

Evaluation of a biosimilar granulocyte colony-stimulating factor (filgrastim XM02) for peripheral blood stem cell mobilization and transplantation: a single center experience in Japan

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Background: Biosimilar granulocyte colony-stimulating factor (G-CSF) has recently been introduced into clinical practice. G-CSFs are used to mobilize CD34⁺ cells and accelerate engraftment after transplantation. However, in Asia, particularly in Japan, data for peripheral blood stem cell (PBSC) mobilization by this biosimilar G-CSF are currently lacking. Therefore, the clinical efficacy and safety of biosimilar G-CSF for hematopoietic stem cell transplantation needs to be evaluated in a Japanese context.

Materials and methods: The subjects included two groups of patients with malignant lymphoma and multiple myeloma. All patients received chemotherapy priming for the mobilization of PBSCs. All patients were treated with chemotherapy followed by the administration of either the biosimilar G-CSF, filgrastim XM02 (FBNK), or the originators, filgrastim, or lenograstim.

Results: There were no significant differences among FBNK, filgrastim, and lenograstim treatments in the numbers of CD34⁺ cells in harvested PBSCs, the scores for granulocyte/macrophage colony forming units, or for malignant lymphoma and multiple myeloma patients evaluated as separate or combined cohorts. In addition, there were no significant differences in safety, side effects, complications, or the time to engraftment after autologous hematopoietic stem cell transplantation.

Conclusion: Biosimilar FBNK shows the same efficacy and safety as originator G-CSFs for facilitating bone marrow recovery in Japanese malignant lymphoma and multiple myeloma patients undergoing stem cell transplantation. In addition, it is less expensive than the originators, reducing hospitalization costs.

Keywords: G-CSF, biosimilar, peripheral blood stem cell, hematological malignancy, autologous hematopoietic stem cell transplantation

Introduction

Transplantation of mobilized peripheral blood stem cells (PBSCs) is used to facilitate hematologic recovery after high-dose chemotherapy.^{1,2} Although several methods for mobilization of PBSCs have been described,^{3–5} leukapheresis is a commonly used collection procedure. PBSC yield is enhanced if collection is performed at the time of recovery from chemotherapy, and while patients are receiving treatment with granulocyte colony-stimulating factors (G-CSFs).^{5,6}

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Recently, biosimilar G-CSF products have been introduced to the market. Some trials have revealed their noninferiority for treatment of neutropenia during chemotherapy, compared with the originator.^{7–10} The US Food and Drug Administration describes biosimilars as highly similar to a previously approved biological product, known as the biological reference product, and as having been shown to have no clinically meaningful differences from the reference product. Furthermore, published data from prospective randomized and retrospective studies on the use of biosimilar filgrastim for PBSC mobilization in an autologous setting suggest a substantially similar efficacy and safety in comparison with the originator.^{11–21} However, in Asia, particularly in Japan, there is currently a lack of data for PBSC mobilization by biosimilar G-CSF. Therefore, evaluation in a Japanese context is needed to assess the clinical efficacy and safety of biosimilar G-CSF for hematopoietic stem cell transplantation, including autologous stem cell transplantation (ASCT). Filgrastim BS-NK (FBNK) (Nippon Kayaku Co., Ltd., Tokyo, Japan) is a genetically modified biosimilar G-CSF drug and is the same as Tevagrastim® (XM02).¹¹ The production and sale of FBNK was approved in Japan in February, 2013. In this study, we evaluated the efficacy of FBNK compared

with the originators for peripheral blood cell mobilization and transplantation.

Materials and methods

Study subjects

The subjects included two groups, treated with biosimilar or originator G-CSF. 1) Biosimilar group: from July 2014 to October 2015, 14 consecutive patients affected by malignant lymphoma (ML) and multiple myeloma (MM) were scheduled for collection of PBSCs for ASCT, after induction chemotherapy. None of the patients had previously received any mobilization therapy. 2) Originator group: 57 consecutive patients who underwent the same procedure between December 2006 and July 2013 were enrolled. The originator G-CSF was filgrastim for 34 patients and lenograstim for 23 patients.

