Original Article

Prophylactic administration of mecapegfilgrastim after chemotherapy in patients with lymphoma

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Background: Neutropenia is a common and serious complication encountered during chemotherapy treatment of cancer patients. The incidence of neutropenia increases the risk of infection and can influence the chemotherapy treatment in terms of drug dosage and treatment duration. Mecapegfilgrastim is a novel, long-acting pegylated recombinant human granulocyte-colony stimulating factor (PEG-rhG-CSF) designed to prevent the incidence of neutropenia. The study aims to observe the effectiveness and safety of mecapegfilgrastim as prophylaxis for chemotherapy-induced neutropenia in patients with lymphoma.

Methods: Ninety-one patients with lymphoma were enrolled and received mecapegfilgrastim as either primary or secondary prophylaxis. The incidence of grade III/IV neutropenia, the duration of grade III/IV neutropenia in the overall population, and the differences between the primary and secondary prophylaxis groups were investigated. Adverse events were also recorded.

Results: During the first chemotherapy cycle, the incidence of grade III and grade IV neutropenia was 5% and 7%, respectively. Of the 71 patients who received mecapegfilgrastim as primary prophylaxis, the incidence of grade III and grade IV neutropenia was 4% and 1%, respectively. Of the 20 patients who received mecapegfilgrastim as secondary prophylaxis, the incidence of grade III and grade IV neutropenia was 10% and 25%, respectively. The mean duration of grade III neutropenia was 0.85 days. The mean duration of grade III neutropenia in patients who received mecapegfilgrastim as primary prophylaxis was one day less than patients who received mecapegfilgrastim as secondary prophylaxis. Fever and bone/muscle pain were the most frequently observed adverse events.

Conclusions: Mecapegfilgrastim is more effective in reducing the incidence of grade III/IV neutropenia and the mean duration of febrile neutropenia (FN) when used as primary prophylaxis rather than secondary prophylaxis in patients with lymphoma. The toxicity of mecapegfilgrastim was tolerable.

Keywords: Mecapegfilgrastim; lymphoma; neutropenia

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Introduction

Lymphoma is the most common form of hematological malignancy. The two main types of lymphoma are Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). Lymphoma, with a death rate of 36.2 per million people, was the tenth most fatal cancer in China in 2015 (1). Lymphoma is a systemic disease. Except for those with limited lesions (early stage/stage I) who choose radiotherapy or surgery for treatment, most patients should first receive

systemic chemotherapy.

Among cancer patients receiving myelosuppressive chemotherapy, febrile neutropenia (FN) is a potentially life-threatening complication (2-4). FN usually leads to a longer hospital stay, an increase in treatment costs, and a reduction or delay in the dose of chemotherapy, thereby affecting the quality of life of the patient and increasing the risk of death (5-7). Prophylactic use of granulocyte-colony stimulating factor (G-CSF) for patients with myelosuppressive chemotherapy can reduce the incidence of FN, agranulocytosis, and infection (8-11).

Mecapegfilgrastim is a long-acting pegylated recombinant human granulocyte-colony stimulating factor (PEG-rhG-CSF) which has been developed to reduce the incidence of FN. Mecapegfilgratim only needs to be administered once per chemotherapy cycle. This is more convenient than short-acting G-CSF and will elevate the compliance of patients receiving chemotherapy. The efficacy and safety of mecapegfilgrastim in breast cancer and non-small cell lung cancer patients has been studied in two pivotal trials (12,13). Compared with short acting G-CSF (filgrastim), mecapegfilgrastim was superior on reducing duration of grade ≥3 neutropenia in breast cancer patients treated with chemotherapy (14). However, research on the use of mecapegfilgrastim in lymphoma patients is lacking.

We present the following article in accordance with the TREND reporting checklist (available at https://dx.doi.org/10.21037/apm-21-3209).

Methods

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was registered on Chinese Clinical Trial Registry (https://www.chictr.org.cn/index.aspx) (No.: ChiCTR2100048123). The study was approved by Chinese Ethics Committee of Registering Clinical Trials (No.: ChiECRCT20210350). All patients signed informed consent forms.

