Abstract. Factors affecting peripheral blood hematopoietic stem cell (PBSC) mobilization and collection were investigated in patients with multiple myeloma (MM) and lymphoma who were undergoing chemotherapy. Clinical data from 128 patients, including 53 MM and 75 malignant lymphoma (7 Hodgkin's lymphoma and 68 non-Hodgkin's lymphoma) cases were retrospectively analyzed. Autologous PBSCs were mobilized using granulocyte-colony stimulating factor (G-CSF) during chemotherapy, and collected using a continuous flow cell separation instrument. The yields of CD34+ cells per kilogram of patient body weight <2.0x10^6/kg, >2.0x10^6/kg or >5.0x10^6/kg were defined as a failure, a success or ideal mobilization, respectively. In MM and lymphoma patients, the success rates of CD34+ cell acquisition were 73.6 (39/53) and 58.7% (44/75), the ideal rates were 43.4 (23/53) and 30.7% (23/75), and the failure rates were 26.4 (14/53) and 41.3% (31/75), respectively. Univariate and multivariate statistical analysis revealed that negative factors for PBSC mobilization in patients with MM were lenalidomide treatment, multiple chemotherapies, incomplete disease remission and low-level blood hemoglobin; in patients with lymphoma, the negative factors were the histological disease type, incomplete disease remission, being beyond the first-line of previous chemotherapy, multiple chemotherapies, chemotherapy with the HyperCVAD-B mobilization scheme, high-dose MTX/Ara-c (methotrexate/cytarabine) treatment, prolonged administration of G-CSF and low-hematocrit levels. In the present study, different factors influencing PBSC mobilization and collection in MM and lymphoma cases were identified. PBSC mobilization yielded sufficient CD34+ cell counts both in MM and lymphoma patients; however, the failure rates were relatively high.

Introduction

High-dose chemotherapy combined with autologous hematopoietic stem cell transplantation (ASCT) has been widely used in the treatment of hematologic malignancies, including multiple myeloma (MM) and a number of different types of lymphoma. This combination therapy has been proven to significantly improve the progression-free survival (PFS) and overall survival (OS) times of patients (1). Although since 2000, a large number of targeted treatments have been used in clinical drug therapy, ASCT still results in the most favorable patient outcome (1-3). Efficient acquisition of autologous stem cells is the premise of successful ASCT. Peripheral blood hematopoietic stem cells (PBSCs) are the stem cell sources for almost all ASCTs. Compared with ASCT with bone marrow hematopoietic cells, it is generally accepted that ASCT with PBSCs requires fewer cells for infusion; additionally, the collection procedure for PBSCs is simpler, and patients recover more quickly, thus resulting in a shorter period of hospitalization. During the PBSC mobilization process, monitoring the mononuclear and CD34+ cell count in the peripheral blood enables the prediction of acquisition efficiency, and helps to determine the timing of acquisition. Hübel et al (3) used peripheral blood CD34+ cells as a routine predictive indicator. However, few studies have reported precise changes in the CD34+ cell count during the mobilization process.

MM and lymphoma are the major hematologic malignancies treated with ASCT and further studies are required to improve PBSC mobilization, as well as to accurately identify patients at a high risk of mobilization failure. In the present study, in order to identify the factors influencing hematopoietic stem cell mobilization, the clinical data of 128 MM and lymphoma patients who received ASCT were retrospectively analyzed.
Materials and methods

Patients. The present study was approved by the ethical committee of the Bone Marrow Transplantation Center of the First Affiliated Hospital, Zhejiang University, and all participants provided written informed consent for participation. The clinical data of MM and lymphoma patients admitted to the center between April 2006 and October 2013 were retrospectively analyzed. All participating patients were recruited following routine clinical examinations, and were suitable for, and agreed to accept ASCT therapy. A total of 128 patients (72 male and 56 female; mean age, 44 years; age range, 16-64 years) were studied. There were 53 cases with MM and 75 cases with lymphoma; 7 of these were Hodgkin’s lymphoma (HL) and 68 were non-Hodgkin’s lymphoma (NHL) based on the World Health Organization diagnostic criteria (4). Most of the patients accepted PBSC mobilization and collection for the first time, but three patients underwent re-collection after first-time failure.

