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Mecapegfilgrastim for prophylaxis of febrile neutropenia in children and adolescents with rhabdomyosarcoma or Ewing sarcoma: a prospective, single-arm, pilot study

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Abstract

Background The chemotherapy regimens recommended for both rhabdomyosarcoma (RMS) and Ewing sarcoma (ES) patients are myelosuppressive and can reduce the absolute neutrophil count (ANC) and subsequently increase the risk of febrile neutropenia (FN). However, only a few studies have focused on the efficacy and safety of granulocyte-colony stimulating factor (G-CSF) drugs in pediatric and adolescent patients with RMS and ES. Our objective was to investigate the efficacy and safety of mecapegfilgrastim, a biosimilar of pegfilgrastim, in prophylaxis of FN for pediatric and adolescent patients with RMS or ES.

Methods In this single-arm, single-center, prospective study, pediatric and adolescent patients with RMS or ES were enrolled to receive either VAC (vincristine, cyclophosphamide, dactinomycin) regimen or VDC (vincristine, cyclophosphamide, doxorubicin) regimen in a 3-week cycle, followed by treatment with mecapegfilgrastim (100 μg/kg, maximum 6 mg) given at 24 h after completing chemotherapy. The primary endpoint was the incidence rate of FN. Secondary endpoints included the incidence rate of grade 4 neutropenia, duration of ANC $\leq 0.5 \times 10^9$/L, incidence rate of chemotherapy delay or reduction, use of antibiotics, and safety profile.

Results In total, 2 of the 30 (6.7%, 95% CI: 0.82–22.07) patients experienced FN after the first cycle of chemotherapy. Eight (26.7%, 95% CI: 12.28–45.89) patients experienced grade 4 neutropenia after receiving prophylactic mecapegfilgrastim. Eight patients experienced ANC $\leq 0.5 \times 10^9$/L with a median duration of 4.5 days; among them, 6 patients reached the lowest point of their ANC level on day 7, and 5 of them recovered by day 10. No dose reductions, delays, or discontinuation of chemotherapy was reported. Twenty-one (70.0%) patients received antibiotics during the treatment period. No patient experienced FN in the 0–5 years and the 13–18 years groups, and 2 patients experienced FN in the 6–12 years group. Two patients, 6 patients, and no patient experienced grade 4 neutropenia in the 0–5 years, 6–12 years, and 13–18 years groups, respectively.

Conclusion Mecapegfilgrastim showed acceptable efficacy and safety profile in pediatric and adolescent patients with RMS or ES. Further randomized studies with large sample size are warranted.

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Keywords Rhabdomyosarcoma, Ewing sarcoma, Febrile neutropenia, Granulocyte colony-stimulating factor, Pegfilgrastim

Introduction

For pediatric and adolescent patients with malignancies, rhabdomyosarcoma (RMS) is the most commonly diagnosed soft tissue sarcoma, and Ewing sarcoma (ES) is the second most common bone tumor [1, 2]. Currently, the consensus in the treatment of RMS and ES are multimodality therapies consisting of surgery, chemotherapy and radiotherapy. The chemotherapy regimen recommended for RMS is based on vincristine, dactinomycin, and cyclophosphamide (VAC), whereas the standard-of-care chemotherapy for ES consists of vincristine, adriamycin, and cyclophosphamide followed by ifosfamide and etoposide (VDC/IE) [2, 3].

Unfortunately, these two chemotherapy regimens are both myelosuppressive and can reduce absolute neutrophil count (ANC), causing neutropenia and subsequently increasing the risk of febrile neutropenia (FN) [4]. FN is a life-threatening complication defined as patients with oral temperature above 38℃ while experiencing chemotherapy-induced neutropenia, and it exhibited significant association with mortality rate of pediatric and adolescent patients [5, 6]. Currently, granulocyte-colony stimulating factor (G-CSF) drugs have been recognized as one of the most commonly used regimens for prophylaxis of chemotherapy-induced FN and neutropenia, however, only a few studies have focused on the efficacy and safety of G-CSF drugs in pediatric and adolescent patients. In addition, compared with short-acting G-CSF, pegylated recombinant human G-CSF (PEG-rhG-CSF) has a longer plasma half-life and requires a lower injection frequency; thus, it is preferred for children and adolescents in clinical practice [7, 8].

