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ORIGINAL ARTICLE

Evaluation of a novel medical device for pegfilgrastim administration

Tomoyuki Aruga[1] | Hiroyoshi Doihara[2] | Yasuhiro Yanagita[3] | Takanori Ishida[4] | Toshinari Yamashita[5] | Kanou Uehara[6] | Tetsuhiko Taira[7] | Junji Tsurutani[8] | Takashi Takeshita[9] | Shigeru Tsuyuki[10] | Koji Kaneko[11] | Tohru Ohtake[12] | Yusuke Yamaguchi[13] | Yui Hara[13] | Shigehira Saji[14]

[1]Department of Breast Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

[2]Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan

[3]Department of Breast Oncology, Gunma Prefectural Cancer Center, Gunma, Japan

[4]Department of Breast and Endocrine Surgical Oncology, Tohoku University Graduate School of Medicine, Sendai, Japan

[5]Department of Breast and Endocrine Surgery, Kanagawa Cancer Center, Yokohama, Japan

[6]Department of Surgery, Nahanishi Clinic, Naha, Okinawa, Japan

[7]Department of Medical Oncology, Sagara Hospital, Kagoshima City, Kagoshima, Japan

[8]Advanced Cancer Translational Research Institute, Showa University, Tokyo, Japan

[9]Department of Breast Surgery, Hokkaido University Hospital, Sapporo, Japan

[10]Department of Breast Surgery, Osaka Red Cross Hospital, Osaka, Japan

[11]Department of Breast Oncology, Niigata Cancer Center Hospital, Niigata, Japan

[12]Department of Breast Surgery, School of Medicine, Fukushima Medical University, Fukushima, Japan

[13]Kyowa Kirin Co., Ltd., Tokyo, Japan

[14]Department of Medical Oncology, Fukushima Medical University, Fukushima, Japan

Correspondence
Tomoyuki Aruga, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo 113-8677, Japan.
Email: aruga@cick.jp

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Abstract

Pegfilgrastim, a pegylated form of granulocyte colony-stimulating factor, has reduced the risk of developing febrile neutropenia, which is associated with an increase in severe infection and prolonged hospitalization. However, pegfilgrastim administration requires that patients visit hospital following cancer chemotherapy, thus imposing a burden on patients and those around them. An on-body injector (OBI), which automatically administers pegfilgrastim about 27 hours after chemotherapy, was used in this study. The OBI, which consists of a main pump unit and infusion set, is a drug delivery device designed to be attached to the patient's body, with a timer-controlled dosing function. This study was conducted in breast cancer patients to evaluate the safety of pegfilgrastim administered subcutaneously via the OBI. The study period

Abbreviations: AE, adverse event; CI, confidence interval; COVID 19, coronavirus disease 2019; ECOG PS, Eastern Cooperative Oncology Group performance status; FN, febrile neutropenia; G-CSF, granulocyte colony-stimulating factor; IC, informed consent; JAPIC, Japan Pharmaceutical Information Center; MedDRA, Medical Dictionary for Regulatory Activities; OBI, on-body injector; PT, preferred term in MedDRA; SD, standard deviation; SOC, system organ class in MedDRA; TC therapy, docetaxel plus cyclophosphamide therapy; TEAE, treatment-emergent adverse event.

Clinical trial register and clinical registration number: The study was registered at Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information; Japic CTI-205130.

consisted of screening and treatment observation periods involving four cycles of neoadjuvant or adjuvant chemotherapy with docetaxel plus cyclophosphamide. One 3.6-mg pegfilgrastim dose was administered subcutaneously via OBI during each cycle of chemotherapy. The study enrolled 35 patients, and no serious adverse events or febrile neutropenia occurred. Administration of pegfilgrastim was successfully completed at all times when the OBI was attached to the patient, and no safety concerns associated with OBI function arose. For outpatients requiring pegfilgrastim following cancer chemotherapy, the use of an OBI was considered to be a safe option to reduce the need for outpatient visits that restrict their activities of daily living.

