Research Article

Gastrointestinal Bleeding Secondary to High-Dose Melphalan Pretreatment in Patients with Multiple Myeloma Was Associated with the Mode of Melphalan Administration

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Objective. To analyze the characteristics of gastrointestinal bleeding secondary to high-dose melphalan pretreatment in patients with multiple myeloma.

Methods. Between 1 January 2016 and 31 October 2021, 26 patients with multiple myeloma after autologous peripheral blood hematopoietic stem cell transplantation with high-dose melphalan pretreatment were recruited. They were assigned to either the oral administration group or the intravenous administration group according to the administration modes, or to either the gastrointestinal bleeding group or the nongastrointestinal bleeding group. Analyses were performed based on the differences in general gastrointestinal symptoms and hemorrhage between different administration modes and on the differences in the general gastrointestinal symptoms, platelet alterations, and the intestinal microecology before pretreatment between patients with and without gastrointestinal bleeding.

Results. Of the 26 included patients, heavy secondary gastrointestinal bleeding was found in 6 patients with intravenous pretreatment. In patients given intravenous melphalan, those with gastrointestinal bleeding showed more pronounced general symptoms such as nausea and vomiting versus those without. There was no significant difference in platelet alterations between the two groups. Gastrointestinal bleeding was associated with more significant microecological disturbances than no bleeding.

Conclusion. Gastrointestinal bleeding secondary to high-dose melphalan pretreatment in patients with multiple myeloma was associated with the mode of melphalan administration, adverse symptoms at pretreatment, and the intestinal microecology prior to pretreatment. Thus, improvement of the intestinal microecology prior to pretreatment and mitigation of adverse gastrointestinal symptoms during pretreatment may contribute to a lower incidence of secondary gastrointestinal bleeding and enhanced transplantation safety.

1. Introduction

High-dose melphalan is the preferred pretreatment for autologous peripheral blood hematopoietic stem cell transplantation in patients with multiple myeloma. It features high efficiency and low relapse, prolongs disease-free survival, and does not aggravate myelosuppression [1, 2]. The most common side effect of this regimen is gastrointestinal mucosal damage, which in severe cases may lead to life-threatening conditions such as sepsis and heavy gastrointestinal hemorrhage. In 2002, high-dose melphalan was the treatment of choice for patients with multiple myeloma [3], and the efficacy of cyclophosphamide + etoposide + busulfan (CVB) pretreatment regimen in multiple myeloma was comparable to that of high-dose melphalan, but CVB was associated with higher hematologic toxicity and significant thrombocytopenia, which prolongs fever and antibiotic use and leads to increased anti-infective costs. Currently, oral mucositis and diarrhea are the most studied complications related to high-dose melphalan [3, 4], while little attention has been paid to gastrointestinal bleeding which is a major risk factor for the life safety of patients with multiple myeloma during transplantation. To this end, the present study was undertaken to analyze the characteristics of
gastrointestinal bleeding secondary to high-dose melphalan pretreatment in patients with multiple myeloma and provide a clinical reference to further reduce the risk of hemorrhage.

2. Materials and Methods

2.1. Material Sources. Between 1 January 2016 and 31 October 2021, 26 patients with multiple myeloma after autologous peripheral blood hematopoietic stem cell transplantation with high-dose melphalan pretreatment were recruited. The research was approved by the Ethics Committee of the Ningbo First Hospital, approval no. 79797/104.

Inclusion criteria: patients with a confirmed diagnosis of multiple myeloma, exclusion of contraindications to transplantation, with single-agent high-dose melphalan (200 mg/m²) pretreatment, and no previous history of gastrointestinal bleeding. They were assigned to either the oral administration group or the intravenous administration group according to the administration modes, or to either the gastrointestinal bleeding group or the non-gastrointestinal bleeding group.

2.2. Outcome Measures.

(1) The general gastrointestinal symptoms, including nausea, vomiting, oral ulcers, and diarrhea, after pretreatment were compared between the oral and intravenous administration groups

(2) The symptoms of gastrointestinal bleeding, including positive fecal occult blood, black stool, vomiting blood, and bloody stool, after pretreatment were compared between the oral and the intravenous medication groups

(3) The general gastrointestinal symptoms and platelet changes during transplantation were compared between patients with and without gastrointestinal bleeding

(4) The changes in intestinal microecology including the types and numbers of intestinal probiotics before pretreatment in patients with and without gastrointestinal bleeding were compared

2.3. Statistical Analysis. SPSS 23.0 was used for data analyses. The measurement data were expressed as (X ± s) and processed using the t-test. The count data were expressed as the number of cases (rate) and analyzed using the chi-square test. Differences were considered statistically significant at

\[ P < 0.05 \]

3. Results

3.1. Patient Characteristics. Of the 26 patients included, 10 patients received oral administration of melphalan and 16 patients received melphalan through intravenous injection, with the dose of melphalan of 200 mg/m². There were 15 males and 11 females, aged 38–71 years, with a median age of 57 years.

