Original Article

Prophylaxis of neutropenia with mecapegfilgrastim in patients with non-myeloid malignancies: a real-world study

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Background: Chemotherapy-induced neutropenia is commonly encountered in clinical practice. The management of neutropenia has been evolving from short-acting granulocyte colony-stimulating factors (G-CSFs) to long-acting G-CSFs. However, an evaluation of the safety and effectiveness of long-acting G-CSFs in clinical practice is still lacking.

Methods: This multicenter, non-interventional study was aimed at exploring the safety and effectiveness of mecapegfilgrastim in different cancer patients in China. All patients provided written informed consent prior to the study and were treated according to routine clinical practice. Different prophylactic strategies (primary or secondary prophylaxis) were also compared.

Results: This study included 638 patients from May 2019 to November 2020. More than half of the participants were breast cancer patients. The mean age of all the patients was 56 years. White blood cell increase (6.2%) was the most frequently reported adverse event (AE) possibly related to the study drug. No unexpected AEs were reported. Grade ≥3 neutropenia in chemotherapy treatment cycle 1 was reported in 36 (5.6%) patients. Incidence of grade ≥3 neutropenia in cycle 1 in the primary and secondary prophylaxis subgroups were of 4.3% and 9.2%, respectively. A decreasing trend of severe neutropenia incidence was observed from cycle 1 to cycle 4.

Conclusions: Mecapegfilgrastim was generally well tolerated, and no unexpected AEs were observed in this study. Primary administration of mecapegfilgrastim led to a lower incidence of neutropenia than did secondary administration. Continuous administration of mecapegfilgrastim could keep the incidence of neutropenia to a relatively low level.

Keywords: Mecapegfilgrastim; granulocyte colony-stimulating factor; neutropenia; real-world

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Introduction

Chemotherapy-induced neutropenia, characterized as a decreased absolute neutrophil count (ANC) with or without fever, is frequently observed in non-myeloid malignancies (1). Neutropenia is one of serious chemotherapy-related hematological adverse events (AEs) that could lead to dose reductions/delays and may compromise treatment outcomes (2-4). Chemotherapy-induced neutropenia also incurs a great economic burden on cancer patients via hospitalization and follow-up care, and may even by life-threatening (5,6).

Granulocyte colony-stimulating factor (G-CSF) is one of the hematopoietic growth factors that facilitates the differentiation of committed granulocyte progenitors into mature granulocytes (e.g., neutrophils) (7). It has been widely used to prevent neutropenic complications of myelosuppressive chemotherapy. G-CSF was first developed as a short-acting formula. As shorting-acting G-CSF requires daily administration during chemotherapy, the long-acting formula, a pegylated G-CSF, was developed to overcome this inconvenience. Mecapegfilgrastim (HHPG-19K) is a novel long-acting G-CSF which was approved by the Chinese National Medical Products Administration (NMPA) in 2018. With the nature of a pegylated G-CSF, the half-life was greatly prolonged comparing to short-acting G-CSF. The administration of mecapegfilgrastim was only required once in each chemotherapy cycle, as a consequence, the compliance of patients was better than patients using short-acting G-CSF which required to be administrated each day during chemotherapy. The efficacy and safety profiles of mecapegfilgrastim has been investigated in 2 pivotal phase 3 randomized clinical trials (8,9). The results showed that mecapegfilgrastim was non-inferior and even superior to short-acting G-CSF in reducing the incidence/duration of severe neutropenia in breast cancer and non-small cell lung cancer patients. Furthermore, the safety profiles of mecapegfilgrastim and filgrastim are similar (8,9).

Despite the efficacy and safety of mecapegfilgrastim in prophylaxis of neutropenia being studied in several trials (8-10), the effectiveness and safety have not been well studied under a real-world setting in a large group of patients. Therefore, we initiated this real-world study to explore the effectiveness and safety profile of mecapegfilgrastim in patients with different types of cancer.

We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/atm-21-2449).

Methods

Study design

This was a prospective, multicenter, non-interventional, real-world study. The enrollment of patients began from May 2019. All patients provided written informed consent prior to the study and were treated in accordance with the Declaration of Helsinki (as revised in 2013) and routine clinical practice. This study was approved by the ethics committee of all study centers (No. 2019-006). The commercial electronic data capture system was applied to collect data. Source document verification was also conducted.

Eligible criteria

Patients were included if they were at least 18 years old, signed the informed consent forms, were pathologically or cytohistologically confirmed to have non-myeloid malignancy (including solid tumor and hematological tumor), and were considered able to tolerate mecapegfilgrastim by investigators. Patients were excluded if they were females who were pregnant or breastfeeding, hypersensitive to mecapegfilgrastim, recombinant human granulocyte colony-stimulating factor (rhG-CSF), pegylated rhG-CSF (PEG-rhG-CSF) or other similar biological agents; or were otherwise deemed by investigators to be not eligible for the study.

