J Infect Chemother xxx (2017) 1–7

Contents lists available at ScienceDirect

Journal of Infection and Chemotherapy

journal homepage: http://www.elsevier.com/locate/jic

Original Article

Clinical safety and efficacy of "filgrastim biosimilar 2" in Japanese patients in a post-marketing surveillance study

Kazuo Tamura [a, *], Kazue Hashimoto [b], Kiyohiro Nishikawa [c]

[a] General Medical Research Center, Faculty of Medicine, Fukuoka University, Japan
[b] Regional Compliance & Quality Assurance Division, Teva Takeda Pharma Ltd., Japan
[c] Quality & Pharmacovigilance Division, Pharmaceuticals Group, Nippon Kayaku Co., Ltd., Japan

ARTICLE INFO

Article history:
Received 6 September 2017
Received in revised form
11 December 2017
Accepted 17 December 2017
Available online xxx

Keywords:
Filgrastim
Biosimilar
Post-marketing surveillance
Neutropenia

ABSTRACT

We conducted a post-marketing surveillance to evaluate the safety and efficacy of TKN732, approved as "filgrastim biosimilar 2", in Japanese patients who developed neutropenia in the course of cancer chemotherapy or hematopoietic stem cell transplantation. A total of 653 patients were registered during the 2-year enrollment period starting from May 2013, and 627 and 614 patients were eligible for safety and efficacy analyses of the G-CSF biosimilar, respectively.

Forty-three adverse drug reactions were reported in 33 patients (5.26%). Back pain was most frequently observed and reported in 20 patients (3.19%), followed by pyrexia (1.28%) and bone pain (0.96%). Risk factors for adverse reactions identified by logistic regression analyses were younger age, presence of past medical history, and lower total dose at the onset of adverse reactions.

Among the 576 cancer patients who developed Grade 2–4 neutropenia after chemotherapy, recovery to Grade 1/0 was reported in 553 patients (96%) following filgrastim biosimilar 2 treatment. The median duration of neutrophil counts below 1500/μL was 5 days. In addition, all 11 patients who underwent hematopoietic stem cell transplantation had good responses to filgrastim biosimilar 2.

In conclusion, this study showed that filgrastim biosimilar 2 has a similar safety profile and comparable effects to the original G-CSF product in the real world clinical setting.

1. Introduction

There have been no large scale studies on biosimilar products of granulocyte-colony stimulating factor (G-CSF) in Japanese patients. TKN732, a biosimilar of filgrastim was approved in Japan in 2013 as "filgrastim biosimilar 2" (F-BS2). The product contains the same active recombinant human G-CSF protein as XM02, which has been extensively used in the EU since 2008 and in the US since 2012.

The original filgrastim was clinically introduced in the US and Japan in 1991 and, since then, its clinical application has expanded to various indications. The recombinant human Met-G-CSF expressed in *E. coli* has comparable effects to natural G-CSF in increasing mature neutrophils by stimulating the growth and differentiation of bone marrow precursor cells. The G-CSF formulation is widely used for neutropenia induced by cancer chemotherapeutic agents and has become an essential supportive care product. In addition, filgrastim is essential for bone marrow and peripheral blood stem cell transplantation (PBSCT), to stimulate the engraftment of hematopoietic stem cells and to mobilize stem cells to the peripheral blood. After the expiration of patents and after the lapse of the exclusivity period of reexamination of the original filgrastim product, several biosimilar products, including F-BS2, have been developed and used due to the associated economic benefit and comparative biological effects and quality.

In the development of F-BS2 overseas, the pharmacokinetics (PK) and pharmacodynamics (PD) profiles were examined in cross-over clinical studies with the original filgrastim [1,2], and three multinational multicenter randomized controlled phase III trials were conducted in breast cancer, lung cancer, and non-Hodgkin lymphoma patients [3–5]. In addition to similar PK and PD profiles, comparability of efficacy and similarity of safety were shown in all 3 comparative studies. Meta-analysis data suggested the same safety and efficacy, irrespective of tumor type and chemotherapeutic regimens employed [6]. Furthermore, the filgrastim biosimilar exhibited

* Corresponding author. 7-45-1 Nanakuma, Jonan-ku, Fukuoka 810-0180, Japan.
E-mail address: ktamura@fukuoka-u.ac.jp (K. Tamura).

https://doi.org/10.1016/j.jiac.2017.12.011

efficacy in mobilization of hematopoietic stem cells and stimulation of transplanted stem cell growth [7–11]. In the development of TKN732 in Japan, clinical PK and PD studies were conducted in healthy Japanese volunteers [12,13] in accordance with the Guideline on Policies for the Assurance of the Quality, Safety and Efficacy of Biosimilar Products established in 2009, and comparability and similarity with the original G-CSF product was demonstrated, and approval for TKN732 was granted in Japan as F-BS2. Although no racial differences were expected based on the results of previous PK and PD studies, clinical outcomes from Japanese patients were limited. Therefore, Nippon Kayaku and Teva Takeda Pharma conducted a post-marketing surveillance (PMS) in more than 600 Japanese patients treated with F-BS2 in order to analyze the safety and efficacy of the product in the real world clinical setting.