KEYWORDS
breast cancer, chemotherapy, febrile neutropenia, medical device, pegfilgrastim

1 | INTRODUCTION

Neutrophils serve as the primary defense mechanism against bacterial and fungal infection, and a decrease in their number leads to an increased risk of infection. Many anticancer drugs exert a cytotoxic effect on both target cancer cells and normal hematopoietic cells in the bone marrow, where neutrophils are produced. Thus, neutropenia occurs in a substantial number of cancer patients given chemotherapy that has an intense anticancer effect. Neutropenia accompanied by fever is called febrile neutropenia (FN), a condition associated with more severe infection and prolonged hospitalization. A longer duration of neutropenia has been shown to be associated with a higher risk of FN.[1,2] Chemotherapy-induced neutropenia used to be treated with first-generation granulocyte colony-stimulating factor (G-CSF) (e.g., filgrastim) administered until neutrophil recovery. Administration of G-CSF enables early neutrophil recovery and prevents FN and severe infection.[3] However, because of its short half-life in blood, G-CSF needs to be administered daily, requiring more hospital visits and thus imposes a heavy burden on patients, their supporting family members, and healthcare providers.

To resolve these issues, a second-generation G-CSF with an extended half-life in blood (pegfilgrastim) has become available. In a clinical study of Japanese breast cancer patients receiving docetaxel plus cyclophosphamide therapy (TC therapy), the incidence of FN in patients administered pegfilgrastim was 1.2% (2/173), compared with 68.8% (119/173) in the placebo group.[4] Subsequently, pegfilgrastim has freed patients from the burden of daily administration in cancer chemotherapy, enabled safer administration of highly myelosuppressive chemotherapy regimens, contributing to wider implementation of outpatient cancer chemotherapy. Pegfilgrastim has been approved in more than 80 countries or regions, including the United States, Europe, and Japan as of January 31, 2020, and is mainly indicated for reduction in the duration of neutropenia, incidence of FN, and incidence of infection as manifested by FN in patients with malignancy receiving cytotoxic chemotherapy.[5]

Although pegfilgrastim enabled a reduction in G-CSF dosing frequency and lowered the risk of FN in patients undergoing cancer chemotherapy, its safety has not been established when administered between 14 days before and 24 hours after administration of cancer chemotherapy. Pegfilgrastim administration requires patient visit to the hospital just after chemotherapy, which is burdensome to some patients for physical, mental, and socioeconomic reasons such as moving to a hospital, and often involves a long waiting time at the hospital with its associated physical discomfort. Furthermore, many patients do not want to impose a burden on their supporting family members and thus want to maintain their daily routine as much as possible. Medical institutions also have multiple challenges in dealing with the increasing numbers of outpatients receiving cancer chemotherapy, such as maintaining adequate staffing levels of those with specialized skills and reducing waiting times at reception and cashiers. In addition, the coronavirus disease 2019 (COVID-19) pandemic may change the way outpatient chemotherapy is conducted in the future. In order to reduce the risk of COVID-19 infection, efforts to prevent neutropenia should be made even more assiduously than before, and the frequency of hospital visits should be reduced.[6]

An on-body injector (OBI), which automatically administers pegfilgrastim about 27 hours after the chemotherapy, can thus be expected to address the unmet medical needs of these patients by reducing the number of hospital visits. This study was therefore conducted to evaluate the safety of automatic pegfilgrastim administration using an OBI in breast cancer patients, to whom the OBI was attached after cancer chemotherapy.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

This was a phase one, multicenter, uncontrolled, open-label study in breast cancer patients to evaluate the safety of pegfilgrastim subcutaneous administration via the OBI during adjuvant chemotherapy. The study protocol was approved by the institutional review boards at all participating sites. The study was conducted in accordance with the

principles of Good Clinical Practice and the Declaration of Helsinki. The study was registered at Japan Pharmaceutical Information Center (JAPIC) Clinical Trials Information; Japic CTI-205130.

All patients provided written informed consent (IC) before enrollment. Patients were selected using inclusion and exclusion criteria, with the key criteria specified below.

2.1.1 | Key inclusion criteria

The inclusion criteria included the following: Japanese women aged 20 to <70 years at the time of consent, histologically diagnosed with stage I or II primary invasive breast carcinoma, scheduled to receive four cycles of TC therapy as neoadjuvant or adjuvant cancer chemotherapy, and able to participate in the study from cycle 1 of TC therapy with the intention to use full-dose levels.