Mecapegfilgrastim, a PEG-rhG-CSF, is a biosimilar of pegfilgrastim that has shown promising clinical benefit in the prevention of chemotherapy-induced FN and neutropenia in many solid tumors, such as lung cancer [9] and breast cancer [10, 11]. Nevertheless, the efficacy and safety of mecapegfilgrastim in pediatric and adolescent patients with RMS or ES have not been investigated.

On the basis of the above information, we conducted this pilot, single-arm study aimed to explore the efficacy and safety of mecapegfilgrastim for the prophylaxis of FN in pediatric and adolescent patients with RMS or ES.

Methods

Study design and patients

This was a single-arm, single-center, prospective study conducted from September 2019 to August 2021 at Beijing Children's Hospital. Pediatric and adolescent patients with RMS or ES were enrolled. If the patients were older than 8 years, written informed consent was signed by both the patients and their parents; if the patients were under 8 years, written informed consent was signed only by the patients' parents.

The present study was registered in the Chinese Clinical Trial Registry (No. ChiCTR1900022249) and approved by the ethics committee of Beijing Children's Hospital (IEC-C-006-A03-V.05).

Patients who met the following criteria were included: (1) aged < 18 years; (2) had rhabdomyosarcoma or Ewing sarcoma confirmed by pathological examination; (3) underwent at least one cycle of treatment with the VAC or VDC regimen; (4) had Karnofsky performance score (KPS) ≥ 70; (5) had a life expectancy longer than 3 months; and (6) had a laboratory test result of ANC $\geq 2.0 \times 10^9$/L, alanine aminotransferase ≤ 2.5 × upper limit of normal (ULN), and aspartate aminotransferase ≤ 2.5 × ULN.

Patients were excluded if they (1) had severe infection; (2) had autoimmune diseases; (3) had severe hepatic, renal, cardiac, or pulmonary dysfunction; or (4) were allergic to rhG-CSF, PEG-rhG-CSF, or other products derived from *Escherichia coli*.

Procedure

The VAC regimen (vincristine, 1.5 mg/m^2, intravenously, on day 1; cyclophosphamide, 1.2 g/m^2, intravenously, on day 1; dactinomycin, 0.045 mg/kg, intravenously, on day 1) was administered to RMS patients over a 3-week cycle. The dosage was reduced by half when patients were younger than 12 months or lighter than 12 kg.

The VDC regimen (vincristine, 1.5 mg/m^2, intravenously, on day 1; cyclophosphamide, 1.2 g/m^2, intravenously, on day 1; doxorubicin 30 mg/m^2·d, intravenously, on day 1, day 2) was administered to ES patients in a 3-week cycle. For patients younger than 3 years or with a body surface area under 0.6 m^2, vincristine of 0.05 mg/kg and cyclophosphamide of 40 mg/kg were performed.

Mecapegfilgrastim was given 24 h after completing chemotherapy. The administration dose was 100 μg/kg, with a maximum dose of 6 mg.

Outcomes and assessment

The primary endpoint was the incidence rate of FN defined as a temperature of > 38.3℃ or two consecutive readings of > 38.0℃ for 2 h and an absolute neutrophil count (ANC) of $< 0.5 \times 10^9$/L, or expected to fall below 0.5×10^9/L [8]. Secondary endpoints included the incidence rate of grade 4 neutropenia defined as an ANC $< 0.5 \times 10^9$/L according to Common Terminology Criteria for Adverse Events, version 3.0; and duration of ANC $\leq 0.5 \times 10^9$/L; the incidence rate of chemotherapy delay or reduction, the usage of antibiotics, and the safety profile.