The study protocol was approved by Institutional Review Board in Kansai Medical University and written informed consent was obtained from each patient. Patients' characteristics and underlying diseases are shown in Table 1.

PBSC harvest

For mobilization of PBSCs, all patients received chemotherapy priming consisting of various regimens (Table 1).

Table 1 Patient demographics and indications for stem cell harvest

		FBNK	Filgrastim	Lenograstim	P-value
N		12	34	23	
Sex	M	7 (58%)	17 (50%)	15 (65%)	0.510
	F	5 (42%)	17 (50%)	8 (35%)	
Age (range)		55 (23–66)	58 (30–72)	56 (28–69)	0.764
Disease	ML (NHL or HL)	10 (83%)	27 (79%)	19 (83%)	0.656
	MM	2 (17%)	7 (21%)	3 (13%)	
	APL	0	0	1 (4%)	
BM involvement (ML)		3 (25%)	12 (35%)	11 (47%)	0.425
	I	5 (41%)	17 (50%)	12 (52%)	
	2	7 (58%)	16 (47%)	9 (39%)	
No of previous regimens	3	0	1 (2%)	1 (4%)	0.929
	>4	0	0	1 (4%)	
	mean (range)	1.58 (1–3)	1.52 (1–3)	1.78 (1–8)	
Mobilization regimen	ML (R)CHOP	4 (33%)	14 (41%)	9 (39%)	
	CHASE	0	1 (3%)	1 (4%)	
	DeVIC	0	3 (9%)	1 (4%)	
	ESHAP	5 (42%)	4 (12%)	4 (17%)	
	ICE/IVAC	1 (8%)	0	0	
	CY	0	2 (6%)	1 (4%)	
	ETP	0	1 (3%)	3 (13%)	
	G-CSF	0	1 (3%)	0	
	MM CY	2 (17%)	7 (21%)	3 (9%)	
No of aphereses	I	9 (75%)	17 (50%)	12 (52%)	
	2	3 (25%)	17 (50%)	7 (30%)	
	3	0	0	4 (17%)	

Note: Data presented as n (%) of total numbers.

Abbreviations: HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; ML, malignant lymphoma; MM, multiple myeloma; G-CSF, granulocyte colony-stimulating factor; M, male; F, female; FBNK, filgrastim BS-NK; CY, cyclophosphamide; (R)CHOP, (rituximab) cyclophosphamide, adriamycin, vincristine, prednisolone; CHASE, dexamethasone, cyclophosphamide, Ara-C, etoposide; DeVIC, dexamethasone, etoposide, ifosfamide, carboplatin; ESHAP, etoposide, steroids, cytarabine, cisplatin; IVAC, ifosfamide, etoposide, high-dose cytarabine; ETP, etoposide; ICE; ifosfamide, carboplatin; etoposide.

PBSCs from patients with ML were either harvested after cyclophosphamide and G-CSF treatment, or following a cycle of chemotherapy including rituximab, ifosfamide, etoposide, or cytarabin. The patients with MM were primed with cyclophosphamide and G-CSF. All patients were treated with chemotherapy followed by the administration of FBNK, filgrastim, or lenograstim (5 µg/kg). Leukapheresis was performed with a cell separator (COBE Spectra, Gambro K.K., Tokyo, Japan). The procedure was commenced when the white blood cell count recovered to $1 \times 10^9/\text{L}$, and continued until the number of harvested mononuclear cells exceeded $3 \times 10^8/\text{kg}$ body weight. A total blood volume of 10 L was processed in each apheresis session. The apheresis product was enriched for mononuclear cells, cryopreserved in 6% hydroxyethyl starch, 5% dimethylsulfoxide, and 4% human albumin, and then stored at -80°C .