Treatment schemes and PBSC mobilization protocol. All MM patients were treated with high-dose cyclophosphamide (CTX; 3-4 g/m² every two days). Of the 75 patients with lymphoma, 33 patients were treated with chemotherapy adopting the CHOP scheme (cyclophosphamide, epidurubicin, vincristine and prednisone), five cases of which were supplemented with rituximab, 20 cases with etoposide, and five cases with rituximab and etoposide; 17 patients were treated with a high-dose of CTX, two cases in which rituximab was additionally included; nine patients underwent chemotherapy adopting the HyperCVAD part A scheme (high-dose cyclophosphamide, doxorubicin, dexamethasone and vincristine); another nine patients received chemotherapy adopting the HyperCVAD part B scheme (high-dose cytosine arabinoside and methotrexate), two cases in which rituximab was additionally included; seven patients were treated with chemotherapy adopting a MINE scheme (mitoxantrone, ifosfamide and etoposide) and three cases in which rituximab was also included.

Prior to stem cell collection, all 128 patients were treated with granulocyte-colony stimulating factor (G-CSF; Kyowa Hakko Kirin China Pharmaceutical Co., Ltd.) at the median dose of 5.10 μg/kg (range, 3.57-8.49) for the median period of 5 days (range, 1-16) by subcutaneous injection. When the peripheral white blood cell count decreased to 1.0-2.0x10⁹/l and the patient’s body weight: ≥2.0x10⁶/kg was a mobilization failure; and >2.0x10⁶/kg was a successful mobilization; <2.0x10⁶/kg was a mobilization failure; and >5.0x10⁶/kg was an ideal mobilization (5,6). In addition, the peripheral blood mononuclear cell (B-MNC) count, the level of hemoglobin (Hb), the hematocrit level (Rct) and the blood platelet (Plt) count were determined in peripheral blood cell samples, using a Sysmex XN-9100™ Automated Hematology system (Sysmex Corporation).

Statistical analysis. Continuous data that conform to the normal distribution are presented as the mean ± standard deviation; continuous data that are not normally distributed are presented as the median (range), and classified data are presented as an actual number (rate). The χ² test was used for the comparison of rate differences and the Mann-Whitney U test (two groups) or Kruskal-Wallis test (multi groups) for the comparison of continuous datasets. Multiple regression models were used to analyze factors influencing stem cell mobilization and collection. When univariate analysis produced statistical significance, further multivariate analysis with a stepwise regression model was performed. Statistical analysis was conducted using SPSS (version 17.0; SPSS Inc.), and P<0.05 was considered to indicate a statistically significant difference.

Results

Patient baseline status and PBSC mobilization. Of the 53 patients with MM, the therapeutic outcome of PBSC mobilization treatment was a partial response (PR) in 19 patients, and a complete response (CR) in 34 cases (Table I). In 75 patients with lymphoma, 40 (53.3%) achieved a CR (Table II).

Parameters of stem cell collection. The patients (113 of 128 cases, 88.3%) were subjected to stem cell collection for two consecutive days, while four patients were subjected to collection only once, and 15 patients three times. The first and second acquisition of CD34+ cells represented 54.0 and 42.2% of the total CD34+ cells collected, respectively. In the cell samples, the peripheral blood mononuclear cell (B-MNC) count was 1.9x10⁹/l (range, 0.1-8.2), the level of hemoglobin (Hb) was 104.2 g/l (range, 66.0-142.0), the hematocrit level (Rct) was 30.8% (range, 19.5-42.7), and the blood platelet (Plt) count was 88.0x10⁹/l (range, 19.0-250.0).

Collection of CD34+ cells. The median CD34+ cell count collected from all patients was 3.12x10³/kg (range, 0.03-24.07). The median CD34+ counts in MM and lymphoma patients were 4.16x10³/kg (range, 0.10-19.02) and 2.40x10³/kg (range, 0.03-24.07), respectively. Greater numbers of CD34+ cells were collected from patients with MM compared with patients with lymphoma; however, the difference was not statistically significant (P=0.064). In addition, ≥2.0x10⁶/kg CD34+ cells were obtained in 83 of the 128 patients (64.8%), and ≥5.0x10⁶/kg cells were successfully collected from 45 patients (35.2%). The success rate of CD34+ cell collection was 73.6% (39/53) in patients with MM and 58.7% (44/75) in patients with lymphoma, and the ideal rates were 43.4 (23/53) and 30.7% (23/75), respectively (Table I and II). This demonstrates that both the success and ideal rates were greater in patients with MM compared with patients with lymphoma; however, the difference was not statistically significant (P=0.064).