3.2. General Gastrointestinal Symptoms and Bleeding due to Different Administration Methods. 10 patients pretreated with oral melphalan through intravenous injection had a mean age of 58.4 years, a mean nadir platelet count of 27.2 × 10³/μL, a mean nadir platelet duration of 11 d, and a mean duration of platelet implantation of 11 d. There were 8 cases (80%) of nausea and vomiting, 6 cases (60%) of oral ulcers, 2 cases (20%) of diarrhea, and no cases of gastrointestinal bleeding.

16 patients pretreated with melphalan through intravenous injection had a mean age of 56.0 years, a mean nadir platelet count of 12.125 × 10³/μL, a mean nadir platelet duration of +7.31 d, and a mean duration of platelet implantation of +10.56 d. There were 14 cases (87.5%) of nausea and vomiting, 14 cases (87.5%) of oral ulcers, 13 cases (81.25%) of diarrhea, and 6 cases (37.5%) of gastrointestinal bleeding, including 6 cases of occult blood in stool, 4 cases of black stool, 2 cases of vomiting blood, and 1 case of bloody stool (Tables 1 and 2).

3.3. General Gastrointestinal Symptoms and Platelet Changes. Of the 16 patients pretreated with melphalan through intravenous injection, 6 patients with a mean age of 57.17 years had gastrointestinal bleeding and 10 patients with a mean age of 55.30 years had no gastrointestinal bleeding (57.17 ± 5.04 vs. 55.3 ± 10.36, P < 0.05). There were no statistical differences in nadir platelet count, nadir platelet duration, and duration of platelet implantation (13.6 ± 9.73 vs. 11.2 ± 5.92, 7.67 ± 4.37 vs. 7.1 ± 0.86, 11.17 ± 0.98 vs. 10.2 ± 1.23, P > 0.05). Gastrointestinal bleeding was associated with a higher incidence of general gastrointestinal symptoms such as nausea and vomiting, mouth ulcers, and diarrhea compared to those without gastrointestinal bleeding. All patients with gastrointestinal bleeding experienced nausea and vomiting and oral ulcers before the occurrence of hemorrhage (Table 3).

3.4. Intestinal Microecology before Pretreatment. Patients with gastrointestinal bleeding had lower counts of Bifidobacterium (8.28 ± 0.24 vs. 8.69 ± 0.38) and Lactobacillus (8.29 ± 0.13 vs. 8.97 ± 0.23) and higher counts of E. coli (8.77 ± 0.11 vs. 8.16 ± 0.18), Enterococcus (9.70 ± 0.85 vs. 9.08 ± 0.15), and fungi (4.76 ± 0.10 vs. 3.71 ± 0.72) compared to those without gastrointestinal bleeding (P < 0.05) (Table 4).

4. Discussion

Currently, clinical trials such as IFM0901 and SWOG S0777 use the lenalidomide + bortezomib + dexamethasone regimen for multiple myeloma, which is a unanimously accepted first-line treatment regimen in Western countries [5–7], but there is a dearth of relevant research in China. The common hematologic adverse events of this regimen are thrombocytopenia and neutropenia, and the common non-hematological adverse events are abnormal liver function and peripheral neuropathy. Despite the improvement of remission rates and prolonged survival in patients with
Table 1: Autologous hematopoietic stem cell transplantation in 26 cases of multiple myeloma.