CD34 analysis

A sample of each leukapheresis product was analyzed according to the method in our previous reports.^{22,23} All samples were washed to remove platelets and were stained with an anti-CD34 monoclonal antibody (QBEND-10; Immunotech, Marseille, France). After staining, the erythrocytes were lysed with ammonium chloride. Flow cytometric analysis was performed using an Epics XLMCL (Beckman Coulter, Brea, CA, USA). It is very difficult to predict the quantity of CD34⁺ cells collected from patients or donors, because the collection efficiency of CD34⁺ cells differs between individuals. Therefore, we counted the numbers of CD34⁺ cells used, with 65,500 cells being analyzed per sample, according to previous reports.^{24,25} After gating for forward and right scatter, a second gate was drawn around the CD34⁺ lower right scatter population to determine the percentage of hematopoietic progenitors corrected for the control. The target dose of PBSCs to collect was $>2 \times 10^6$ CD34⁺ cells/kg for patients affected by ML, and $>4 \times 10^6$ CD34⁺ cells/kg for patients affected by MM.

Colony forming assay

Colony forming cells were assayed with methyl cellulose as the support medium. Mononuclear cells (2×10^5) were cultured in triplicate in semisolid medium (0.8% methylcellulose in α -medium) supplemented with 10 ng/ml recombinant G-CSF, 10 ng/mL recombinant human granulocyte/macrophage-CSF, 100 IU/mL recombinant human interleukin-3, 2 U/mL recombinant human erythropoietin, and 10% placental conditioned medium as a source of CSF. Culture plates were incubated for 14 days at 37°C in a humidified

atmosphere (5% CO_2 in air) and granulocyte/macrophage colony forming units (CFU-GM) were counted under an inverted microscope.

ASCT

The choice of conditioning regimen was based on the patient's diagnosis (Table 1). On day 0, all patients received an infusion of previously cryopreserved autologous PBSCs. Administration of recombinant human G-CSF (biosimilar or originator) was started on day 5 after the PBSC infusion, at a daily dose of 5 µg/kg administered subcutaneously, except for some patients for whom support therapy was anticipated because of their indications. To evaluate the impact of G-CSF on the ASCT, we calculated the median times to leucocyte engraftment, defined as an absolute neutrophil count of $>0.5 \times 10^9/\text{L}$ on the first 3 consecutive days, and to platelet recovery, defined as a platelet count of $>20 \times 10^9/\text{L}$ for 2 consecutive days without platelet transfusions.

Statistics

ML and MM patients were evaluated both as separate cohorts, and combined into a single cohort. Data were recorded as mean \pm SD and were analyzed as appropriate. Welch's *t*-test was used for the comparison of data for each case before and after G-CSF treatment. Between-group comparisons were analyzed using Scheffe's test. All analyses were performed using the StatFlex program, version 6 (Artec Inc., Osaka, Japan).

Results

Figure 1 shows the change in leukocyte numbers before and after PBSC harvest. The numbers of all leukocytes, neutrophils, and monocytes peaked on day 5 after G-CSF treatment. There were no significant differences among the FBNK, filgrastim, and lenograstim groups.

Different parameters to characterize the yield and composition of the grafted cells are displayed in Figure 2 as dot plots. The upper three graphs show the total CD34⁺ cell numbers, the CD34⁺ cells/kg and the CFU-GM scores for all patients. The lower graphs show the CD34⁺ cells/kg and the CFU-GM scores for ML versus MM patients. There were no significant differences in CD34⁺ cell numbers and CFU-GM scores among the FBNK, filgrastim, and lenograstim treatments, not only for the combined patient cohort, but also for ML and MM patients evaluated separately. In addition, there were no significant differences in the frequencies of side effects induced by the three G-CSF drugs (Table 2).