ANC was monitored by routine blood examination on day 0, 7, 10, 14, and 21 after the completion of chemotherapy. Adverse events such as neutropenia and FN were assessed via routine blood tests according to the Common Terminology Criteria for Adverse Events (CTCAE 3.0).

Statistical analysis

No formal sample size estimation was conducted because this was an exploratory study. Efficacy and safety were analyzed based on the full analysis set, in which all enrolled patients received at least one dose of the study treatment.

For categorical data, the number of patients (n) and percentage (%) in each category, as well as the number and percentage of patients with missing data, were calculated. For continuous data, the number of nonmissing subjects (n), arithmetic mean, standard deviation, median, minimum, and maximum value were reported. Binary endpoints were summarized as the number of patients (n) and percentage (%) with the corresponding exact 2-sided 95% confidence intervals (CIs) estimated by the Clopper–Pearson method. All analyses were performed with SAS version 9.4 (SAS Institute Inc.).

Results

Baseline characteristics

In total, 30 patients were screened and enrolled in the present study between September 2019 and August 2021 (Supplementary Fig. 1). The median age of these patients was 7.1 years (range: 0–17), among whom 13 were younger than 6 years, 15 were aged from 6 to 13 years, and 2 were aged from 13 to 18 years. The male to female ratio was 2:1. The median weight was 32.7 kg (range: 10–71). Twenty-one (70%) patients were diagnosed with RMS and treated with VAC, and the remaining 9 (30%) patients with ES were treated with VDC. The median white blood cell count and neutrophil count at baseline were 7.2 and 3.9×10^9/L, respectively (Table 1).

Efficacy

Overall, 2 of the 30 (6.7%, 95% CI: 0.82–22.07) patients experienced FN after the first cycle of chemotherapy. Eight (26.7%, 95% CI: 12.28–45.89) patients experienced grade 4 neutropenia after receiving prophylactic mecapegfilgrastim, and the median duration time of ANC $\leq 0.5 \times 10^9$/L was 4.5 days.

Among the 8 patients who experienced ANC $\leq 0.5 \times 10^9$/L, 6 patients reached the lowest point of their ANC level on day 7. Subsequently, 5 of them recovered by day 10, while 1 patient's recovery was not recorded until day 14 due to unknown data on day 10. The remaining 2 patients reached their lowest ANC level on day 10 and recovered on day 14 (Fig. 1). Twenty-one (70.0%) patients received antibiotics during the treatment period. No dose reductions, delays, or discontinuation were reported (Table 2).

Regarding chemotherapy regimens, no patients in the VAC group developed FN. Only 1 (4.8%) patient experienced grade 4 neutropenia.

Table 1 Patient characteristics

Characteristics	Mecapegfilgrastim (*N* = 30)
Age (years)	
Median	7.1
Range	0–17
【0–6)	13 (43.4%)
【6–13)	15 (50.0%)
【13–18)	2 (6.7%)
Sex, n (%)	
Boys	20 (66.7%)
Girls	10 (33.3%)
Weight (kg),	
Median	32.7
Range	10–71
Baseline ANC ($\times 10^9$/L), mean ± SD (min, max)	7.2 ± 1.97 (3, 12)
Baseline WBC ($\times 10^9$/L), mean ± SD (min, max)	3.9 ± 1.86 (1, 10)
Cancer Type, n (%)	
Rhabdomyosarcoma	21 (70.0%)
Ewing sarcoma	9 (30.0%)
Chemotherapy, n (%)	
VAC	21 (70.0%)
VDC	9 (30.0%)

ANC absolute neutrophil count, *WBC* white blood cell count, *VAC* vincristine + cyclophosphamide + dactinomycin, *VDC* vincristine + cyclophosphamide + doxorubicin