Outcomes

The primary outcome was incidence of any AEs, including changes in clinical laboratory values, vital signs, and physical examinations. The grading of the AEs was done according to National Cancer Institute – Common Terminology

Criteria for Adverse Events (version 5.0). The association between AEs and the investigated drug was evaluated by investigators.

The secondary outcomes were the incidence of grade ≥3 and grade 4 neutropenia (defined as ANC less than 1.0×10^9/L and less than 0.5×10^9/L, respectively) in cycle 1 and the incidence of grade ≥3 and grade 4 neutropenia from cycle 1 to cycle 4.

Study drug administration

The administration of study drug followed the routine clinical practice. In general, patients received mecapegfilgrastim subcutaneously by fixed dose (6 mg) or by weight (100 μg/kg) up to 1–3 days after each chemotherapy cycle. The National Comprehensive Cancer Network (NCCN) guideline for the management of neutropenia (version 1.2019) was followed to guide the investigators' practice.

Statistical analysis

This study included patients who completed the study from May 2019 to November 2020.

The full analysis set (FAS) was defined as enrolled patients who received mecapegfilgrastim at least once. The modified full analysis set (mFAS) was defined as the patients in FAS who had completed at least 4 treatment cycles and documented the ANC. The safety set (SS) was defined as the patients received mecapegfilgrastim at least once and had safety records.

The baseline characteristics of patients were presented with descriptive statistics in FAS. The primary outcome was evaluated in SS. The secondary outcomes were evaluated in FAS and mFAS.

Subgroup analysis (stratification factors: prophylaxis, primary or secondary; 1-, 2- , 3-, or 4-week chemotherapy) was conducted for the incidence of neutropenia in cycle 1.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

From May 2019 to November 2020, 638 patients received the study drug at least once, and those that completed the study were included in the FAS. A further 613 patients from the FAS who had safety records were included in the SS, while 175 patients from the FAS who had an ANC documentation of 4 cycles were considered for the mFAS and used to explore the effectiveness trend from chemotherapy cycle 1 to cycle 4.

Most of the patients were female (68.5%), and about half of the participants were breast cancer patients. The mean age was 55.7 years, and 26.6% were 65 years or older. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 constituted 92.3% of the population, and 77.3% of patients received mecapegfilgrastim as primary prophylaxis. The detailed baseline characteristics are presented in *Table 1*.

Safety

All patients in the SS (n=613) experienced an AE at least once. Adverse drug reactions (ADRs), as identified by investigators, were reported in 133 patients (21.7%). The most frequently reported ADR was white blood cell count increase (6.2%). White blood cell count decrease, nausea, and vomiting were reported as ADRs in about 3% patients. Neutrophil count increase and anemia were reported as ADRs in about 2% patients (*Table 2*). No grade 4 or higher ADRs were reported. In the SS, 16 (2.6%) patients reported serious AEs, with 1 being considered possibly related to the study drug.

Effectiveness

Incidence of neutropenia

During the first chemotherapy cycle, 36 (5.6%) patients experienced grade ≥3 neutropenia with 10 (1.6%) being grade 4 neutropenia. From cycle 1 to cycle 4, the incidence of grade 3 neutropenia had an overall decreasing trend (5.7%, 2.9%, 2.9% and 1.7%, respectively). A trend toward a lower incidence of grade 4 neutropenia was also observed with the continuous administration of mecapegfilgrastim (from cycle 1 to cycle 4, 4%, 0.6%, 1.7% and 1.7%, respectively) (*Figure 1*).

Subgroup analysis of effectiveness

In the subgroup analysis, 21 (4.3%) patients in the primary prophylaxis group and 13 (9.2%) patients in secondary prophylaxis group experienced grade ≥3 neutropenia in cycle 1.

Meanwhile, 6 (1.2%) patients in the primary prophylaxis group and 4 (2.8%) patients in secondary prophylaxis group