2.1.2 | Key exclusion criteria

The exclusion criteria included the following: patients who previously received cancer chemotherapy with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or more, any abnormality on the most recent laboratory tests performed within the 14 days before cycle 1 of TC therapy (e.g., absolute neutrophil count <2000 /μL), previous receipt of pegfilgrastim, and receipt of G-CSF within 14 days before consent.

2.2 | Structure and function of the OBI

The OBI used in this study was a drug delivery device with a timer-controlled dosing function designed to be attached to the patient's body surface. Detailed information on the OBI is shown in Figure 1. The OBI, which is a single-use, disposable device, consists of a main pump unit and an infusion set. The main pump unit had an electro-mechanical drive and drug-loaded cartridge prefilled with pegfilgrastim and connected to the infusion set, intended for single-dose subcutaneous injection. To apply the device, the infusion set is placed on the patient's body surface, and the infusion set is then connected to the main pump unit. Subsequently, the main pump unit is placed on the abdomen, using adhesive attached to the skin. The electro-mechanical drive in the main pump unit is set to operate automatically, approximately 27 hours after activation of the device, pushing the stopper to continuously deliver pegfilgrastim from the drug-loaded cartridge at a constant flow rate, providing subcutaneous injection through the catheter of the infusion set. When the OBI begins to operate, this is signaled by a lamp that lights up and can be checked by looking through a check window to confirm that the stopper has been pushed to the end. After confirming completion of pegfilgrastim administration by the OBI, the patient herself removes the device. In this study, we also confirmed that the patient had returned the used OBI to hospital and that administration was completed correctly.

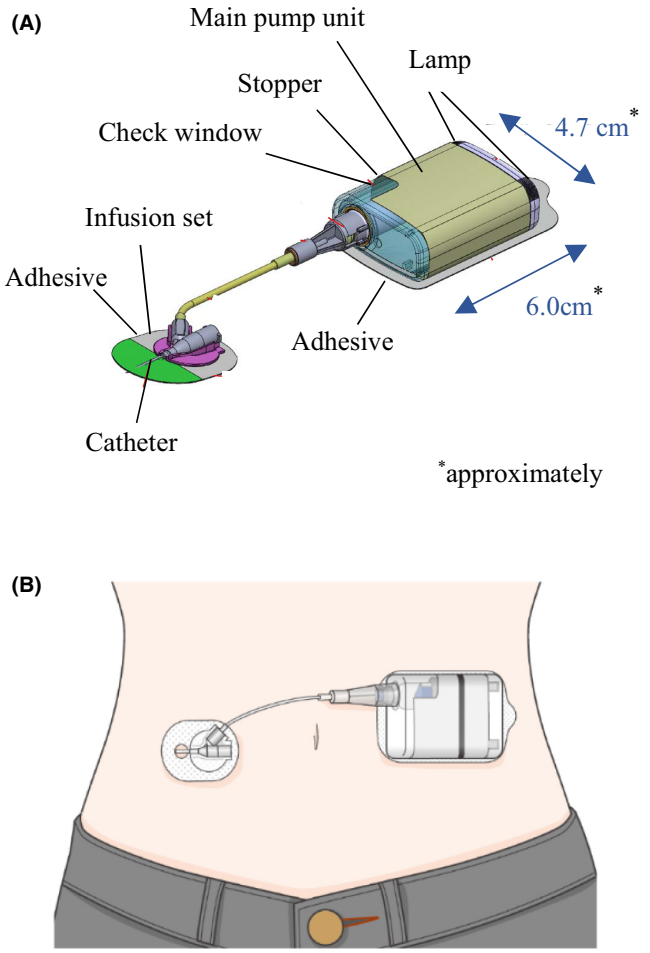


FIGURE 1 On-body injector (OBI). A, On-body injector components (weight*: 40 g). B, Illustration of the OBI applied to the abdomen (Source: "Instructions for Use of KRN125* Auto-injector Device": information material used in this study. *Study drug, pegfilgrastim)

2.3 | Treatment procedures

The study period consisted of a screening period of up to 28 days and a treatment observation period involving four cycles of TC therapy (docetaxel 75 mg/m^2 and cyclophosphamide 600 mg/m^2 intravenous injection). The treatment observation period was defined as the period from the day of cycle 1 administration of TC therapy to the end of protocol-specified tests in cycle 4. One dose of pegfilgrastim was administered via the OBI per cycle of TC therapy (Figure 2). Patients were admitted to the study site on either cycle 1 day −1 or cycle 1 day 1 and received TC therapy on cycle 1 day 1. Following TC therapy, the OBI was activated and applied to the abdomen at the hospital. Approximately 27 hours later (cycle 1 day 2), the OBI automatically delivered a single subcutaneous dose of pegfilgrastim. Patients confirmed completion of pegfilgrastim administration and