| Case no. | Gender | Age | Pretreatment | Nadir platelet count | Nadir platelet duration | Duration of platelet implantation | Nausea and vomiting | Oral ulcers | Diarrhea | Occult blood in stool | Black stool | Vomiting blood | Bloody stool |
|----------|--------|-----|--------------|----------------------|-------------------------|----------------------------------|---------------------|-------------|---------|-----------------------|------------|---------------|-------------|
| 1        | Male   | 59  | Po           | 13                   | +6 d                    | +15 d                            | +                   | −           | −       | −                     | −          | −             | −           |
| 2        | Male   | 50  | Po           | 3                    | +9 d                    | +20 d                            | +                   | +          | +       | −                     | −          | −             | −           |
| 3        | Male   | 68  | Po           | 7                    | +10 d                   | +20 d                            | +                   | −           | −       | −                     | −          | −             | −           |
| 4        | Male   | 67  | Po           | 26                   | +15 d                   | +12 d                            | +                   | −           | −       | −                     | −          | −             | −           |
| 5        | Female | 54  | Po           | 15                   | +11 d                   | +12 d                            | +                   | −           | −       | −                     | −          | −             | −           |
| 6        | Female | 52  | Po           | 70                   | +9 d                    | +12 d                            | −                   | −           | −       | −                     | −          | −             | −           |
| 7        | Female | 66  | Po           | 36                   | +11 d                   | +15 d                            | +                   | +          | +       | +                     | −          | −             | −           |
| 8        | Male   | 53  | Po           | 52                   | +13 d                   | +14 d                            | −                   | −           | −       | −                     | −          | −             | −           |
| 9        | Female | 52  | Po           | 35                   | +11 d                   | +12 d                            | +                   | −           | −       | −                     | −          | −             | −           |
| 10       | Female | 63  | Po           | 15                   | +15 d                   | +20 d                            | +                   | −           | −       | −                     | −          | −             | −           |
| 11       | Male   | 48  | Iv           | 5                    | +7 d                    | +8 d                             | −                   | −           | −       | −                     | −          | −             | −           |
| 12       | Male   | 51  | Iv           | 11                   | +6 d                    | +11 d                            | +                   | +          | +       | +                     | −          | −             | −           |
| 13       | Male   | 48  | Iv           | 14                   | +8 d                    | +11 d                            | +                   | +          | +       | +                     | −          | −             | −           |
| 14       | Female | 38  | Iv           | 10                   | +8 d                    | +11 d                            | +                   | −           | −       | −                     | −          | −             | −           |
| 15       | Female | 63  | Iv           | 12                   | +11 d                   | +13 d                            | +                   | +          | +       | +                     | −          | −             | −           |
| 16       | Male   | 60  | Iv           | 5                    | +7 d                    | +12 d                            | −                   | −           | −       | −                     | −          | −             | −           |
| 17       | Female | 69  | Iv           | 11                   | +7 d                    | +11 d                            | +                   | +          | +       | +                     | −          | −             | −           |
| 18       | Male   | 49  | Iv           | 22                   | +6 d                    | +9 d                             | +                   | +          | +       | −                     | −          | −             | −           |
| 19       | Male   | 49  | Iv           | 20                   | +8 d                    | +9 d                             | +                   | +          | +       | −                     | −          | −             | −           |
| 20       | Male   | 59  | Iv           | 8                    | +9 d                    | +11 d                            | +                   | +          | +       | −                     | −          | −             | −           |
| 21       | Male   | 59  | Iv           | 2                    | +10 d                   | +11 d                            | +                   | +          | +       | −                     | −          | −             | −           |
| 22       | Female | 58  | Iv           | 31                   | +9 d                    | +10 d                            | +                   | +          | +       | +                     | −          | −             | −           |
| 23       | Female | 55  | Iv           | 10                   | +8 d                    | +11 d                            | +                   | +          | +       | −                     | −          | −             | −           |
| 24       | Male   | 63  | Iv           | 5                    | +8 d                    | +10 d                            | +                   | +          | +       | −                     | −          | −             | −           |
| 25       | Male   | 56  | Iv           | 15                   | −1 d                    | +11 d                            | +                   | −           | −       | +                     | −          | −             | −           |
| 26       | Male   | 71  | Iv           | 13                   | +6 d                    | +10 d                            | −                   | +          | −       | −                     | −          | −             | −           |

Note: +: development of corresponding symptoms; −: no symptoms.

Table 2: Patients under single-agent high-dose melphalan pretreatment.

| Administration | n | Mean age | Nadir platelet count | Nadir platelet duration | Duration of platelet implantation | Nausea and vomiting (%) | Oral ulcers (%) | Diarrhea (%) | Occult blood in stool (%) | Black stool (%) | Vomiting blood (%) | Blood stool (%) |
|----------------|---|----------|----------------------|-------------------------|----------------------------------|-------------------------|-----------------|--------------|-------------------------|----------------|-------------------|----------------|
| Oral           | 10| 58.4 ± 27.2| +11 d | +15.1 d | 80 | 60 | 20 | 0 | 0 | 100 | 100 | 83.33 |
| Intravenous    | 16| 56 | 12.125  | +7.31 d | +10.56 d | 87.5 | 87.5 | 81.25 | 37.5 | 25 | 12.5 | 6.25 |

*P < 0.05 and ^P > 0.05.