Table 1 Characteristics of the participants

Characteristic	FAS (n=638)
Sex, n (%)	
Male	200 (31.3)
Female	437 (68.5)
Missing	1 (0.2)
Age, mean ± SD	55.7 (12.23)
Age group, n (%)	
<65	466 (73.0)
≥65	170 (26.6)
Missing	2 (0.4)
ECOG PS, n (%)	
0–1	589 (92.3)
≥2	4 (0.6)
Missing	45 (7.1)
Prior G-CFS, n (%)	
Yes	142 (22.3)
No	493 (77.3)
Missing	3 (0.4)
Prophylaxis strategy, n (%)	
Primary	493 (77.3)
Secondary	142 (22.3)
Missing	3 (0.4)
Radiotherapy history, n (%)	
Yes	66 (10.3)
No	566 (88.7)
Missing	6 (1.0)
Cycle length, n (%)	
1 week	20 (3.1)
2 weeks	41 (6.4)
3 weeks	407 (63.8)
4 weeks	14 (2.3)
Missing	156 (24.4)
Study drug dosage, n (%)	
Fixed dosage (6 mg)	626 (98.1)
Weight-adjusted dosage (100 μg/kg)	12 (1.9)
Cancer type, n (%)	
Solid tumor:	
Breast cancer	323 (50.6)
Colorectal cancer	51 (8.0)
Non-small cell lung cancer	43 (6.7)
Gastric cancer	35 (5.5)
Small cell lung cancer	33 (5.2)
Esophageal cancer	22 (3.4)
Ovarian cancer	16 (2.5)
Pancreatic cancer	13 (2.0)
Nasopharyngeal cancer	9 (1.4)
Cervical cancer	7 (1.1)
Head and neck cancer	4 (0.6)
Hematological tumor:	
DLBCL	9 (1.4)
Other B-cell lymphoma	6 (0.9)
T-cell lymphoma	3 (0.5)
Others	5 (0.8)
Cancer stage	
I	32 (5.1)
II	133 (20.8)
III	133 (20.8)
IV	137 (21.5)
Missing	209 (32.8)

ECOG PS, Eastern Cooperative Oncology Group performance status; FAS, full analysis set; G-CFS, granulocyte colony-stimulating factor; DLBCL, diffused large-B cell lymphoma.

Table 2 The most frequently reported adverse events possibly related to study drug

Adverse events	SS (n=613)
White blood cell count increase, n (%)	38 (6.2)
White blood cell count decrease, n (%)	19 (3.1)
Nausea, n (%)	20 (3.3)
Vomiting, n (%)	19 (3.1)
Anemia, n (%)	13 (2.1)
Neutrophil count increase, n (%)	14 (2.3)

SS, safety set.

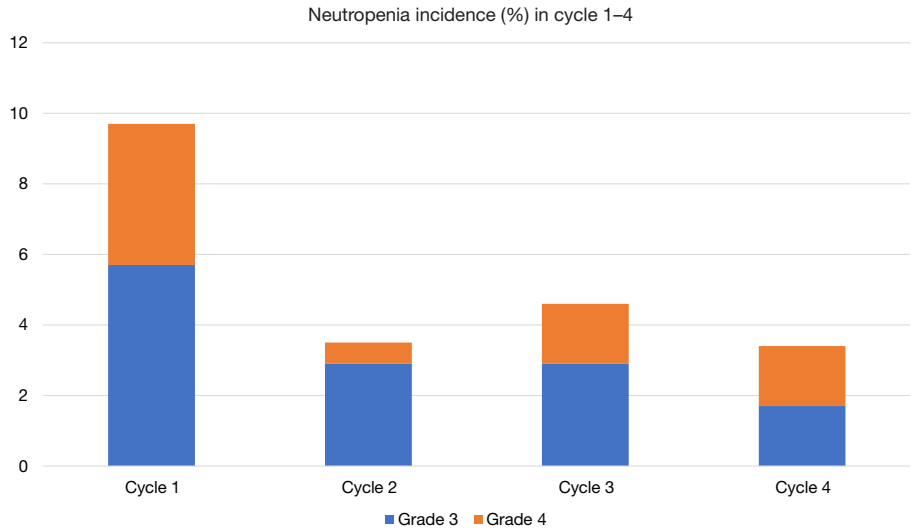

Figure 1 Incidence of neutropenia from cycle 1 to cycle 4 in participants with absolute neutrophil count records in all 4 cycles (mFAS, n=175).

Table 3 Effectiveness by different subgroups in chemotherapy cycle 1

Treatment	Endpoints	
	Grade ≥3 neutropenia, n (%)	Grade 4 neutropenia, n (%)
Prophylaxis strategy		
Primary (n=493)	21 (4.3)	6 (1.2)
Secondary (n=142)	13 (9.2)	4 (2.8)
Chemotherapy		
1 week (n=20)	3 (15)	3 (15)
2 weeks (n=41)	1 (2.4)	0
3 weeks (n=407)	28 (6.9)	6 (1.5)
4 weeks (n=14)	1 (7.1)	0

experienced grade 4 neutropenia in cycle 1. Patients with a 1-week chemotherapy plan had the highest incidence of neutropenia (*Table 3*). Approximately 7% of patients with non-small cell lung cancer had grade ≥3 neutropenia in cycle 1, which was the highest proportion according to cancer type and was followed by breast cancer (6.2%), small cell lung cancer (6.1%), hematological cancer (4.8%), colorectal cancer (3.9%), and gastric cancer (2.9%).

