Long-acting granulocyte colony-stimulating factor in primary prophylaxis of early infection in patients with newly diagnosed multiple myeloma

Xinjing Ding

First Affiliated Hospital of Nanchang University

Jianghua Ding (✉ doctor0922@126.com)

Jiujiang Medical College: Jiujiang University Medical College <https://orcid.org/0000-0003-4476-4398>

Hong Gu

Jiujiang University

Chuanxiang Zhong

Jiujiang University Medical College

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Abstract

Purpose

This study sought to compare the efficacy of prophylactic long-acting and standard granulocyte colony-stimulating factor (G-CSF) on febrile neutropenia, early infections, and treatment delay in patients with newly diagnosed multiple myeloma receiving the therapeutic regimen of bortezomib, lenalidomide, and dexamethasone (BLD).

Methods

A prospective study with 68 consecutive patients with multiple myeloma was conducted in three regional hospitals. Participants were randomly treated with the BLD regimen in combination with prophylactic long-acting G-CSF (treatment group) or standard G-CSF (control group). The primary endpoints were the incidence rates of febrile neutropenia, early infection, and treatment delays. The secondary endpoint was clinical outcomes.

Results

Thirty-three patients were assigned to the treatment group and thirty-five patients were assigned to the control group. The incidence of febrile neutropenia was 6.1% and 17.1% in the treatment and control groups, respectively ($p = 0.297$). However, the rates of early infection and treatment delay were markedly lower in the treatment group than in the control group (6.1% vs. 25.7% and 9.1% vs. 31.4%; $p < 0.05$). Notably, all early infections occurred during the first four cycles of BLD therapy, and the most common type of infection was pneumonia. No significant difference in clinical efficacy was found between the two groups. All participants achieved at least partial remission.

Conclusions

Prophylactic administration of domestic long-acting G-CSF markedly reduced the rates of early infection and treatment delay as compared with standard G-CSF in patients newly diagnosed with multiple myeloma. Notably, all early infections occurred during the first four cycles of BLD therapy. As such, it seems appropriate to administer long-acting G-CSF with the aim of primary prophylaxis of early infection, particularly within the first four courses of chemotherapy in the setting of newly diagnosed multiple myeloma.

1. Introduction

Patients with multiple myeloma (MM) experience an increased chance of infection than the general population, with the risk being 13 times more than that for pneumonia and 30 times more than that for

sepsis [1, 2]. The greater risk of infection in patients with MM can be attributed to advanced age; disease-related immunodeficiency involving humoral immunity and treatment-related toxicity, particularly for myelotoxicity; and comorbidities such as diabetes and chronic obstructive pulmonary diseases. Notably, the infection itself also contributes to the progression of MM via the production of interleukin-6 and the activation of Toll-like receptors on myeloma cells [3]. Importantly, infection is the leading cause of morbidity and mortality among patients with MM, with around 45% of deaths in this population resulting from infection [2]. Currently, with the continual advent of several novel anti-myeloma drugs, the five-year survival rate of patients with MM has risen to about 60% [4]. Therefore, it is of paramount importance to continue efforts to prevent deaths from infection among these individuals.

The entry of infectious organisms, including bacteria and viruses, into the body can occur during any treatment phase in patients with MM. The result of the FIRST study, which examined the prevalence of infections among patients with MM, showed that the infection rate was 56.2% over the initial four cycles of the treatment period. In particular, 30% of infections occurred in the first month of treatment [5]. So, more attention should be paid to the prevention of infection during the first and second courses of treatment in patients with MM. As is well known, the most common therapy for bacterial infections is the use of antibiotics. However, European Organization for Research and Treatment of Cancer (EORTC) guideline does not recommend universal antibacterial prophylaxis in patients with hematological and solid tumors, including those with MM [6, 7].

In patients with MM, neutropenia not only causes treatment delays or dose reductions but is also seen as an independent risk factor for a poor prognosis [3]. The national cancer center network (NCCN) guideline on managing febrile neutropenia (FN) recommends prophylactic treatment of granulocyte colony-stimulating factor (G-CSF) for patients receiving chemotherapy and at high risk of more than 20% of developing FN. For patients newly diagnosed with MM, up to 56.2% experienced infections during their initial four courses of chemotherapy [5]. Importantly, there is a direct correlation between a lower neutrophil cell count and a greater risk of infection (mainly bacterial and fungal infections) in patients with MM [8]. Therefore, it is reasonable to adopt prophylactic use of G-CSF for infection in patients with MM with neutropenia.