Eligibility criteria

Patients with HL or NHL from Shanxi Tumor Hospital who received at least one cycle of chemotherapy were enrolled. The inclusion criteria were as follows: age ≥18 years; the ability to complete at least one cycle of chemotherapy as planned (patients with an intermediate risk of FN needed to have more than one risk factor); a normal bone marrow hematopoietic function with no bleeding tendency; absolute neutrophil count (ANC) $\geq 2.0\times10^9$/L, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤1.5 times of upper limits of normal (ULN), serum total bilirubin (TBIL) ≤1.5 times of ULN, and serum creatinine (Scr) ≤1.5 times of ULN. The exclusion criteria were as follows: presence of acute infection and receipt of systemic anti-infection treatment in the 72 hours before chemotherapy; presence of hematological diseases affecting the hematopoietic function of bone marrow; patients who had bone marrow or stem-cell transplantation within the past 3 months; presence of other uncured or brain metastatic malignant tumors; allergic or intolerable to the study drugs; presence of mental or nervous system disorders; women who were pregnant or breast feeding; women of childbearing age who refused contraceptive use; patients who had previously received PEG-rhG-CSF; and some special cases that the investigators determined should be excluded.

Mecapegfilgrastim administration

Primary prophylaxis: In accordance with the National Comprehensive Cancer Network (NCCN) guidelines (NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors, version 2.2019), G-CSF was administered to patients with a higher than 20% risk of developing FN after the first chemotherapy cycle; for patients with an overall risk of developing FN between 10% and 20%, G-CSF was considered after evaluation of patient risk factors.

Secondary prophylaxis: An incidence of FN or a dose-limiting neutropenia event in the previous chemotherapy cycle suggested administration of G-CSF in the next chemotherapy cycle.

Eligible patients were given mecapegfilgrastim (fixed dose, 6 mg) 48 h after chemotherapy by a single subcutaneous injection.

Effectiveness assessment

The primary endpoint was the incidence of grade III/IV neutropenia (ANC $<1.0\times10^9$/L) in the first cycle after mecapegfilgrastim administration. The secondary efficacy endpoints included the mean duration of grade III/IV neutropenia in the first cycle after mecapegfilgrastim administration; the incidence of grade III/IV neutropenia in patients receiving primary or secondary prophylaxis; and

Table 1 Baseline characteristics of patients

Characteristics	n (%)
Age group	
18–65	22 (24.2)
>65	69 (75.8)
Sex	
Male	54 (59.3)
Female	37 (40.7)
The Karnofsky performance scale	
60	2 (2.2)
70	13 (14.3)
80	71 (78.0)
90	5 (5.5)
Tumor type	
Diffused large B-cell lymphoma	49 (53.8)
T-cell lymphoma	13 (14.3)
B-cell lymphoma	11 (12.1)
Other non-Hodgkin's lymphoma	15 (16.5)
Classic Hodgkin's lymphoma	3 (3.3)
Tumor stage	
I	7 (7.7)
II	22 (24.2)
III	21 (23.1)
IV	41 (45.0)

the mean duration of grade III/IV neutropenia in patients receiving primary or secondary prophylaxis.

Safety assessment

Adverse events in eligible patients were recorded.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics, effectiveness, and safety data. All statistical analysis was applied with SPSS 17.0. Categorial variables were presented as number and percentage, n (%). Continuous variables were classified into different groups and presented as n (%). Adverse events were recorded and presented as n (%).

Results

Patients

From January 2018 to September 2019, 91 eligible patients were administered mecapegfilgrastim after a single cycle of chemotherapy. Sixty-nine (76%) patients were older than 65 years. Fifty-four (59%) were male patients. Seventy-one (78%) patients had Karnofsky Performance Scale (KPS) scores of 80. Forty-nine (54%) patients had Diffuse large B-Cell lymphoma. Sixty-two (67%) patients were classified as phase III/IV lymphoma (*Table 1*).

Effectiveness

During the first chemotherapy cycle, 11 (12%) patients had grade III/IV neutropenia. The mean duration of grade III/IV neutropenia was 0.85 days.

In 71 patients receiving primary prophylaxis, the incidence of grade III and grade IV neutropenia was 4% and 1%, respectively. The mean duration of grade III/IV neutropenia of these patients was 0.63 days (*Table 2*).

In 20 patients receiving secondary prophylaxis, the incidence of grade III and grade IV neutropenia was 10% and 25%, respectively. The mean duration of grade III/IV neutropenia of these patients was 1.6 days (*Table 2*).