Discussion

The efficacy and safety of mecapegfilgrastim had been explored in non-small cell lung cancer patients and breast cancer patients previously. In this study, we investigated the tolerability and effectiveness of mecapegfilgrastim in various cancer patients in routine clinical practice. Administration of mecapegfilgrastim in real-world setting could reduce the incidence of grade ≥3 neutropenia and there were no unexpected AEs were reported.

In a phase 2 study of breast cancer patients treated with 100 μg/kg of mecapegfilgrastim, it was reported that leukocytopenia occurred in 10% patients, while neutrophilia, leukocytosis, and thrombocytosis occurred in 6.7% patients; the non-hematologic AEs with an incidence of greater than 5% were nausea, vomiting, anorexia and myalgia (10). A pivotal phase 3 study of mecapegfilgrastim in breast cancer patients found that the most frequently reported treatment-related AEs were hemoglobin decline (12.6% and 13.6%) and fatigue

(15.3% and 13.6%) in a 100 μg/kg group and a fixed dose 6 mg group respectively (9). Another pivotal phase 3 study of mecapegfilgrastim in non-small cell lung cancer patients found leukocytosis (8.5% and 2.1%) and fatigue (4.3% and 6.3%) in a 100 the μg/kg group and fixed dose 6 mg group, respectively (8). In the previous key trials of breast cancer patients, the most frequently reported AE possibly related to pegfilgrastim was skeletal/bone pain (more than 25%) (11,12). Our real-world study found that the most frequently reported AE possibly related to the study drug was white blood cell count increase. Only 1 (0.2%) patient reported back pain, representing a lower incidence of back pain (less than 0.9%) than that reported in the previous phase 3 breast cancer trial. There were 137 (22.3%) patients who received an analgesic drug combination, which could have been the cause of the relatively low incidence of bone pain.

In a phase 3 study of mecapegfilgrastim. about 50% and 30% breast cancer patients experienced grade ≥3 and grade 4 neutropenia, respectively, after administration of mecapegfilgrastim in cycle 1. This was probably related to the highly toxic chemotherapy (Anthracyclines and Taxane, AT or Adriamycin and Cyclophosphamide, AC) used for these patients (9). There was also decreasing trend of incidence of neutropenia from cycle 1 to cycle 4 reported in breast cancer patients after administration of mecapegfilgrastim (9). This trend was also reported in the 2 phase 3 trials in breast cancer patients given pegfilgrastim (11,12). In our study, we did not find a high incidence of neutropenia in cycle 1 as compared to the previous phase 3 breast cancer trial (9). The chemotherapy used for breast cancer patients in this study was more diverse and of lower toxicity compared with the chemotherapy (AC or AT) used several years ago. The incidence of grade ≥3 neutropenia in cycle 1 of non-small cell lung cancer patients was similar to that of a pivotal phase 3 trial (8), while a similar decreasing trend of neutropenia incidence rate from cycle 1 to cycle 4 was identified in these key trials and in this real-world study.

In terms of the prophylactic strategy of G-CSF, primary or secondary prophylaxis has been explored in several studies. A real-world study in Belgium and Luxembourg found that patients receiving lipegfilgrastim had a lower incidence of grade 3 and grade 4 neutropenia than did those receiving it secondarily (13). Another prospective, non-interventional, multicenter study conducted in Germany also reported that primarily administration of lipegfilgrastim demonstrated a lower incidence of severe neutropenia compared with secondary administration (14). These findings are in line with our results.

Pegfilgrastim has not been recommended for weekly administration in patients treated with cytotoxic chemotherapy, as there is insufficient supporting data (15). The high incidence of neutropenia in patients of 1-week chemotherapy was observed in this real-world study and is likely linked with the mechanism of long-acting G-CSF.

There were several limitations to our research that should be noted. First, the number of patients included for analysis was still relatively small. Second, all analyses were descriptive, and no formal statistical assumptions were applied. Nonetheless, this study provides support for continuing this line of research and insights into clinical practice.

Conclusions

Mecapegfilgrastim was well tolerated in different cancer patients, and no unexpected AEs were observed in this real-world setting. Primary prophylactic administration of mecapegfilgrastim could lower the incidence of neutropenia as compared to secondary usage. Administration of mecapegfilgrastim continuously could keep the incidence of neutropenia at a relatively low level.

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Footnote

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Data Sharing Statement: Available at http://dx.doi.org/10.21037/atm-21-2449

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-21-2449). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. This study was approved by the ethics committee of all study centers (No. 2019-006). The commercial electronic data capture system was applied to collect data. All patients provided written informed consent prior to the study and were treated in accordance with the Declaration of Helsinki (as revised in 2013) and routine clinical practice.

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