In recent years, long-acting G-CSF therapies, such as pegfilgrastim and biosimilar drugs, have been widely applied in cancer-related supportive care due to their higher efficacy and better adherence. The vast majority of clinical studies have focused on the mobilization outcome of pegfilgrastim in autologous stem cell transplantation of MM [9]. In contrast, only a few studies (including just three clinical trials and three observational studies) have considered primary prophylaxis with pegfilgrastim for FN in refractory and relapsed patients with MM who received lenalidomide- or bendamustine-based regimens [10–15]. These studies reported the supportive role of pegfilgrastim in ensuring scheduled chemotherapy and decreasing the rates of neutropenia and infection; however, all investigations were both single-armed or retrospective studies and merely focused on patients with recurrent or refractory MM. As mentioned above, the risk of infection is highest during the first four months of treatment, thanks to the huge tumor burden and frail physical status typically present in patients with MM [5]. In the present study, we

included patients newly diagnosed with MM, aiming to compare the primary prophylactic efficacy of early infection using long-acting and standard G-CSF. The primary endpoints were the incidence rates of early infection and treatment delays in patients newly diagnosed with MM.

2. Methods

2.1. Patients

A total of 68 consecutive patients with MM were included from March 1, 2019 to July 20, 2021, at three regional hospitals. The eligibility criteria for inclusion in this study were as follows: (1) newly diagnosed with systematic MM; (2) aged 18–75 years; (3) Eastern Cooperative Oncology Group (ECOG) score of less than three points; and (4) no history of cardiac arrhythmias, congestive heart failure, or severe coronary artery disease.

All patients received anti-myeloma therapy, except autologous hematopoietic stem cell transplantation. The last study follow-up date was June 30, 2021. Patients with amyloidosis or without a willingness to receive treatment were excluded.

2.2. Treatment protocol

According to medication use of long-acting or standard G-CSF, all patients were randomly divided into two groups of 33 patients treated with the chemotherapy with long-acting G-CSF (treatment group) and 35 patients treated with the chemotherapy with standard G-CSF (control group).

The specific chemotherapy protocol, known as the BLD regimen, was as follows: 1.3 mg/sqm of bortezomib (Qilu-pharma, Jinan, China) on days 1, 4, 8, and 11; 20–25 mg/d of lenalidomide (SL Pharm, Beijing, China) for 14 days; and 20 mg/d of dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12. According to the regimens described in the literature by Cerchione et al. [13], the patients in the treatment group were given long-acting G-CSF (6 mg) (Qilu-pharma, Jinan, China) subcutaneously with a single administration performed on the sixth day as primary prophylaxis, while the patients in the control group were treated by primary prophylaxis of standard G-CSF (5 µg/kg/day on days 6–8 of each cycle) (Qilu-pharma, Jinan, China). For the purposes of this study, a treatment cycle was 28 days in length, and all patients underwent 6–8 courses of chemotherapy and then continued to receive lenalidomide therapy until an unacceptable adverse event or disease progression occurred.

Blood routine, liver and kidney functions, C-reactive protein level, immunoglobulin concentration, and serum-free light chain results were examined before and after chemotherapy of each cycle.

2.3. Study endpoints

The primary endpoints were the incidence rates of FN, early infection, and treatment delay. An episode of FN was defined as follows: (1) fever, a single axillary temperature greater than 38.0°C or an axillary temperature greater than 37.5°C lasting 1 h and (2) neutropenia, defined according to the FN guidelines

from NCCN [16]. The criteria for infection in this study were defined as an increased body temperature of above 37.5°C or the isolation of a microbial agent in patients with concomitant clinical symptoms (such as pneumonia) and/or an increased C-reactive protein level above the normal value [17]. Early infection was deemed as that occurring during the first four months of treatment [5]. Treatment delay referred to chemotherapy administration occurring more than two days after the scheduled date. The secondary endpoint was patient clinical outcomes.

Efficacy was assessed every two cycles of treatment according to the new categories from the International Myeloma Working Group, which include stringent complete remission (sCR), complete remission (CR), very good partial remission (VGPR), partial remission (PR), minimal response (MR), stable disease, and progressive disease [18].

2.4. Statistical analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences software program (version 26; IBM Corporation, Armonk, NY, USA). An independent *t*-test was run to examine the differences between the two groups. *Fisher's* exact test and a chi-squared test were employed to compare the binary outcomes. The degree of clinical efficacy was analyzed by *Ridit* analysis. A *p*-value less than 0.05 was considered to be statistically significant, based on a two-sided test.