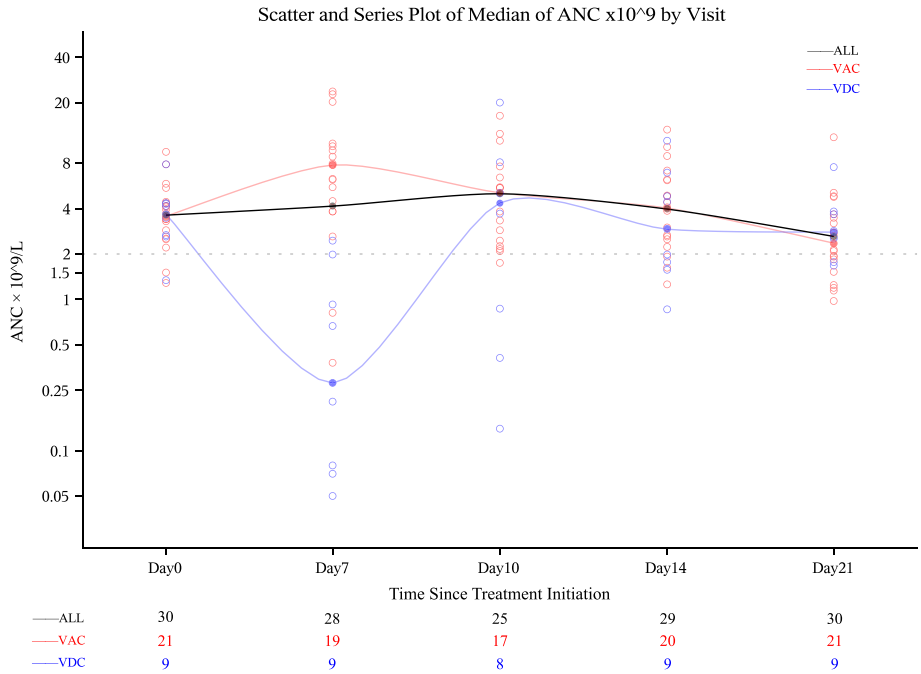

Fig. 1 ANC recovery time

Table 2 Efficacy

Items	Mecapegfilgrastim (*N* = 30)
Primary Endpoint	
Incidence of FN, n (%) 95% CI	2 (6.7%) (0.82–22.07)
Secondary Endpoints	
Incidence of grade 4 neutropenia, n (%) 95% CI	8 (26.7%) (12.28–45.89)
median recovery time (Q1,Q3) (d)	4.5 (4.0, 6.5)
Use of antibiotics, n (%)	21 (70.0%)
Delay of chemotherapy, n (%)	0 (0%)
Discontinuation of chemotherapy, n (%)	0 (0%)

FN febrile neutropenia

Table 3 Subgroup analysis of different chemotherapy regimens

Items	VAC (*N* = 21)	VDC (*N* = 9)
Primary Endpoint		
Incidence of FN, n (%)	0 (0.0%)	2 (22.2%)
Secondary Endpoints		
Incidence of grade 4 neutropenia, n (%)	1 (4.8%)	7 (77.8%)

VAC vincristine + cyclophosphamide + dactinomycin, *VDC* vincristine + cyclophosphamide + doxorubicin, *FN* febrile neutropenia

In the VDC group, 22.2% (2/9) of patients experienced FN, and 7 (77.8%) of patients experienced grade 4 neutropenia (Table 3).

Regarding different age groups, in patients between 0–5 years old, no patient experienced FN, 2 patients experienced grade 4 neutropenia. In patients between 6 to 12 years, 2 patient experienced FN, 6 patients experienced grade 4 neutropenia. In patients between 13 to 18 years, no patient experienced FN and grade 4 neutropenia (Table 4).

Safety

Overall, a total of 20 (66.7%) patients experienced treatment-emergent AEs (TEAEs), and 9 (30.0%) patients experienced treatment-related AEs (TRAEs). The most common type of TEAE was vomiting (8/30, 26.7%), followed by fever (6/30, 20.0%), infection (4/30, 13.3%), and neutrophilia (4/30, 13.3%). The most common TRAE was

Table 4 Subgroup analysis of different age groups

Items	0–5 Years (*N* = 15)	6–12 Years (*N* = 13)	13–18 Years (*N* = 2)
Primary Endpoint			
Incidence of FN, n (%)	0 (0.0%)	2 (13.3%)	0 (0.0%)
Secondary Endpoints			
Incidence of grade 4 neutropenia, n (%)	2 (15.4%)	6 (40.0%)	0 (0.0%)

