylaxis. As far as we know, there has been no study on the safety and effectiveness of Fraven®, a biosimilar, whereas many studies have been conducted on the effectiveness and safety profile of Zarzio®, which is used in Europe. In a meta-analysis, the incidence of febrile neutropenia was found to be 2.2% in patients receiving Zarzio® prophylaxis, while the incidence of grade 4 neutropenia was 8.5%.[10] In our study, febrile neutropenia occurred in 1.17% of patients who took Zarzio®. Another study looked at patients who received Zarzio® prophylaxis and docetaxel-based chemotherapy and found that the frequency of febrile neutropenia was 7.2%.[11]

In our study, there was no statistical difference between the two biosimilars in terms of febrile neutropenia, severe neutropenia, neutropenia-related hospitalizations, neutropenia-related dose delays, and RDI.

Study Limitations

There are several restrictions on our study. The main limitation of the research is that it was carried out retrospectively and in a single center. The lack of a large patient group and the fact that patients receive various biosimilars during different cycles are two more limitations. As a result of the study's retrospective design, statistical analysis was done cycle by cycle because not every patient received the same biosimilar treatment per cycle. On the other hand, the strength of our study is that it is the first to assess the efficacy of G-CSF molecules, which are widely used in routine oncology practice, in a homogeneous patient population.

CONCLUSION

According to our findings, both biosimilar drugs Fraven® and Zarzio® are effective for the primary prevention of chemotherapy-induced neutropenia in breast cancer patients. More prospective trials are needed to validate the efficacy and safety of the G-CSF biosimilar Fraven®.

Ethics

Ethics Committee Approval: The Ankara Etlik City Hospital Ethical Committee approved the study (approval number: AEŞH-EK1-2023-776, date: 10.01.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.K.K., Ö.B.Ç.Ö., O.S., Design: E.K.K., O.S., Data Collection or Processing: E.K.K., Analysis or Interpretation: E.K.K., Ö.B.Ç.Ö., O.S., Literature Search: E.K.K., O.S., Writing: E.K.K., Ö.B.Ç.Ö., O.S.

Conflict of Interest: No conflict of interest was declared by the authors.

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REFERENCES

1. Krendyukov A, Schiestl M, Höbel N, Aapro M. Clinical equivalence with G-CSF biosimilars: methodologic approach in a (neo) adjuvant setting in non-metastatic breast cancer. Support Care Cancer. 2018;26(1):33-40. [Crossref] [PubMed] [PMC]
2. Kosaka Y, Rai Y, Masuda N, et al. Phase III placebo-controlled, double-blind, randomized trial of pegfilgrastim to reduce the risk of febrile neutropenia in breast cancer patients receiving docetaxel/cyclophosphamide chemotherapy. Support Care Cancer. 2015;23(4):1137-1143. [Crossref] [PubMed] [PMC]
3. Network, N.C.C. Hematopoietic Growth Factor (v1.2025). 07.01.2025]; Available from: [Crossref]
4. Tsuruta LR, Lopes dos Santos M, Moro AM. Biosimilars advancements: moving on to the future. Biotechnol Prog. 2015;31(5):1139-1149. [Crossref] [PubMed] [PMC]
5. Bor Tekdemir Z, Seckin AI, Kacar T, Yilmaz E, Bekiroglu S. Evaluation of structural, biological, and functional similarity of biosimilar granulocyte colony stimulating factor to its reference product. Pharm Res. 2020;37(11):215. [Crossref] [PubMed]
6. Jones SE, Savin MA, Holmes FA, et al L. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol. 2006;24(34):5381-5387. Erratum in: J Clin Oncol. 2007;25(13):1819. [Crossref] [PubMed]
7. Younis T, Rayson D, Thompson K. Primary G-CSF prophylaxis for adjuvant TC or FEC-D chemotherapy outside of clinical trial settings: a systematic review and meta-analysis. Support Care Cancer. 2012;20(10):2523-2530. [Crossref] [PubMed]
8. Do T, Medhekar R, Bhat R, Chen H, Niravath P, Trivedi MV. The risk of febrile neutropenia and need for G-CSF primary prophylaxis with the docetaxel and cyclophosphamide regimen in early-stage breast cancer patients: a meta-analysis. Breast Cancer Res Treat. 2015;153(3):591-597. [Crossref] [PubMed]
9. Fernandes R, Mazzarello S, Stober C, et al. Optimal primary febrile neutropenia prophylaxis for patients receiving docetaxel-cyclophosphamide chemotherapy for breast cancer: a systematic review. Breast Cancer Res Treat. 2017;161(1):1-10. [Crossref] [PubMed]
10. Gascón P, Tesch H, Verpoort K, et al. Clinical experience with Zarzio® in Europe: what have we learned? Support Care Cancer. 2013;21(10):2925-2932. [Crossref] [PubMed] [PMC]
11. Harbeck N, Gascón P, Krendyukov A, Hoebel N, Gattu S, Blackwell K. Safety profile of biosimilar filgrastim (zarzio/zarxio): a combined analysis of phase iii studies. Oncologist. 2018;23(4):403-409. [Crossref] [PubMed] [PMC]