Stem cell mobilization and univariate/multivariate analysis of stem cell mobilization data. Univariate analysis demonstrated that the success rate of mobilization was lower in
patients MM who had previously received lenalidomide, underwent >4 courses of treatment or had a peripheral blood Hb level <100 g/l (Fig. 1A). These factors reduced the yield of CD34+ cells, identifying them as negative factors that adversely affect stem cell mobilization and collection. However, multivariate analysis showed that only a low peripheral blood Hb level was significantly associated with poor mobilization (P=0.041; OR, 1.040; 95% CI, 1.002‑1.080; Table III).

Table I. Baseline characteristics of MM patients and the outcome of PBSCs mobilization.

| Patient characteristics                        | Patients, n (%) | Mobilization, n (%) | P-value |
|-----------------------------------------------|-----------------|---------------------|---------|
|                                               | Success | Failure |         |
| Number                                        | 53 (100) | 39 (74) | 14 (26) | 0.424   |
| Age, years<sup>a</sup>                        | 55 (24-64) | 55 (24-64) | 55.5 (43-64) | 0.075   |
| Sex<sup>b</sup>                               |         |         |         |         |
| Male                                          | 29 (55) | 21 (54) | 8 (57) | 0.832   |
| Female                                        | 24 (45) | 18 (46) | 6 (43) |         |
| Status of disease<sup>b</sup>                 |         |         |         | 0.524   |
| PR/VGPR                                       | 19 (36) | 13 (33) | 6 (43) |         |
| CR/nCR                                        | 34 (64) | 26 (67) | 8 (57) |         |
| Number of prior lines<sup>b</sup>             |         |         |         | 1.000   |
| 1                                             | 48 (91) | 35 (90) | 13 (93) |         |
| ≥2                                            | 5 (9)   | 4 (10) | 1 (7) |         |
| Previous lenalidomide treatment<sup>b</sup>   |         |         |         | 0.004   |
| Yes                                           | 4 (8)   | 0 (0) | 4 (29) |         |
| No                                            | 49 (92) | 39 (100) | 10 (71) |         |
| Previous thalidomide treatment<sup>b</sup>    |         |         |         | 0.919   |
| Yes                                           | 9 (17) | 6 (15) | 3 (21) |         |
| No                                            | 44 (83) | 33 (85) | 11 (79) |         |
| Previous velcade treatment<sup>b</sup>        |         |         |         | 0.322   |
| Yes                                           | 41 (77) | 32 (82) | 9 (64) |         |
| No                                            | 12 (23) | 7 (18) | 5 (36) |         |
| Treatment courses<sup>b</sup>                 |         |         |         | 0.075   |
| 1-4                                           | 22 (42) | 19 (49) | 3 (21) |         |
| ≥5                                            | 31 (58) | 20 (51) | 11 (79) |         |
| Isolation times<sup>b</sup>                   |         |         |         | 0.755   |
| 2                                             | 42 (79) | 30 (77) | 12 (86) |         |
| >2                                            | 11 (21) | 9 (23) | 2 (14) |         |
| G-CSF dosage (µg/kg)<sup>a</sup>              | 5.0 (3.6-7.7) | 5.1 (3.6-7.7) | 5.0 (4.0-7.5) | 0.531 |
| G-CSF duration (d)<sup>a</sup>                |         |         |         | 0.682   |
| 1-5                                           | 40 (75) | 30 (77) | 10 (71) |         |
| >5                                            | 13 (25) | 9 (23) | 4 (29) |         |
| Hematological values                          |         |         |         |         |
| B-MNC (x10<sup>9</sup>/l)<sup>a</sup>         | 2.1 (0.3-8.2) | 2.2 (0.4-8.2) | 1.8 (0.3-4.3) | 0.143 |
| Hb (g/l)<sup>l</sup>                          | 111 (66.3-142) | 112.2 (74-142) | 103.7 (66.3-122) | 0.083 |
| Rct (%)<sup>l</sup>                           | 33 (20.1-42.7) | 33.2 (21.8-42.7) | 31.4 (20.1-38.2) | 0.125 |
| Plt (x10<sup>9</sup>/l)<sup>l</sup>            | 90 (26.3-238.5) | 90 (26.3-238.5) | 89.5 (45-173) | 0.896 |

<sup>a</sup>Mann-Whitney U test; <sup>b</sup>χ<sup>2</sup> test. PR/VGPR, partial response/very good partial response; CR/nCR, complete response/near CR; G-CSF, granulocyte-colony stimulating factor; B-MNC, blood mononuclear cell; Hb, hemoglobin; Rct, reticulocyte; Plt, platelet.