2. Patients and methods

2.1. Patients

Japanese patients were registered into the PMS of F-BS2 during a 2-year period starting from May 2013, with a target number of 600 patients in order to detect at least one patient reporting adverse reactions at an incidence of 0.5% at a 95% or higher probability. The patients were registered via a central registration system and the surveillance was conducted in accordance with the Good Post-marketing Surveillance Practice Ordinance of the Ministry of Health, Labour and Welfare.

The indications of G-CSF usage for enrolled patients were limited to (1) neutropenia caused by cancer chemotherapy, (2) mobilization of hematopoietic stem cells into peripheral blood for autologous PBSCT, (3) enhancement of engraftment of transplanted hematopoietic stem cells, and (4) neutropenia due to HIV infection.

2.2. Surveillance methods

Besides patient characteristics, the treatment modality of F-BS2, and concomitantly administered medications, information concerning adverse drug reactions (ADRs), including clinical laboratory test data and a description of objective/subjective symptoms were collected.

In addition, if the physician suspected the generation of anti-filgrastim antibodies in a patient, collected blood sample from the patient was to be examined by ELISA and determined neutralizing activity.

Responses to F-BS2 were evaluated by the primary care physician and categorized as effective, ineffective, or not evaluable. Changes in blood cell counts measured at appropriate time points before and after F-BS2 treatment were used for objective analyses.

The observation period lasted until 3 weeks after the last dose of F-BS2, or up to 3 months after the first dose of F-BS2 if the product was used in multiple cycles.

2.3. Evaluation methods

In addition to each physician's assessment of the safety and efficacy, Efficacy and Safety Evaluation Committee meetings were convened to identify evaluable patients and to evaluate the safety and efficacy of F-BS2 objectively. The adverse events reported by physicians were comprehensively re-evaluated by the Committee in terms of causal relationship with administered agents and were graded based on CTCAE (Common Terminology Criteria for Adverse Events) ver. 4.0. Preferred terms and system organ class based on MedDRA/J (Medical Dictionary for Regulatory Activities/Japanese version) ver. 19.0 were used to code ADRs.

In order to evaluate efficacy, changes in neutrophil counts (alternatively, 1/2 of the white blood cell counts if neutrophil counts were not available) during the first treatment cycle of chemotherapy were evaluated and (1) nadir of neutrophil counts, (2) maximum neutrophil counts after F-BS2 administration, and (3) duration of neutrophil counts less than 1500/μL were calculated. The grade of neutropenia was evaluated based on CTCAE as Grade 4: less than 500/μL, Grade 3: 500–1000/μL, Grade 2: 1000–1500/μL, and Grade 1/0: 1500/μL or higher.

2.4. Statistical analysis

To evaluate the risk factors affecting adverse reactions of F-BS2 in cancer patients treated with cancer chemotherapy, Fisher's exact test or a chi-square test was used in the univariate analyses. A logistic regression analysis using a stepwise method was utilized for multivariate analyses.

The time to recovery from neutropenia was expressed as cumulative recovered patient proportion estimated by the Kaplan-Meier method, and the difference in recovery periods between patient subgroups was evaluated by the Generalized Wilcoxon test.

3. Results

3.1. Patients and administration status

A total of 653 patients were registered from 67 institutions, and 643 case report forms were collected. Sixteen patients were excluded from the analyses due to errors in the registration process and safety data reporting, and 627 patients were evaluated in the safety analyses. In these 627 patients, F-BS2 was used in 616 patients for neutropenia associated with cancer chemotherapy, 6 for mobilization of autologous hematopoietic stem cells into peripheral blood, and 5 for the enhancement of engraftment of hematopoietic stem cell transplants. There were no patients with HIV infection registered. The case report forms for 13 cancer patients had insufficient information on blood counts and, therefore, these patients were excluded from the efficacy analysis set (Fig. 1).

The approved dosage and modality of F-BS2 varies depending on the indication, and a different administration route, dosage and treatment period were employed accordingly for the patients in this surveillance. For solid tumors, including malignant lymphomas, subcutaneous injection was mainly used in 591 out of 595 patients, 4 patients were treated intravenously, and the median daily dose and duration was 50 μg/m^2 (range: 38–245 μg/m^2) and 4

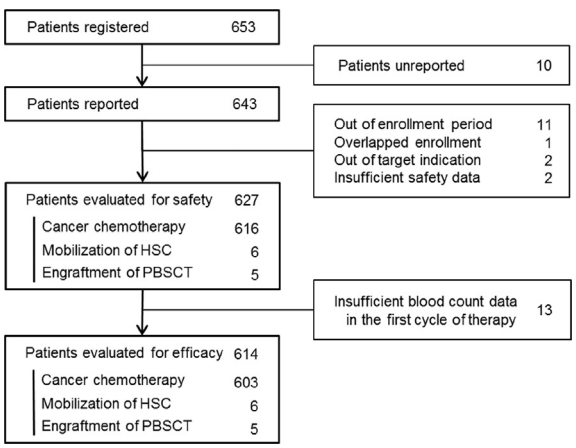

Fig. 1. Breakdown of patients in the Japanese post-marketing surveillance of filgrastim biosimilar 2. HSC: hematopoietic stem cell, PBSCT: peripheral blood stem cell transplants.

Please cite this article in press as: Tamura K, et al., Clinical safety and efficacy of "filgrastim biosimilar 2" in Japanese patients in a post-marketing surveillance study, J Infect Chemother (2017), https://doi.org/10.1016/j.jiac.2017.12.011