Figure 3 shows the leukocyte numbers before and after ASCT. The numbers of all leukocytes, neutrophils, and

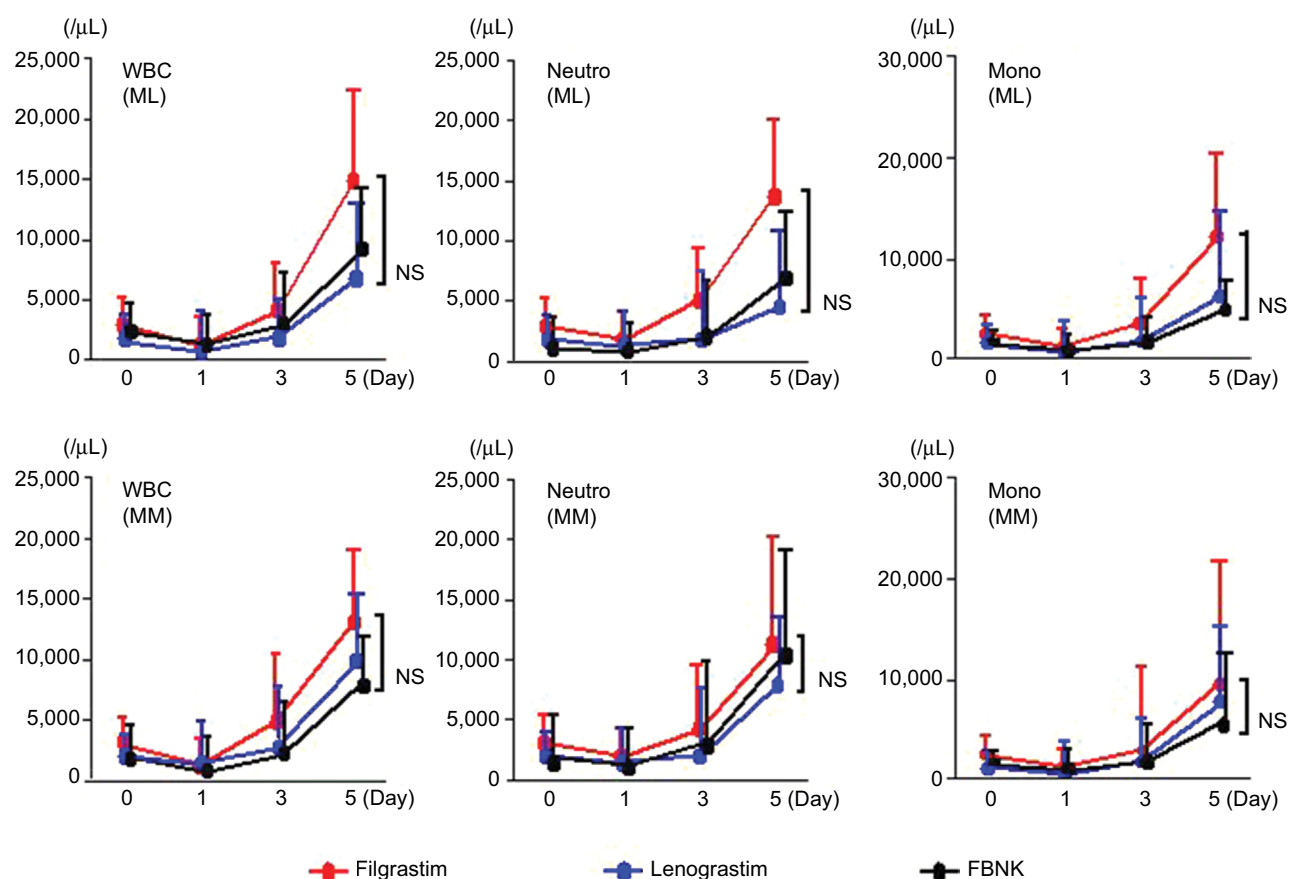


Figure 1 White blood cell numbers after G-CSF administration and PBSC harvest in patients with ML and MM.

Notes: Values are mean \pm SD. Welch's *t*-test was used for comparison of data for the each case before and after G-CSF treatment.