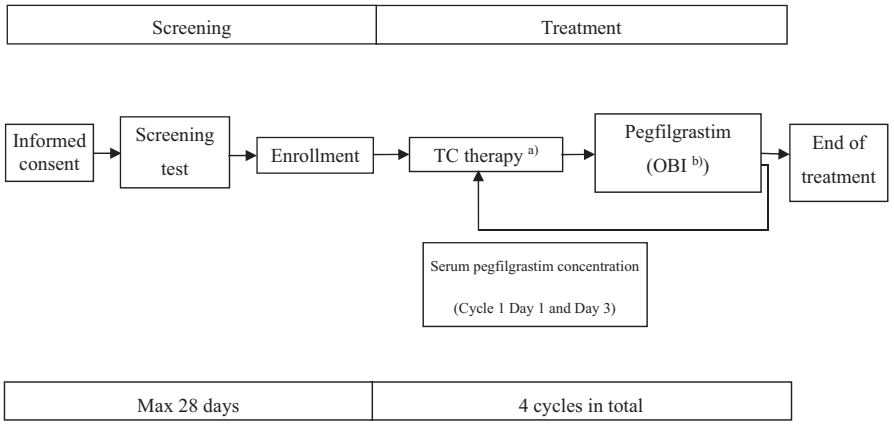
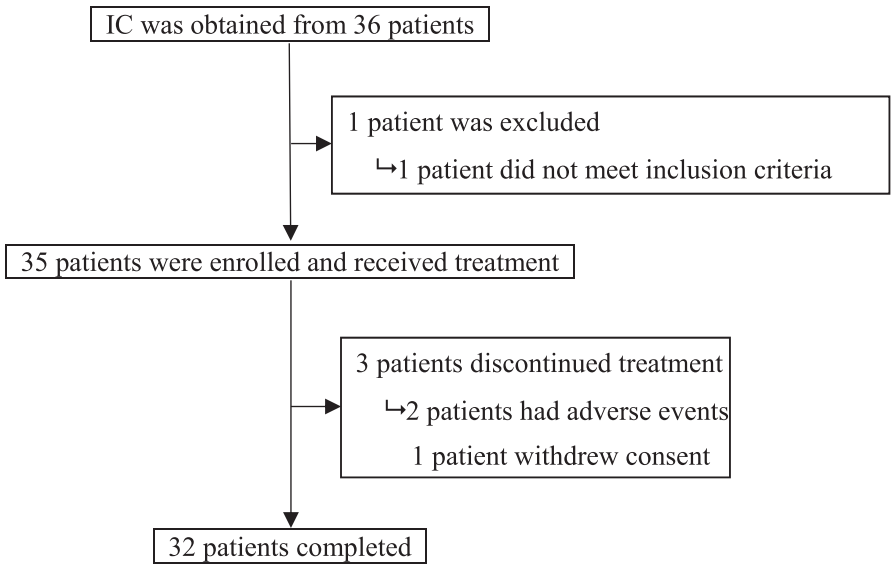


FIGURE 2 Schematic overview of the study design. [a]TC therapy: Docetaxel plus cyclophosphamide therapy. [b]OBI, on-body injector. The OBI was activated following TC therapy in the hospital, to deliver one 3.6-mg pegfilgrastim dose subcutaneously approximately 27 h later (say 2 of each cycle). From cycle 2 onward, TC therapy and OBI activation/application were performed on an outpatient basis

a) TC therapy: Docetaxel plus cyclophosphamide therapy

b) OBI: On-body injector. The OBI was activated following TC therapy in the hospital, to deliver one 3.6 mg pegfilgrastim dose subcutaneously approximately 27 hours later (Day 2 of each cycle). From Cycle 2 onward, TC therapy and OBI activation/application were performed on an outpatient basis.