The analysis showed that the factors negatively affecting stem cell mobilization and collection were disease without complete remission, previous chemotherapy beyond the first-line, >8 courses chemotherapy treatment, previous treatment with high dose MTX/Ara-c, application of the HyperCVAD-B mobilization scheme, administration of G-CSF for >5 days, and collected B-MNC, Hb, Rct and Plt values below 1.9×10<sup>9</sup>/l, 100 g/l, 29% and 80×10<sup>9</sup>/l, respectively (Table II). The association between these influencing factors...
and the yield of CD34+ cells is shown in Fig. 1B. Multivariate regression analysis revealed that the disease remission status, usage of MTX/Ara-c, and the Rct value significantly affected the success rate of mobilization and acquisition of CD34+ cells. However, HyperCVAD-B mobilization scheme and Plt value below 80x10^9/l were negative affecting factors (Table IV).
and Fig. 1C). In 20 of 35 patients (57.1%) who did not achieve CR, stem cell collection failed. The failure rate of patients who were previously treated with high dose MTX/Ara-c was 64.7%. The failure rates of patients whose Rct was <29% or Plt was <80x10^9/l, were 61.5 and 57.9% respectively, and those patients who adopted the HyperCVAD scheme plan A or B were 67.7 (6/9) and 77.8% (7/9), respectively (data not shown).

**Adverse events.** The main adverse event in patients was agranulocytosis and the median duration time of neutrophil granulocyte deficiency was 3 days (range, 0-15 days). In 27 patients including 12 MM and 15 lymphoma patients, the deficiency lasted >5 days, and in two lymphoma patients the duration was > 10 days; 13 patients were free from agranulocytosis. Other adverse events included gastrointestinal reactions during chemotherapy, fever due to granulocyte deficiency, hypokalemia, fever associated with G-CSF treatment, and lower limb, waist or back pain, which did not exceed level 2 and were completely resolved following treatment (Table V). No enlargement of the spleen or spleen rupture, and no other serious adverse events were observed.

**Discussion**

A key factor in successful ASCT is efficient PBSC acquisition. The general requirement of CD34+ cell numbers for ensuring successful hematopoietic functional reconstruction is 2.0x10^6 cells/kg of patient weight. The acquisition of 5x10^6 cells/kg of CD34+ cells is considered to be ideal and this number is sufficient for quick reconstruction of hematopoiesis (7-9). G-CSF has been widely used as a PBSC mobilization stimulator. Early studies found that G-CSF alone could increase PBSCs by 10 to 100 times, with the peak of the drug concentration in plasma occurring on the fifth day (10). G-CSF may interfere with the interaction between stromal cell-derived factor-1 (SDF1) and the CXC chemokine type 4 receptor (CXCR4), and affect the expression of bone marrow stromal cell related adhesion molecules (11,12). Even though its precise mechanism is not well understood, G-CSF treatment resulted in a higher yield of PBSCs, even when hematopoiesis was inhibited during chemotherapy. Therefore G-CSF has been widely used clinically (7-9,13-16); however, no consensus recommendation for the selection of chemotherapy schemes has been established.

In our center, all PBSC mobilization was performed by chemotherapy combined with G-CSF. In accordance with other centers, patients with MM received chemotherapy with high-dose CTX (8,17-19), while patients with lymphoma underwent chemotherapy with various regimens. The present study revealed that adverse events due to treatment were at acceptable levels, but there was a significant difference in the success rates of stem cell mobilization. The combined
The success rate of CTX, CHOP and MINE therapeutic schemes was 68.4%, while that of HyperCVAD scheme plans A or B was only 27.8%, suggesting that HyperCVAD might not be a suitable treatment option for patients with lymphoma. Other studies recommended various schemes with a success rate >70%, which included high-dose CTX, intermediate dose cytarabine, cytarabine combined with etoposide, ESHAP/DSHAP and ICE/RICE (8,20-23).