Abbreviations: WBC, white blood cell; Neutro, neutrophil; Mono, monocyte; ML, malignant lymphoma; MM, multiple myeloma; G-CSF, granulocyte colony-stimulating factor; PBSC, peripheral blood stem cell; SD, standard deviation; FBNK, filgrastim BS-NK; NS, not significant.

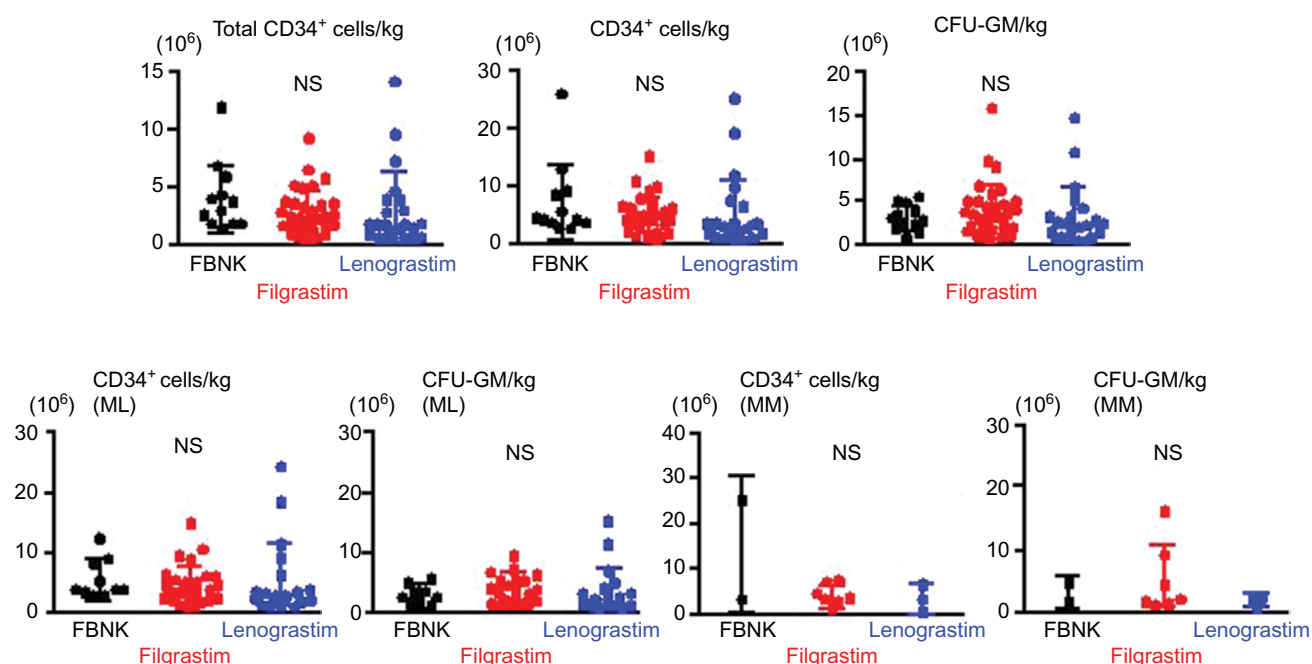


Figure 2 Comparison of PBSC mobilized by either the biosimilar or the originator (filgrastim or lenograstim).