TABLE 1 Study patients' profile



learned how to remove the OBI from the abdomen on their own. Patients were discharged from hospital either after OBI removal on cycle 1 day 2 or after completion of protocol-specified observations and tests on cycle 1 day 3. Subsequent outpatient visits were in principle made on day 1 of each cycle of TC therapy to undergo protocol-specified observations and tests. Serum pegfilgrastim concentrations were measured on cycle 1 day 1 (before TC therapy) and cycle 1 day 3 (51 hours [within + 24 hours] after the OBI activation).

2.4 | Endpoints

Safety and exploratory endpoints were evaluated. The safety endpoints were adverse events (AEs), laboratory tests, vital signs, and device complaints, which were defined as "any reported problem with the OBI that occurred during pegfilgrastim administration to the patient by the OBI." The complaint-reporting period was from the day of cycle 1 administration of TC therapy until study completion (or discontinuation).

The exploratory endpoints were the proportion of successful administrations, usage questionnaires, and serum pegfilgrastim concentrations. A successful administration is deemed to have occurred when the following criteria are met: no liquid remains in the primary container after pegfilgrastim administration, and the green lamp on the device turns on after pegfilgrastim administration. A usage questionnaire survey was also conducted among the healthcare providers and patients to obtain information regarding study drug administration using the OBI (device activation, insertion/application, dosing, and retrieval after dosing). The questionnaires were completed by the healthcare providers on day 1 of each cycle (after OBI application), and by the patients on day 2 of each cycle (after OBI removal from the abdomen following completion of dosing via the OBI).

2.5 | Statistical analysis

Sample size was set to gain evaluable experience with device usage and to evaluate the safety of pegfilgrastim. The number of patients receiving pegfilgrastim via the OBI was set to 30. No statistical sample size estimation was performed for this study. Categorical data are reported as *n* (%); continuous data are reported as mean (standard deviation [SD]), minimum, and maximum. Safety was assessed in all patients who used the OBI. The incidence and types of treatment-emergent adverse events (TEAEs) coded by the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PT) and system organ class (SOC) are presented using the number and percentage of patients with an event. The number of patients with device-related TEAEs by SOC and PT are presented by maximum severity. Device complaints were assessed in all patients who were prescribed at least one dose of any study treatment. All device complaints for each cycle and overall are summarized by reported term for the device complaint, aggregated based on the number of times that the OBI was attached.

3 | RESULTS

3.1 | Patients

A total of 36 patients at 12 investigational sites provided IC to participate in this study between February 2020 and August 4, 2020, of whom 35 were enrolled in this study. All 35 patients received pegfilgrastim via the OBI at least once. Safety and device complaints were assessed in 35 patients. Three patients were withdrawn from the study (Table 1).

The median (range) age of the patients was 49.0 (26-68) years. Lymph node metastases were present in 31.4% (Table 2). Other primary disease demographics are shown in Table 3.

TABLE 2 Patient demographics

Parameter (unit)	*N* = 35, *n* (%)
Age (years)	
Median (range)	49.0 (26-68)
Sex	
Female	35 (100.0)
Adjuvant treatments setting	
Postoperative	35 (100.0)
Primary disease history	
Lesion site	
Unilateral	31 (88.6)
Bilateral (synchronous)	4 (11.4)
Lymph node metastasis	
No	24 (68.6)
Yes	11 (31.4)

3.2 | Treatment outcomes

In this study, 32 of the 35 enrolled patients were able to complete pegfilgrastim administration by the OBI in all four cycles of TC therapy. From the three patients who were withdrawn from this study, two were withdrawn in cycle 2 because of AE onset (hypersensitivity and eczema, respectively), and one patient was withdrawn in

TABLE 3 Primary disease demographics

Parameter (unit)	N_1[a] = 39, n_1[a] (%[b])
Primary disease history	
TNM classification (T)	
Tis	3 (7.7)
1	19 (48.7)
2	16 (41.0)
3	1 (2.6)
4	0
TNM classification (N)	
0	28 (71.8)
1	11 (28.2)
Tumor stage	
0	3[c] (7.7)
I	13 (33.3)
IIA	17 (43.6)
IIB	6 (15.4)
ER[d]	
−	3 (7.7)
+	36 (92.3)
PgR[e]	
−	6 (15.4)
+	33 (84.6)
HER2[f]	
−	35 (89.7)
+	4 (10.3)
Nuclear grading	
I	8 (20.5)
II	16 (41.0)
III	13 (33.3)
Unknown/not applicable	2 (5.1)
Histological grading	
I	3 (7.7)
II	23 (59.0)
III	10 (25.6)
Unknown/not applicable	3 (7.7)

[a]Sum of lesions, including data for both left and right sides, for bilateral breast cancer in 4 of 35 patients.
[b]Percentages calculated from 39 lesion data (N_1).
[c]Data for the patients with bilateral breast cancer.
[d]Estrogen receptor.
[e]Progesterone receptor.
[f]Human epidermal growth factor receptor 2.