In the present study, the overall mobilization failure rate was 35.2% (45 of 128 patients), the failure rate of MM patients was 26.4% (14 of 53 patients) and that of lymphoma patients was 41% (31 of 75 patients). The mobilization failure rate appeared to be relatively higher than previously reported rates of 5-30% (8,18,19,21-26). The reasons for this discrepancy are unknown; however, some invariable or variable factors might have played a role, such as mobilization timing, mobilization schemes, and various parameters set by the separator. Further investigation is required to elucidate whether altering these factors could optimize PBSC mobilization in lymphoma, as well as in MM patients. Lymphoma and MM share the same malignant tumor cell origin and their therapeutic strategies are similar. However, in the present study the failure rate of lymphoma patient treatment was two times greater than that of MM patients. It has been reported that in NHL and HL, both G-CSF mobilization alone and G-CSF combined with chemotherapy resulted in similar failure rates, and these rates were four times greater than those of MM (8,9). It may be that previous high-dose chemotherapy in lymphoma patients affected stem cell mobilization and collection. In MM patients, treatment with multiple courses of lenalidomide (27), high-dose chemotherapy, administration of purine analogues, and 1-3 lines of chemotherapy were reported to be adverse factors for mobilization (21,25). In accordance with this, lenalidomide treatment, multiple courses of chemotherapy, incomplete alleviation of disease, large-doses of cytarabine or MTX, and previous chemotherapy of more than 2 lines, were

### Table III. Univariate and multivariate statistical analysis of factors influencing mobilization in 53 patients with MM.

| Prognostic factors                  | Univariate | Multivariate |
|-------------------------------------|------------|--------------|
|                                     | P-value    | OR           | 95% CI       | P-value    | OR           | 95% CI       |
| Without treatment of lenalidomide   | 0.027      | 1.400        | 1.005-1.950  | NS         | -            | -            |
| Treatment courses (≤4)              | 0.024      | 3.483        | 0.840-14.449 | NS         | -            | -            |
| Hb (≥100 g/l)                       | 0.014      | 2.500        | 0.685-9.121  | 0.041      | 1.040        | 1.002-1.080  |

OR, odds ratio; CI, confidence interval; Hb, hemoglobin; NS, not significant. P<0.05 was considered to indicate a statistically significant difference.

### Table IV. Univariate and multivariate statistical analysis of factors influencing mobilization in 75 lymphoma patients.

| Prognostic factors                  | Univariate | Multivariate |
|-------------------------------------|------------|--------------|
|                                     | P-value    | OR           | 95% CI       | P-value    | OR           | 95% CI       |
| Histopathology (WHO)                | 0.049      | -            | -            | NS         | -            | -            |
| Disease status (Not CR)             | 0.002      | 0.284        | 0.108-0.746  | 0.024      | 0.212        | 0.055-0.813  |
| Number of prior lines (1)           | 0.014      | 2.602        | 1.006-6.729  | NS         | -            | -            |
| G-CSF administration duration (1-5 d) | 0.010      | 8.632        | 2.178-34.211 | NS         | -            | -            |
| High dose MTX/Ara-c (none)          | 0.003      | 0.287        | 0.093-0.891  | 0.045      | 0.197        | 0.040-0.963  |
| Treatment courses (1-8)             | 0.021      | 3.706        | 1.306-10.513 | NS         | -            | -            |
| HyperCVAD-B mobilization scheme     | 0.029      | -            | -            | 0.030      | 1.975        | 1.070-3.646  |
| B-MNC ≥1.9                          | <0.001     | 4.500        | 1.681-12.046 | NS         | -            | -            |
| Hb ≥100                             | <0.001     | 5.558        | 2.009-15.379 | NS         | -            | -            |
| Rct (≥29%)                          | <0.001     | 8.176        | 2.826-23.650 | 0.008      | 1.229        | 1.056-1.431  |
| Plt ≥80x10^9/l                      | <0.001     | 4.278        | 1.591-11.505 | 0.032      | 1.017        | 1.001-1.034  |

OR, odds ratio; CI, confidence interval; WHO, World Health Organization; Not CR, not complete response; G-CSF, granulocyte-colony stimulating factor; MTX/Ara-c, Ara-c methotrexate/cytarabine; B-MNC, mean value of peripheral blood mononuclear cells; Hb, hemoglobin; Rct, reticulocyte; Plt, platelet; NS, not significant; P<0.05 was considered to indicate a statistically significant difference.
found to be unfavorable factors for successful mobilization in MM patients. These factors may have negatively affected patient's bone marrow function, and more effective mobilization strategies should be considered.

Additionally, the efficiency of stem cell collection after the second round of mobilization was evaluated; three of 45 patients who failed the first round of mobilization underwent a second round. However, the yield of CD34+ cells was insufficient, which confirmed the general concept that if the first mobilization failed, despite the type of disease and mobilization scheme, the success rate of a second mobilization was also low (8,23,25,28). Therefore, it should be emphasized that the optimal yield of CD34+ cells is achieved following the first mobilization. However, several randomized clinical trials have suggested that a new mobilization agent, plerixafor, which inhibits the binding of chemokine SDF-1 to its receptor CXCR4, is ideal for the mobilization of PBSCs, either used alone or in combination with G-CSF (13,14,17,18,24,26,29-32). Plerixafor successfully mobilized PBSCs even in patients who received high-doses of chemotherapy or who failed the first mobilization (14,17,30-32). However, it is not widely used in Chinese clinical practice.