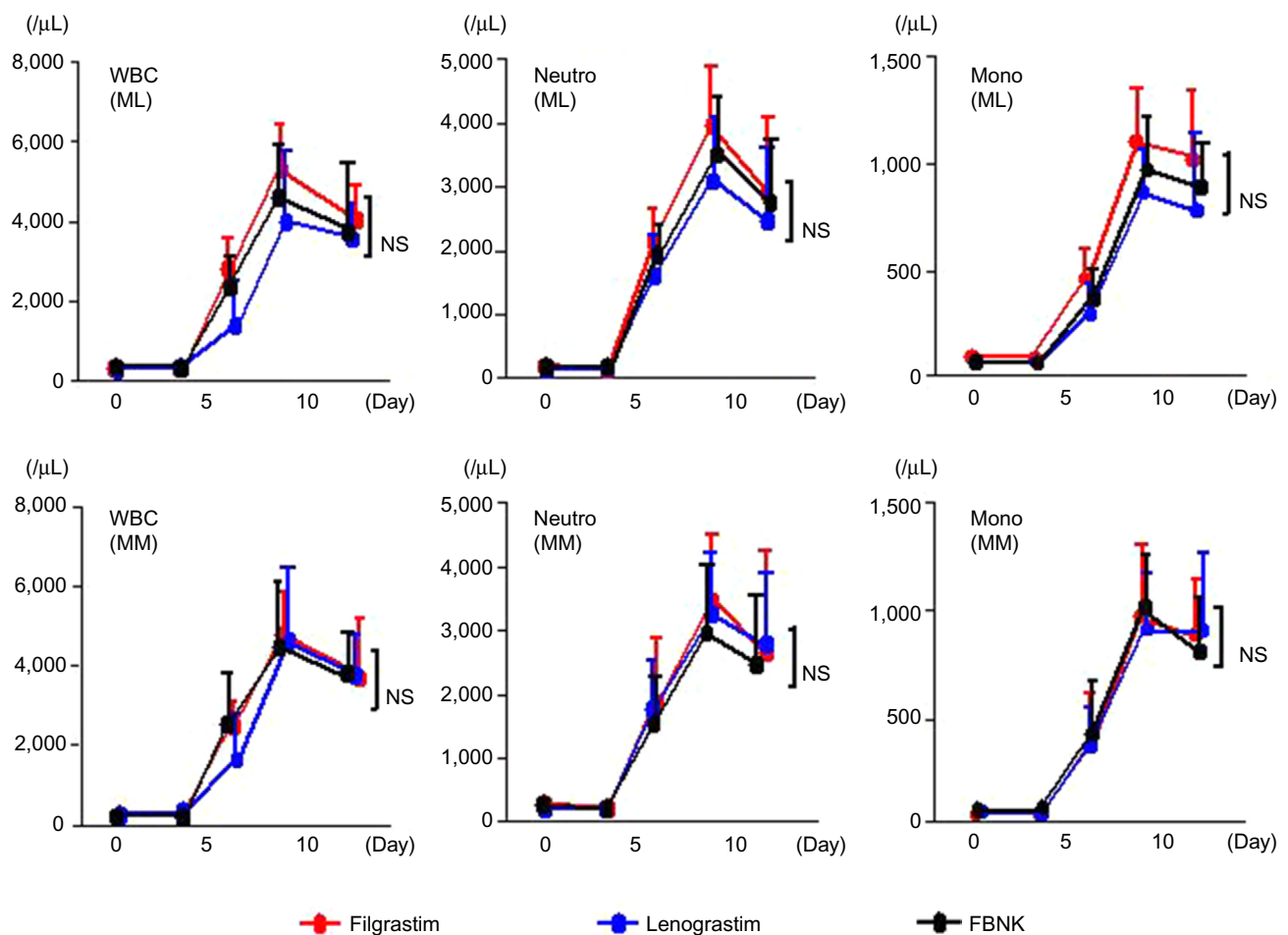
Abbreviations: CFU-GM, granulocyte/macrophage colony forming units; ML, malignant lymphoma; MM, multiple myeloma; PBSC, peripheral blood stem cell; FBNK, filgrastim BS-NK; NS, not significant.

Table 2 Complications after ASCT among three G-CSF drugs

		FBNK	Filgrastim	Lenograstim	P-value
N		11	34	22	
Complication	FN	9	13	9	
	Sepsis	1	12 (shock 1)	3	
	Colitis	0	5	4	
	Pneumonia	0	0	2	
	Total	10 (90%)	30 (88%)	18 (81%)	0.709
	Oral mucotitis	7 (63%)	19 (56%)	16 (72%)	0.572
	HPS	1	1	0	
	Engraftment syndrome	0	2	1	
	Gastrointestinal bleeding	0	1	0	
	Interstitial pneumonia	0	0	1	
	Hemorrhage cystitis	0	0	1	
	Heart failure	0	2	1	
Side effects	Bone pain	25%	14%	8%	0.428
	Fever	16%	20%	21%	0.937

Note: Data presented as n (%) of total numbers.