TABLE 4 Summary of proportions of successful administrations for each cycle

	N = 35			
	Number of times "Successful administration" was achieved	Number of times OBI was attached	Proportion of successful administrations (%)	95%CI[a]
Cycle 1	35	36	97.2	(85.5, 99.9)
Cycle 2	34	34	100.0	(89.7, 100.0)
Cycle 3	32	32	100.0	(89.1, 100.0)
Cycle 4	32	32	100.0	(89.1, 100.0)
Overall	133	134	99.3	(95.9, 100.0)

Note: Proportion of successful administrations (%): 100 × (The number of times "Successful administration" was achieved/The number of times OBI was attached).

Abbreviations: CI, confidence interval; OBI, on-body injector.

[a]Clopper-Pearson.

cycle 1 because of withdrawal of consent; no cases were thus discontinued due to hematological toxicity.

As shown in Table 4, the overall proportion of successful administrations was 99.3%, as a new OBI was applied in one of the two cases with the device complaints described below. However, administration of pegfilgrastim by the OBI was appropriately completed, including administration in those cases with device complaints.

In addition, the usage questionnaires administered to obtain information regarding pegfilgrastim administration by the OBI revealed no reports of concerns or problems from the healthcare providers or patients (data not shown).

3.3 | Safety

No patients had FN or any serious AE during this study. Common AEs noted in this study were alopecia (34 patients, 97.1%), dysgeusia (23 patients, 65.7%), and malaise (20 patients, 57.1%) (Table 5). Grade 3 or higher AEs were lymphocyte count decreased (two patients), white blood cell count decreased (two patients), oedema peripheral (one patient), neutrophil count decreased (one patient), eczema (one patient), and urticaria (one patient), all of which were grade 3. Among all patients, six patients had AEs causally related to the OBI, including erythema (four patients), dermatitis (one patient), dermatitis contact (one patient), and purpura (one patient), but all of these were grade 1.

3.4 | Serum pegfilgrastim concentration

The serum pegfilgrastim concentration at cycle 1 day 1 was below the lower limit of quantification (<0.2 ng/mL) (mean), and that at cycle 1 day 3 after the first pegfilgrastim administration by the OBI was 72.8 ± 69.8 ng/mL (mean ± SD).

3.5 | Device complaints

Two device-related complaints were reported in this study; in both, there was detachment of the main pump unit from the skin. In both cases, although the main pump unit of the OBI fell off after OBI application, the infusion set remained firmly attached. Among these, in one case a new OBI was applied, while in the other the detached OBI was checked by the investigator and reapplied, leading to appropriate completion of pegfilgrastim administration.

4 | DISCUSSION

This study was conducted to evaluate the safety of pegfilgrastim administered to breast cancer patients using an OBI and to confirm that pegfilgrastim was automatically administered via the OBI about 27 hours after cancer chemotherapy. The OBI has a prior product on the market which was released by Amgen in 2014.[7] This OBI called Neulasta Onpro® kit needs to be filled with pegfilgrastim by healthcare providers using the prefilled syringe before application to the patient's skin.[8] In contrast, the OBI used in this study has a drug-loaded cartridge prefilled with pegfilgrastim and eliminates the need for healthcare providers to fill with pegfilgrastim before use to reduce some errors associated with filling.