FN Febrile neutropenia

Table 5 Adverse effects

	Grade 1–2 n (%)	Total n (%)
TEAEs	20 (66.7)	20 (66.7)
Vomiting	8 (26.7)	8 (26.7)
Fever	6 (20.0)	6 (20.0)
Infection	4 (13.3)	4 (13.3)
Neutrophilia	4 (13.3)	4 (13.3)
Leucocytosis	3 (10.0)	3 (10.0)
Nausea	3 (10.0)	3 (10.0)
Neutropenia	3 (10.0)	3 (10.0)
Mononucleosis	2 (6.7)	2 (6.7)
Liver dysfunction	2 (6.7)	2 (6.7)
Rash	2 (6.7)	2 (6.7)
Pain	2 (6.7)	2 (6.7)
Leucopenia	1 (3.3)	1 (3.3)
Constipation	1 (3.3)	1 (3.3)
Electrolyte disturbance	1 (3.3)	1 (3.3)
TRAEs	9 (30.0)	9 (30.0)
Fever	4 (13.3)	4 (13.3)
Leucocytosis	3 (10.0)	3 (10.0)
Neutrophilia	3 (10.0)	3 (10.0)
Constipation	1 (3.3)	1 (3.3)
Liver dysfunction	1 (3.3)	1 (3.3)
Pain	1 (3.3)	1 (3.3)

WBC White blood cell, *ANC* Absolute neutrophil count, *AMC* Absolute monocyte count

fever (4/30, 13.3%), followed by leucocytosis (3/30, 13.3%) and neutrophilia (3/30, 13.3%). No grade 3 or higher AEs were reported, and none of the patients experienced an AE-related treatment delay or discontinuation. No deaths occurred during the follow-up period. The detailed information is presented in Table 5.

Discussion

The present study was a prospective, single-arm, open-label pilot study involving pediatric and adolescent patients with RMS or ES. The results showed that 2 of 30 (6.7%) patients who were treated with mecapegfilgrastim 24 h after chemotherapy developed FN, while 8 patients experienced grade 4 neutropenia. Notably, none of the patients in the VAC group experienced FN, whereas 2 patients in the VDC group experienced FN. The incidence of grade 4 neutropenia was obviously greater in the VDC group than in the VAC group (77.8% versus 4.8%). No patients delayed or discontinued chemotherapy during the treatment period. No deaths or grade 3 or higher TEAEs were reported.

FN is one of the most common and serious complications caused by myelosuppressive chemotherapy in pediatric and adolescent patients. It can lead to treatment delay, discontinuation, and dose reduction, thus increasing the mortality rate [4, 8, 12]. In the entire population, it has been demonstrated that rhG-CSF could decrease the incidence of neutropenia and FN by at least 50% [8]. Similar results have also been demonstrated in patients under 26 years old [13].

In terms of efficacy, an FN rate of 6.7% and a grade 4 neutropenia rate of 26.7% were achieved in patients with RMS or ES, which were consistent with the findings of previous studies [14, 15]. Regarding the VAC regimen, none of the patients in the VAC group experienced FN, and 4.8% patients experienced ANC $\leq 0.5\times10^9$/L. Walterhouse D et al. reported that approximately 90% RMS patients received VAC experienced myelosuppressive toxicities [16, 17]. In the D9803 trial, 85% of patients received the VAC regimen developed grade 3–4 FN, and 63% of patients experienced grade 3–4 neutropenia [18]. All of these abovementioned studies, including our study, involved similar VAC regimens. Based on the above information, prophylactic mecapegfilgrastim yielded encouraging results in RMS patients who received the VAC regimen.