Abbreviations: ASCT, autologous stem cell transplantation; G-CSF, granulocyte colony-stimulating factor; FN, fibrile neutropenia; HPS, hemophagocytic syndrome; FBNK, filgrastim BS-NK.

**Figure 3** Leukocyte numbers before and after ASCT in patients with ML and MM.

Notes: Values are mean \pm SD. Welch's t-test was used for comparison of data for the each case before and after G-CSF treatment.

Abbreviations: WBC, white blood cell; Neutro, neutrophil; Mono, monocyte; ML, malignant lymphoma; MM, multiple myeloma; G-CSF, granulocyte colony-stimulating factor; SD, standard deviation; FBNK, filgrastim BS-NK; NS, not significant.

monocytes peaked on days 8–10 after transplantation. There were no significant differences among the FBNK, filgrastim, and lenograstim treatments. We could not study the number of CD34⁺ cells after transplantation.

Figure 4 shows the times to engraftment for the combined, ML, and MM patient cohorts. Leukocyte numbers before and after ASCT are also shown. There were no significant differences in the time to engraftment among the FBNK, filgrastim, and lenograstim treatments, not only for the combined patient cohort, but also for ML and MM patients evaluated separately. In addition, there were no significant differences in complications after ASCT among the three drugs (Table 2).

Discussion

G-CSF has become widely used to treat therapy-induced neutropenia, for mobilization of PBSCs, and to accelerate engraftment after hematopoietic stem cell transplantation.^{26,27} In addition, several forms of biosimilar nonglycosylated recombinant human G-CSF have recently been clinically developed. These have been approved by the European Medicines Agency.^{28–31} In Japan, applications to approve the production of biosimilars are progressed according to guidelines for efficacy and security notified by the Ministry of

Health, Labour, and Welfare. Three preparations of biosimilar G-CSF have been approved in Japan. FSK0808 is a domestic product, and the others, TKN732 and EP2006, are imported from foreign countries. The FBNK used in the present study corresponds to TKN732, an imported filgrastim biosimilar product sold in Europe as XM02. Therefore, the safety data of 541 overseas phase III randomized controlled trials can be extrapolated to this FBNK product.^{28–31}

There are several publications regarding the use of biosimilar G-CSF for PBSC mobilization.^{11–21,32} However, the World Marrow Donor Association does not recommend the use of biosimilars for stem cell mobilization in healthy adult donors, because the long-term safety is considered poor.³³ In the present study, there were no significant differences in CD34⁺ cell numbers and CFU-GM scores among FBNK, filgrastim, and lenograstim treatments for the total patient, ML and MM patient groups. Similarly, there were no significant differences in the time to engraftment after ASCT among the FBNK, filgrastim, and lenograstim treatments. Lefrère et al¹² reported that no significant difference was found between the biosimilar G-CSF Zarzio® and Neupogen® for stem cell mobilization in 40 patients, compared with an historical control. Andreola et al¹¹ also showed successful