It has been reported that specific parameters prior to PBSC collection, such as the duration time of G-CSF administration and B-MNC, Plt and CD34+ cell counts, may predict mobilization success (15,23,25,26,33,34). However, when used alone, none of these factors were able to predict mobilization outcome. The present study revealed that a higher hemoglobin level was a significant factor for successful mobilization both in MM and lymphoma patients. Conversely, a G-CSF administration time >5 days, and lower numbers of B-MNC and Plt were associated with mobilization failure in lymphoma, but not MM patients. Regardless of the disease and the mobilization scheme applied, the peripheral blood CD34+ cell count measured between mobilization and collection have been reported to correlate with the first day acquisition rate. Hence, the peripheral blood CD34+ cell count appears to be the only factor that could be used to determine the optimal timing of PBSC collection (8,16,23,25). However, due to the retrospective nature of the present study, data on these CD34+ cell counts were unavailable.

In summary, the present study revealed that chemotherapy combined with G-CSF in MM and lymphoma patients yielded CD34+ cells; however, the failure rate was relatively high. Multivariate analyses revealed that Hb values <100 g/l in MM patients who did not achieve CR, high dose MTX/Ara-c medication, HyperCVAD-B mobilization scheme, as well as low Rct (≤29%) and Plt counts (≤80x10^9/l) in lymphoma patients were significant factors for insufficient PBSC mobilization. It is anticipated that the introduction of the mobilization agent plerixafor to the scheme may increase the success rate of mobilization in patients with poor bone marrow function. Therefore, it is important to further investigate the factors associated with successful stem cell mobilization and collection for the establishment of a more efficient and cost-effective ideal protocol, especially for patients with a high risk of failure. However, since the study was limited to a relatively small number of patients, a prospective study with a larger cohort will be required for further confirmation of these findings.

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Table V. Adverse events.

| Adverse events, n (%) | Total (n=128) | Multiple myeloma (n=53) | Lymphoma (n=75) | P-value |
|----------------------|---------------|------------------------|----------------|---------|
| Hematologic events (3/4 grade) |               |                        |                |         |
| Neutropenia a         | 115 (89.8)    | 49 (92.5)              | 66 (88.0)      | 0.850   |
| Thrombocytopenia a    | 40 (31.3)     | 14 (26.4)              | 26 (34.7)      | 0.470   |
| Anemia a              | 12 (9.4)      | 3 (5.7)                | 9 (12.0)       | 0.267   |
| Non-hematological events (all grades) |               |                        |                |         |
| Nausea and vomiting a | 59 (46.1)     | 28 (52.8)              | 31 (41.3)      | 0.438   |
| Infection a           | 66 (51.6)     | 25 (47.2)              | 41 (54.7)      | 0.635   |
| Fatigue a             | 21 (16.4)     | 6 (11.3)               | 15 (20.0)      | 0.265   |
| Kaliopenia a          | 21 (16.4)     | 9 (17.0)               | 12 (16.0)      | 0.901   |
| Diarrhea a            | 9 (7.0)       | 3 (5.7)                | 6 (8.0)        | 0.634   |
| GPT elevation a       | 5 (3.9)       | 2 (3.8)                | 3 (4.0)        | 0.950   |
| Osteodynia            | 2 (1.6)       | 1 (1.9)                | 1 (1.3)        | 0.807   |
| Rash a                | 3 (2.3)       | 1 (1.9)                | 2 (2.7)        | 0.779   |
| Coagulation function a| 1 (0.8)       | 0                      | 1 (1.3)        | 0.402   |

a χ² test.
Availability of data and material
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
GZ, JH, ZC and DH were responsible for the conception and design of the study. All authors were responsible for the data acquisition and analysis. GZ was responsible for statistical analysis. GZ drafted the manuscript. GZ and JH revised and commented on the draft. YL, JS, GW, JS and WZ were responsible for primary data collection. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate
The present study was approved by the ethical committee of the First Affiliated Hospital, Zhejiang University, and all participants of the Bone Marrow Transplantation Center of the First Affiliated Hospital, Zhejiang University, and all participants signed informed consent forms.

Patient consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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