No serious AEs occurred during the study period. Three patients discontinued treatment, due to withdrawal of consent in one patient and occurrence of AEs in two patients (hypersensitivity in one patient and eczema in one patient), both causally unrelated to pegfilgrastim and the OBI. In addition, the serum pegfilgrastim concentration during cycle 1 day 3, after the first pegfilgrastim administration by the OBI, was 72.8 ± 69.8 ng/ml (mean ± SD), and pegfilgrastim was detected in the serum of all patients after administration by the OBI. For a normal syringe, it has been reported that the serum concentration after a single dose (60 μg/kg) of pegfilgrastim administration to lung cancer patients was 74.2 ± 63.5 ng/ml (mean ± SD).[9] Thus, when pegfilgrastim was administered by the OBI, the serum concentration was almost identical with that obtained with administration by a normal syringe.[7] In addition, the criteria for a successful proportion of administrations were met for OBI use in patients, and all pegfilgrastim administrations were completed appropriately in this study. Usage questionnaires also confirmed that pegfilgrastim solution did not leak from the OBI and that patients did not bleed after pegfilgrastim administrations, with no reports of concerns or

TABLE 5 Incidence of treatment-emergent adverse events (TEAEs) occurring in 10% or more of patients

	All grades		≥Grade3	
PT (*N* = 35)	*n*	%	*n*	%
Patients with any TEAE	35	100.0	6	17.1
Alopecia	34	97.1	0	0
Dysgeusia	23	65.7	0	0
Malaise	20	57.1	0	0
Constipation	18	51.4	0	0
Nausea	18	51.4	0	0
Arthralgia	16	45.7	0	0
Myalgia	16	45.7	0	0
Stomatitis	16	45.7	0	0
Diarrhea	13	37.1	0	0
Peripheral sensory neuropathy	13	37.1	0	0
Oedema peripheral	12	34.3	1	2.9
Headache	11	31.4	0	0
Decreased appetite	11	31.4	0	0
Back pain	10	28.6	0	0
Alanine aminotransferase increased	7	20.0	0	0
Pruritus	7	20.0	0	0
Pyrexia	7	20.0	0	0
Lymphocyte count decreased	6	17.1	2	5.7
Nail discoloration	6	17.1	0	0
Anemia	5	14.3	0	0
Insomnia	5	14.3	0	0
Lacrimation increased	5	14.3	0	0
Palmar-plantar erythrodysesthesia syndrome	5	14.3	0	0
Rash	5	14.3	0	0
Aspartate aminotransferase increased	4	11.4	0	0
Eczema	4	11.4	1	2.9
Erythema	4	11.4	0	0
Hepatic function abnormal	4	11.4	0	0
Neutrophil count decreased	4	11.4	1	2.9
Urticaria	4	11.4	1	2.9
White blood cell count decreased	4	11.4	2	5.7

Note: Coding dictionary: MedDRA version 23.1.
Abbreviation: PT, preferred term in MedDRA.

problems from the healthcare providers or patients. There were no notable findings on safety evaluation including laboratory tests and vital signs, and serum pegfilgrastim concentrations were measured correctly after subcutaneous administration of pegfilgrastim using the OBI. In this study, two device complaints were reported, both involving detachment of the OBI from the skin. At the time of OBI removal, it was noted that both patients were sweaty, and sweating may have caused detachment. Therefore, discussions are underway regarding a change to the specification of adhesive used for the main pump unit. In one of the two cases, the entire device was replaced according to the standard clinical study procedures. In the other case, the adhesive on the main pump unit was reattached and secured with an auxiliary medical tape. In consequence, administration of pegfilgrastim was completed the following day without either patient experiencing any problems. In clinical practice, if just the main pump unit falls off after application of the OBI but the infusion set remains firmly attached, it is assumed that the main pump unit will be reattached and secured with an auxiliary medical tape. Instructing the patients not to attach the device while their skin is sweaty was also thought to help prevent the device from coming off.

The results of this study showed that pegfilgrastim can be administered appropriately using the OBI without safety concerns regarding subcutaneous administration in breast cancer patients.

However, these results are limited to a small number of female patients with breast cancer. It is therefore important to accumulate more experience using the OBI for various cancer patients in addition to breast cancer and to confirm that pegfilgrastim can be administered appropriately via the OBI. In addition, prior to using the OBI, training should be provided to patients and healthcare professionals to ensure proper handling of the OBI.

In conclusion, the results of this study showed that the OBI, a new product for pegfilgrastim administration, is effective when used clinically for FN prophylaxis during outpatient cancer chemotherapy. For outpatients who require pegfilgrastim administration following cancer chemotherapy, use of an OBI is expected to reduce the burden on patients by decreasing life-restricting hospital visits.

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ORCID

Tomoyuki Aruga https://orcid.org/0000-0003-3442-8972

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