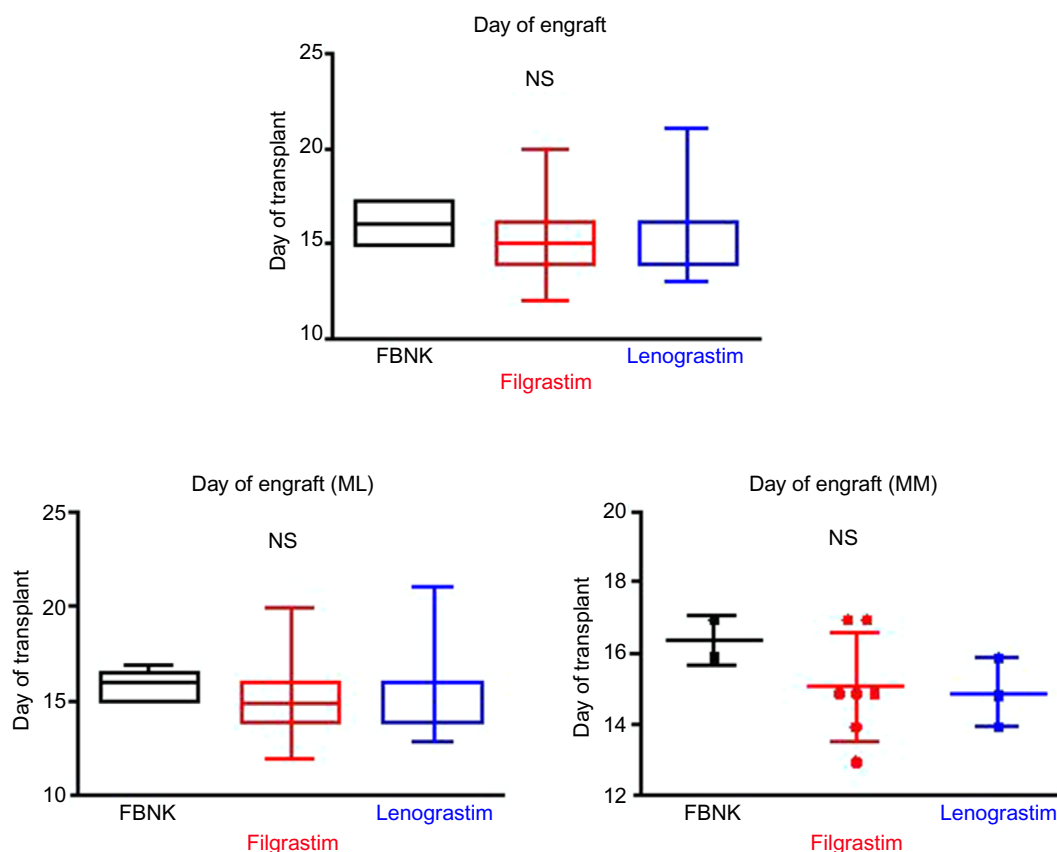


Figure 4 Times to engraftment for all patients.

Abbreviations: ML, malignant lymphoma; MM, multiple myeloma; FBNK, filgrastim BS-NK; NS, not significant.

mobilization and engraftment using Plerixafor and XM02 in a study of 14 patients. Furthermore, Publicover et al¹⁴ and Bassi et al¹⁹ reported the same results using other biosimilars. These previous results support the present study.

The use of biosimilars needs to consider safety in addition to efficacy. The chief physician should monitor drug dosage and patient response, and strict safety monitoring of pharmaceutical products should be performed after marketing.²⁸ Previous phase III randomized controlled trials conducted internationally in many facilities reported that the adverse effects and tolerability were similar between the originator and G-CSF biosimilars.^{28–30} In the present study, there were no significant differences in the frequencies of side effects such as bone pain and fever among the three G-CSF drugs (FBNK, filgrastim, and lenograstim), and there were no significant differences in complications after ASCT.

A study of the effect on medical expenses reported that biosimilar G-CSF is advantageous in this regard in Europe.¹¹ These results appear to be compatible with Japan. However, an original evaluation is necessary, because the Japanese medical system is different from the European medical system. ASCT requires a higher dose of G-CSF than chemotherapy. The use of biosimilars may offer significant cost savings and help reduce health care costs. However, their long-term safety remains unclear. Therefore, further observation will be very important to establish the clinical use of FBNK.

Conclusion

In comparison with the originator G-CSFs, biosimilar FBNK shows the same efficacy and safety for facilitating bone marrow recovery in Japanese patients with ML and MM who undergo stem cell transplantation. In addition, it reduced the patients' hospitalization costs because it is less expensive than the originators.

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Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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