Table 3: General gastrointestinal symptoms and platelet changes (x ± s).

| Groups                    | n   | Mean age  | Nadir platelet count | Nadir platelet duration | Duration of platelet implantation | Nausea and vomiting (%) | Oral ulcers (%) | Diarrhea (%) | Occult blood in stool (%) | Black stool (%) | Vomiting blood (%) | Blood stool (%) |
|---------------------------|-----|-----------|----------------------|-------------------------|----------------------------------|-------------------------|-----------------|--------------|-------------------------|----------------|-------------------|----------------|
| Gastrointestinal bleeding | 6   | 57.1 ± 5.04 | 13.6 ± 9.73 | 7.67 ± 4.37 | 11.17 ± 0.98 | 100 | 100 | 83.33 |
| No gastrointestinal bleeding | 10 | 55.3 ± 10.36 | 11.2 ± 5.92 | 7.1 ± 0.86 | 10.2 ± 1.23 | 80 | 80 | 70 |

*P > 0.05.

Table 4: Intestinal microecology before pretreatment (x ± s).

| Groups                    | n   | E. coli | Bifidobacterium | Lactobacillus | Enterococcus | Fungi |
|---------------------------|-----|---------|-----------------|--------------|-------------|------|
| Gastrointestinal bleeding | 6   | 8.77 ± 0.11 | 8.28 ± 0.24 | 8.29 ± 0.13 | 9.70 ± 0.85 | 4.76 ± 0.10 |
| No gastrointestinal bleeding | 10 | 8.16 ± 0.18 | 8.69 ± 0.38 | 8.97 ± 0.23 | 9.08 ± 0.15 | 3.71 ± 0.72 |

*P < 0.05.
multiple myeloma with new drugs, autologous hematopoietic stem cell transplantation is still predominantly adopted for most patients in China to achieve long-term survival or clinical cure due to the maturity and clinical efficacy of autologous hematopoietic stem cell transplantation. The currently recognized pretreatment regimen is melphalan at a dose of 200 mg/m² administered orally and intravenously, and the intravenous approach is the preferred choice for most bone marrow transplantation regimens due to the higher blood drug concentrations by intravenous administration versus oral administration. However, there are few studies on the differences in side effects between the two modes of administration [8, 9]. Multiple myeloma is a malignant plasma cell disease, in which the increase in plasma cell monoclonal immunoglobulins increases the patient’s blood viscosity, resulting in slow blood flow and increased resistance. Melphalan inhibits the proliferation of plasma cells and the deposition of monoclonal immunoglobulins, thereby reducing blood viscosity and therefore predisposing to gastrointestinal bleeding.

Accordingly, the present study systematically analyzed the differences in side effects due to the two modes of administration, as well as the incidence of secondary gastrointestinal bleeding after melphalan pretreatment and the contributing factors.

In the present study, there were 10 patients pretreated with oral melphalan with a mean age of 58.4 years and 16 patients pretreated with melphalan through intravenous injection with a mean age of 56 years, and no previous history of gastrointestinal bleeding was found in either group. Gastrointestinal symptoms due to both oral and intravenous pretreatment include nausea and vomiting, oral ulcers, and diarrhea, which is consistent with the findings of Zhao et al. [10] and Shi et al. [3]. This study also found a higher incidence of these side effects in the intravenous group compared to the oral group, which is in concordance with the difference in blood drug concentrations between the two groups. In addition, intravenous administration was associated with a shorter platelet implantation time and faster recovery versus oral pretreatment, suggesting a little impact of intravenous medication on platelet implantation. All cases of gastrointestinal bleeding were found in the intravenous administration group.