Regarding the VDC regimen, in an open-label, phase II study, participants under 21 years old were recruited and treated with VDC/IE and prophylaxis pegfilgrastim, and an FN rate of 57% (21/37) was reported. However, the FN rate of patients who received the VDC regimen in our study was 22.2% [19]. Another randomized, prospective study involving patients under 26 years of age who were treated with the VDC regimen revealed that FN occurred in 29% of all chemotherapy treatment cycles [13]. The significant reduction in the incidence of FN and grade 4 neutropenia in our study might be associated with a decreased vincristine dose compared to that in other studies. In summary, patients who are treated with the VDC regimen should be monitored with care even after the use of prophylactic PEG-rhG-CSF in clinical practice.

In the present study, after the first cycle of chemotherapy, 75% (6/8) of all patients who experienced grade 4 neutropenia reached the lowest ANC ($<0.5\times10^9$/L) on day 7. Most of them recovered on day 10, and all of them

returned to normal values on day 14. The recovery time was relatively longer than that in the aforementioned phase II study, in which the median duration of grade 4 neutropenia was 5.0 days [19]. Therefore, the neutrophil count should be monitored 7 to 10 days after chemotherapy in pediatric and adolescent patients with RMS or ES.

In terms of safety, since the predominant pathway of clearance of long-acting G-CSF is neutrophil-mediated, and mecapegfilgrastim is eliminated if there are sufficient neutrophils, the number of white blood cells increases gradually and remains below 30×10^9/L [20].

Notably, an 8-month-old patient with ES who underwent VDC treatment was enrolled in this study. The ANC was 1.34×10^9/L at baseline. After receiving chemotherapy and mecapegfilgrastim, his/her ANC reached the lowest point of 0.41×10^9/L on day 10 and returned to 1.76×10^9/L on day 21. The patient continued chemotherapy normally, and no TRAEs were observed. Previous studies demonstrated that advanced age was an important risk factor for chemotherapy-induced FN, but the difference between pediatric and young adults has not been evaluated [21].

Mecapegfilgrastim has been used in adult patients with non-small cell lung cancer (NSCLC) to prevent neutropenia, and the results suggested that long-acting mecapegfilgrastim had promising clinical effects on patients, including the incidence of grade 3–4 neutropenia and FN and the duration of neutropenia [9]. Moreover, a multicenter, randomized study using PEG-rhG-CSF in NSCLC patients revealed that the FN rate differed among patients who underwent different chemotherapy regimens [22].

There were several limitations in our study. First, the sample size was small because of the single-arm and single-center nature of the study. Second, no control group was established in the study; thus, the results of this study can only be compared with historical data. Third, we only recorded the incidence of neutropenia and FN after the first cycle of chemotherapy.

Conclusion

Mecapegfilgrastim showed acceptable efficacy and safety profile in pediatric and adolescent patients with RMS or ES. Patients who are treated with the VDC regimen should be monitored with caution even after receiving long-acting rhG-CSF drugs. Further randomized studies with large sample sizes and secondary prophylaxis data are warranted.

Abbreviations

RMS	Rhabdomyosarcoma
ES	Ewing sarcoma
ANC	Absolute neutrophil count
FN	Febrile neutropenia
G-CSF	Granulocyte-colony stimulating factor
AE	Adverse event
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event
NSCLC	Non-small cell lung cancer

Supplementary Information

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Supplementary Material 1

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Authors' contributions

All the authors contributed to the study conception and design. The material preparation, data collection and analysis were performed by Yan Su, Rui Zhang, Wen Zhao and Yuchen Zhou. The statistical analysis and data interpretation were performed by Wen Zhao, Xisi Wang and Xiaoli Ma. The first draft of the manuscript was written by Wen Zhao, Cheng Huang, Peiyi Yang, Yan Su, and Rui Zhang. All the authors have read and approved the final manuscript.

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Availability of data and materials

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

According to the ethical guidelines of the Helsinki Declaration, the experimental protocol was established and approved by the ethics committee of Beijing Children's Hospital (IEC-C-006-A03-V.05). If the patients were older than 8 years, written informed consent was signed by both the patients and their parents; if the patients were under 8 years, written informed consent was signed only by the patients' parents.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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