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# Exploratory Analysis of Autologous Stem Cell Transplantation In Newly Diagnosed Multiple Myeloma Patients Treated with Bortezomib, Lenalidomide, Dexamethasone: A Small-Scale Real-World Cohort Study in Viet Nam.

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## ABSTRACT

**Aims:** To assess whether the benefits of autologous stem cell transplantation continue to be maintained in practice when combined with bortezomib, lenalidomide, and dexamethasone in the treatment of newly diagnosed multiple myeloma patients.

**Methods:** A retrospective cohort study of 48 patients who were new diagnosed with multiple myeloma, treated with regimen bortezomib, lenalidomide, dexamethasone (borte, lena, dexam) at Blood Transfusion and Hematology hospital, in which 23 patients were treated in combination with autologous stem cell transplantation.

**Results:** The study found that the VGPR rate in the autologous group was higher than in the non-autologous group, but this difference was not statistically significant. The median PFS time was not reached at the end of the study, with a median follow-up of 36 months. The 2-year PFS probability was 78.3% for the group with and without autologous stem cell transplantation, and 58.7% for the group with and without transplantation. The median OS time was 91.7% for the transplantation group and 88.8% for the non-transplantation group. The group with autologous stem cell transplantation had a significantly higher rate of complications than the group without transplantation. No deaths occurred in either group, including those over 65 years old.

**Conclusion:** The combination treatment of bortezomib, lenalidomide, and dexamethasone is effective and safe for newly diagnosed multiple myeloma patients, including those without transplantation and those eligible for autologous stem cell transplantation. Early stem cell collection is recommended for patients with combined treatment with autologous transplantation.

***Keywords:*** *Autologous stem cell multiple myeloma, transplantation, Vietnam*

## 1. INTRODUCTION

Multiple myeloma is a malignant disease, ranked second in the group of hematological cancers.[1] Multiple myeloma is still an incurable disease, so treatment to prolong progression-free survival (PFS) and overall survival (OS) is still the main goal. This goal has led to the study of new drug groups, such as proteasome inhibitors and immunomodulators, which have gradually become the cornerstone of modern multiple myeloma therapy.[2] Lenalidomide belongs to the group of immunomodulators, combined with bortezomib - a proteasome inhibitor - and with dexamethasone, which has now been accepted by many countries as the standard treatment for newly diagnosed multiple myeloma patients regardless of whether the patient is eligible for autologous stem cell transplantation or not.[3] Although autologous stem cell transplantation (ASCT) remains the optimal treatment option for patients with multiple myeloma[4], its use is not uniform across the globe due to differences in access, costs, management of complications, and resources in different countries. Clinical trial data may not

fully reflect the efficacy and safety of ASCT in diverse patient populations, including the elderly, patients with comorbidities, or those who do not meet study criteria.

Therefore, we conducted a real-world study at our treatment center to answer the question of whether the benefits of stem cell transplantation shown in clinical trials are maintained in real-world practice when combined with bortezomib, lenalidomide, and dexamethasone, thereby supporting clinical decision-making in line with health policy. This study aimed to compare the real-world effectiveness of autologous stem cell transplantation combined with bortezomib, lenalidomide, and dexamethasone versus bortezomib, lenalidomide, and dexamethasone alone in newly diagnosed multiple myeloma patients, focusing on progression-free survival (PFS) and safety. The results will provide data to support individualization of treatment and optimization of disease management strategies. It also helps identify the patient groups who benefit most from ASCT and provides a basis for improving access to this therapy in resource-poor countries. As new therapies emerge and dramatically change the treatment of multiple myeloma, understanding the role of ASCT is essential to balance clinical benefit, quality of life, and treatment burden.

## 2. METHODS

**Study design:** Retrospective study.

### *Data sources*

Data was extracted from the medical record database at the Blood Transfusion Hematology Hospital from June 2019 to the end of June 2023. This is a retrospective study describing medical records, without intervention on patients and without affecting the diagnosis and treatment of clinicians.

### *Study population*

Newly diagnosed multiple myeloma patients according to the 2016 International Multiple Myeloma Working Group (IMWG)[1] criteria and treated with the combination regimen of bortezomib, lenalidomide and dexamethasone between June 2019 and June 30, 2023.