Among the 16 patients receiving intravenous administration, 6 (37.5%) cases developed gastrointestinal bleeding, including 4 cases (66.7%) of black stool and vomiting blood, indicating a high incidence of gastrointestinal bleeding after high-dose melphalan pretreatment through intravenous injection. Oral mucositis is one of the main complications of melphalan and can lead to infection and nutritional disorders in severe cases. High doses of melphalan inhibit the proliferation and renewal of oral mucosal cells, resulting in ulcers due to the gap between the renewal of mucosal epithelial cells and bone marrow suppression, which induce focal infection and aggravate mucosal damage. Oral cryotherapy is available to alleviate the mucositis caused by high doses of melphalan, with good patient tolerance and easy implementation, which reduces patient pain and improves their quality of life. In addition, gastrointestinal bleeding was associated with a higher incidence of nausea and vomiting, oral ulcers, and diarrhea versus no bleeding, with no statistical difference in age, nadir platelet values after pretreatment, and nadir platelet duration and platelet implantation time between the two groups. Moreover, the present study found that patients with gastrointestinal bleeding had lower counts of Bifidobacterium and Lactobacillus and higher counts of E. coli, Enterococcus, and fungi versus those without gastrointestinal bleeding, suggesting a positive role of the balance of intestinal microecology in the prevention of gastrointestinal bleeding. Intestinal flora is an important component of intestinal microecology that protects against the invasion of pathogenic bacteria and maintains normal physiological functions of the intestine [5, 6]. Patients with hematologic tumors generally experience an imbalance in intestinal microecology after chemotherapy, in which the decrease in the species and abundance of Lactobacillus, Bifidobacterium, and Bacillus mimicus and the overgrowth of pathogenic bacteria such as Enterobacter, Enterococcus, and fungi may lead to impaired body immunity [7, 11], increased endotoxins, damage to intestinal mucosal cells, destruction of the intestinal barrier, local inflammation of the intestine and even ulceration, and hemorrhage [12]. Singh et al. found that the use of Lactobacillus showed significantly higher repair and healing capacity of gastric mucosa in mice with gastric ulcers versus mice without probiotics [13]. De et al. showed that intestinal probiotics could induce the proliferation of intestinal epithelial cells by stimulating Toll-like receptors, reinforcing the tight junctions between intestinal mucosal epithelium, mitigating damage to the intestinal mucosa by pathogenic bacteria, and maintaining the intestinal mechanical barrier [14]. Zhang et al. revealed that intestinal probiotics could degrade dietary polysaccharides and resistant starch to synthesize short-chain fatty acids and supply energy to intestinal epithelial cells by binding to "metabolism-sensitive G protein-coupled" receptors to maintain a normal function [15]. The abovementioned studies confirm the role of intestinal microecological balance in the integrity of the gastrointestinal mucosa. The results of the present study demonstrated that patients with disordered intestinal microecology were at a significantly greater risk of gastrointestinal bleeding under pretreatment with melphalan through intravenous injection than those with balanced intestinal microecology, suggesting that improving intestinal microecology prior to pretreatment may lower the incidence of gastrointestinal bleeding. Apurinic/apyrimidinic endonuclease (APE1) and CD38 proteins were coexpressed in multiple myeloma cells and the particularly pronounced APE1 protein expression is detected around the nucleus. Moreover, APE1 expression is higher in relapsed or refractory multiple myeloma than in primary diagnosis. Melphalan induces APE1 expression in multiple myeloma cells, which was proportional to its duration of action and dose. Therefore, the intensity of APE1 protein expression was associated with the efficacy of multiple myeloma, suggesting a potential role of enhanced APE1 gene expression in multiple myeloma resistance to melphalan. A study showed that Shuxuetong injection plus melphalan in
the treatment of multiple myeloma could strengthen the therapeutic effect. Shuxuetong injection is mainly composed of extract of earthworm and leech. The earthworm kinase has highly effective anticoagulant, antithrombotic, and fibrinogenolytic effects [14], and hirudin in leeches is the most potent thrombin inhibitor known [14]. Their binding to thrombin prevents enzyme activation of fibrin, reduces platelet adhesion rate, inhibits thrombus formation, decreases peripheral vascular resistance, dilates blood vessels, and improves microcirculation [15]. Shuxuetong injection can inhibit APE1 gene expression to reduce drug resistance in patients when used in combination with melphalan therapy [7]. Moreover, it promotes the entry of chemotherapeutic drugs into the tissues for action and reduces the production of monoclonal immunoglobulins, which consequently attenuates the feedback inhibition of myeloma cells and enhances the sensitivity of myeloma proliferating cells to chemotherapy.

5. Conclusion

Gastrointestinal bleeding secondary to high-dose melphalan pretreatment in patients with multiple myeloma was associated with the mode of melphalan administration, adverse symptoms at pretreatment, and the intestinal microecology prior to pretreatment. Thus, improvement of the intestinal microecology prior to pretreatment and mitigation of adverse gastrointestinal symptoms during pretreatment may contribute to a lower incidence of secondary gastrointestinal bleeding and enhanced transplantation safety. The limitation of this study is the small sample size included resulting in biased trial results. A multicenter randomized prospective study with an expanded sample size will be conducted in the future to provide more reliable data.

Data Availability

The datasets used during the present study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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