3. Results

3.1 Clinical characteristics

A total of 68 patients with MM were enrolled in this study, including 33 and 35 patients assigned to the treatment and control groups, respectively. As shown in Table 1, the two groups were very similar in terms of baseline characteristics, including age, sex, Revised International Staging System (R-ISS) stage, ECOG score, and cytogenetic abnormalities ($p > 0.05$).

Table 1
Comparison of clinical characteristics between the treatment and control groups

Characteristic	Treatment group, n (%)	Control group, n (%)	<i>p</i> -value
Number	33	35	-
Age, years Median (range)	62 (54–71)	65 (56–75)	0.3538
Sex	18 (54.6%)	16 (45.7%)	0.4666
Male	15 (45.4%)	19 (54.3%)	
Female			
R-ISS stage	16 (48.5%)	15 (42.8%)	0.9253
I–II	17 (51.5%)	20 (57.1%)	
III			
ECOG	28 (84.8%)	27 (77.1%)	0.4193
0–1	5 (15.2%)	8 (22.9%)	
≥ 2			
Cytogenetic abnormality	13 (39.4%)	18 (51.4%)	0.3193
Standard risk	20 (60.6%)	17 (48.6%)	
High risk			

3.2 Incidence rates of FN, early infection, and treatment delay

Throughout the period of chemotherapy, 6.1% and 17.1% of cases of FN were detected in the treatment and control groups, respectively, but there was no statistical difference between the two groups. However, as shown in Table 2, we discovered that the rates of early infection and treatment delay in the treatment group were markedly lower than those in the control group. As shown in Table 3, all early infections occurred during the initial second to fourth cycles.

Table 2
Clinical events between the treatment and control groups

Event	Treatment group (n = 33), n (%)	Control group (n = 35), n (%)	p-value
Febrile neutropenia	2 (6.1%)	6 (17.1%)	0.297
Early infection	2 (6.1%)	9 (25.7%)	0.0278 [#]
Treatment delay	3 (9.1%)	11 (31.4%)	0.0228 [#]
[#] The differences were statistically significant.			

Table 3
Comparison of early infections in patients between the treatment and control groups

Type of infection	Treatment group (n = 33), n	Control group (n = 35), n	Cycle sequence(s) of infection occurrence
Pneumonia	1	5	2–4
Colitis	0	2	2–3
Fever of unknown origin	1	2	2–4
Total	2	9	

3.3 Clinical outcomes

All 68 patients completed at least six cycles of chemotherapy, and 60 (88.2%) patients completed the prescribed eight cycles. As shown in Table 4, there were marked differences in clinical outcomes between the two groups. No stringent complete remission efficacy was found in either group; however, all patients achieved at least PR of their disease.

Table 4
Clinical outcomes between the treatment and control groups

Efficacy	Treatment group (n = 33), n (%)	Control group (n = 35), n (%)	<i>p</i>-value
sCR	0 (0.0%)	0 (0.0%)	0.2305
CR	3 (9.1%)	1 (2.9%)	
VGPR	23 (69.7%)	22 (62.9%)	
PR	7 (21.2%)	12 (34.3%)	
MR	0 (0.0%)	0 (0.0%)	

4. Discussion

In the era of emerging novel treatments, the clinical outcomes of patients with MM have improved greatly to a five-year survival rate of 60% [4]. However, MM remains notorious for placing patients at high risk of infection, thanks to the impairment of host defenses, and ensuring treatment-related immunosuppression. Importantly, the risk of infection is the highest within the first four months after the initial diagnosis. Furthermore, infection contributes to approximately 45% of early deaths [2]. Although the transition from chemotherapy to novel agents has caused a marked decrease in the incidence of severe pneumonia, heightened rates of early infection and pneumonia persist. Nearly all recent studies investigating MM-related infection focused on patients with refractory and relapsed MM [10–15]. As compared with these patients, those newly diagnosed with MM also experience the same risk of infection [19]. Therefore, it is imperative to prevent the occurrence of infection in all patients with MM, particularly early infection within the first four months after diagnosis.