Safety

Of the total 91 patients who received mecapegfilgrastim, 9 (9.9 %) and 6 (6.6 %) patients reported fever and bone/muscle pain, respectively. Nausea, vomiting, and malaise were observed in 3 (3%), 3 (3%), and 3 (3%) patients, respectively. The observed adverse events were mostly grade I or grade II. No adverse event greater than grade III was observed. The detailed adverse events are presented in *Table 3*. Of all the adverse events, the occurrence of bone/muscle pain was considered very likely related to the investigated drug; Fever, nausea, vomiting, and malaise were likely associated with the investigated drug; and pruritus, dyspnea and skin ulceration might not be related to the investigated drug.

Discussion

This study presented the effectiveness and safety of mecapegfilgrastim administration in lymphoma patients in a real-world setting. To our knowledge, this is the first clinical study of mecapegfilgrastim in this circumstance. The results

Table 2 Effectiveness results in cycle one

Variable	Primary prophylaxis, N=71	Secondary prophylaxis, N=20	All, N=91
Grade III neutropenia, n (%)	3 (4.2)	2 (10)	5 (5.5)
Grade IV neutropenia, n (%)	1 (1.4)	5 (25.0)	6 (6.6)
Mean duration of grade III/IV neutropenia, days	0.63	1.60	0.85

Table 3 Adverse events

Adverse events	n (%)
Fever	9 (9.9)
Bone/muscle pain	6 (6.6)
Nausea	3 (3.3)
Vomiting	3 (3.3)
Malaise	3 (3.3)
Pruritus	1 (1.1)
Dyspnea	1 (1.1)
Skin ulceration	1 (1.1)

of this study indicated that prophylactic administration of mecapegfilgrastim in lymphoma patients resulted in an incidence of grade III/IV neutropenia of about 12%. This is lower than the incidence rates in breast cancer (51%) and advanced non-small cell lung cancer (14%) patients in the pivotal trials (12,14). The mean duration of grade III/IV neutropenia in patients with lymphoma was 0.85 days which is shorter than that of breast cancer patients (1.23 days) and longer than that of advanced non-small cell lung cancer patients (0.69 days) in the pivotal trials (12,14).

More than 50% of breast cancer patients experienced grade III or grade IV neutropenia following administration of mecapegfilgrastim in cycle one in the phase 3 study of mecapegfilgrastim (14). In this study, we did not find as high an incidence of neutropenia in cycle one as in the previous phase 3 breast cancer trial. This probably resulted from the chemotherapy (AT, anthracyclines-taxane or AC, adriamycin and

cyclophosphamide) used for the breast cancer patients at that time. The chemotherapy used for lymphoma patients in this study was more diverse and of lower toxicity.

Primary prophylaxis showed a reduction in the incidence of grade III/IV neutropenia and a shorter duration of grade III/IV neutropenia compared with secondary prophylaxis. The safety profile of mecapegfilgrastim administration in lymphoma patients was similar to the safety findings in two pivotal trials. Bone/muscle pain and fever were the most frequently observed adverse events. No serious adverse events have been observed in this study.

Primary or secondary prophylaxis of neutropenia using G-CSF has been investigated in several studies. A study conducted in Belgium and Luxembourg indicated that patients who received long-acting G-CSF as primary prophylaxis had a lower incidence of grade III and grade IV neutropenia than those who received secondary administration (15). Another prospective non-interventional study in Germany also reported that primary administration of long-acting G-CSF had a lower incidence of severe neutropenia compared with secondary administration (16). These findings are in line with our findings in this study. Due to the diverse chemotherapy regimen for patients with lymphoma, the optimize administration schedule and dosage of G-CSF still need to explore in large prospective studies.

There were limitations in this study. This study was conducted with a relatively small-sized population. A larger sample size real-world study is warranted to confirm the validity of the present results. Besides, the follow up time was relatively short. A long-term follow-up of patients would provide valuable information on health-related outcome.

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Footnote

Reporting Checklist: The authors have completed the TREND reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-3209

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-3209). 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. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). This study was registered on Chinese Clinical Trial Registry (No.: ChiCTR2100048123). The study was approved by Chinese Ethics Committee of Registering Clinical Trials (No.: ChiECRCT20210350). All patients signed informed consent forms.

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