As the vast majority of infections are bacterial in nature, it is reasonable, logically, to administer antibiotics for the prevention of infection in patients with MM. A phase III study explored the effects of oral antibiotic prophylaxis, i.e., ciprofloxacin or trimethoprim-sulfamethoxazole, for the first two months on the incidence of infection in patients with newly diagnosed MM; however, this study showed that routine use of prophylactic antibiotics did not reduce the incidence of infection among patients with MM receiving induction chemotherapy [7]. Another retrospective study investigated the effect of levofloxacin prophylaxis for the prevention of severe infections in patients with MM being treated using bortezomib-based regimens and supports the prophylactic use of levofloxacin in MM cases due to the marked decrease in severe infection observed relative to the control group (30.9% vs. 17.5%; $p = 0.037$) [20]. A prospective phase III study (TEAMM) also revealed that prophylactic administration of levofloxacin during the first 12 weeks of anti-myeloma therapy significantly reduced the number of febrile episodes and deaths as compared with the control group (27% vs. 19%; $p = 0.0018$) [21]. Despite such positive results, the use of antibacterial prophylaxis for infection remains to be viewed with caution due to the limitation of about 50% of patients withdrawing from the TEAMM study [21]. Moreover, prophylactic

antibiotics can also increase the risk of *Clostridioides difficile* infection and antibiotic resistance. The discrepancy highlighted above was largely attributed to the significant differences in therapeutic regimens and enrolled patients with MM. Hence, available data on prophylactic antibiotics for early infection remain inconsistent and should not be considered to indicate the best course of action in patients with MM [19]. Currently, prophylactic antibiotics for early infection should be limited to use in high-risk patients who have the heightened potential to experience severe-grade and prolonged neutropenia during anti-myeloma treatment [22].

In the clinical setting, neutropenia has been strongly associated with the incidence of infection in patients with MM [23, 8]. Owing to the fragile performance status and multiple comorbidities (e.g., diabetes) of patients with MM, neutropenia-related infection may be a potentially life-threatening condition in such patients, which also results in treatment delay and the final outcome. Thus, the idea of G-CSF as a feasible treatment option has emerged to prevent neutropenia-related infections in those with MM. As noted previously, long-acting G-CSF has been documented for prophylaxis of infection mainly in refractory and relapsed patients with MM [10–15]. Enlightened by such previous findings, we investigated the effect of long-acting G-CSF on preventing infection among those with newly diagnosed MM.

In our study, the incidence rates of early infection and treatment delay were markedly lower in the long-acting G-CSF group than in the standard G-CSF group. The underlying mechanisms were attributed to the longer circulation half-life and lower immunogenic activity of long-acting G-CSF in comparison with standard G-CSF [24]. However, we detected no significant difference in FN between the two groups (6.1% vs. 17.1%; $p = 0.297$). This result indicated that neutropenia can be classified as one of the causes of infection. Additionally, there were many other risk factors for early infection, such as hypoalbuminemia, the complications of diabetes, and the late staging of ISS in our patients with MM [25]. Further analysis reported that the common types of early infection included pneumonia, colitis, and fever of unknown origin. Of note, pneumonia was the most frequent type of infection, accounting for more than 50% of early infections in our study. This finding was consistent with the results of other research, such as that by Lavi et al. [26], who strongly recommended chest computed tomography as a routine examination for patients with MM at high risk of infection.

In the present study, the BLD regimen was chosen as the front induction therapy due to the reported pronounced improvements in overall response rate, progression-free survival, and overall survival, especially among patients with high-risk features [27]. As for clinical efficacy, there were no significant differences between the long-acting and standard G-CSF groups. All of our participants achieved PR or better outcomes following the BLD plus G-CSF regimen. The favorable efficacy was partially ascribed to the chemo-sensitization activity of G-CSF to bortezomib via the blockade of stromal cell-derived factor-1/CXC receptor 4 (SDF-1/CXCR4) between myeloma and stromal cells [28, 29].

5. Conclusions

For patients newly diagnosed with MM, the results of this study revealed that domestic long-acting G-CSF administered on day 6 led to marked decreases in early infection and treatment delay relative to standard G-CSF, while no difference was detected between these two regimens in terms of the incidence of FN. Moreover, all of the early infections in this study occurred during the initial second to fourth cycles of the BLD regimen, and the most common type of early infection was pneumonia. In light of these results, it appears appropriate to administer long-acting G-CSF for the prevention of early infection, particularly during the first four courses of chemotherapy. However, there were some deficiencies in this study. One was its small sample size, and another was the single kind of standard treatment protocol employed herein. Future clinical studies with larger sample sizes are necessary to confirm our results.

Declarations

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