### *Treatments*

Patients with multiple myeloma treated with a combination regimen of bortezomib, lenalidomide, and dexamethasone, autologous stem cell transplantation depends on the consultation of the treating physician and the patient's decision. The 21-day bortezomib/lenalidomide/dexamethasone regimen includes: bortezomib 1.3 mg/m$^2$ subcutaneously or intravenously on days 1, 4, 8, and 11 combined with lenalidomide 25 mg/day orally from days 1 to 14 and dexamethasone 20 mg intravenously on days 1, 2, 4, 5, 8, 9, 11, and 12. After 3 or 4 cycles of induction treatment, patients are assessed for response according to the IMWG 2016 criteria[1]. If they do not achieve a minimum partial response (PR), they are advised to switch to another treatment regimen. If they achieve PR or higher in the group with autologous stem cell transplantation, patients will undergo stem cell collection using G-CSF, or G-CSF combined with plerixafor when G-CSF fails. After autologous stem cell transplantation, patients will be reinforced with 2 additional cycles of bortezomib/lenalidomide/dexamethasone. All autologous stem cell transplantation cases are conditioned with melphalan at a dose of 140-200 mg/m², depending on the general condition and underlying disease. In the group without autologous stem cell transplantation, if they achieve PR or higher after 4 cycles, patients will continue treatment for 4 more cycles. After completing induction therapy, patients were maintained on lenalidomide 10 mg every 28 days or bortezomib 1 mg/m² every 2 weeks or thalidomide 100 mg every 28 days until disease progression, depending on the standard or high-risk subgroup and patient preference. Patients were all given venous thromboembolism prophylaxis with 81 mg/day on days of lenalidomide administration, and venous thromboembolism complications were treated with low molecular weight heparin. Bisphosphonates were routinely used to prevent fractures. Response levels included very good partial response (VGPR), partial response (PR), minimal response (MR), and progressive disease (PD).

### *Study outcomes*

The primary study objectives included progression-free survival (PFS) and overall survival (OS). Secondary study objectives included the overall response rate and treatment toxicity. Treatment toxicity was assessed throughout the treatment period. Toxicity was graded according to the NCI toxicity grading scale, version 5.0.

### *Data analysis*

Data is entered into data collection forms, compiled and analyzed using Microsoft Excel software and SPSS software version 20.0. Statistical tests used: The t test is used to compare two means if the data follows a normal distribution. The Mann-Whitney U non-parametric test is used to compare two independent groups if the data does not follow a normal distribution. The Chi-square test is used to compare proportions between study groups. Find the correlation between two variables using the Chi-square test. Evaluate long-term outcomes including OS, PFS, EFS: use the Kaplan-Meier method to estimate survival probability and compare using the log-rank test method to assess the impact of subgroups on survival probabilities. Present the results of the data in the form of tables and charts using Excel and SPSS software. A p value $< 0.05$ is considered

statistically significant, with a 95% confidence interval (CI).

## 3. RESULTS

### Patient characteristics by treatment group

**Table 1. Baseline characteristics of the group with autologous stem cell transplantation and the group with bortezomib, lenalidomide, and dexamethasone alone.**

| Characteristics | Transplantation (n = 23) | Borte, lena, dexam alone (n = 22) | p value |
|---|---|---|---|
| **Age (year)** | 55.1 ± 9.6 | 62.3 ± 8.2 | **0.01** |
| **< 45 (n,%)** | 3 (13.0%) | 1 (0.05%) | |
| **45 - < 65 (n,%)** | 18 (78.3%) | 10 (45.5%) | |
| **≥ 65 (n,%)** | 2 (8.7%) | 11 (50.0%) | **0.005** |
| **Creatinine** | 830 (74.2 100% 99.5) | 79.3 (72.2 100% 92.3) | 0.50 |
| **LDH (U/L)** | 167.0 (114.0 100% 215.0) | 174.0 (140 100% 274.0) | 0.23 |
| **β2- microglobulin (mg/L)** | 4.4 (3.3 100% 5.9) | 4.4 (3.9 100% 8.0) | 0.72 |
| **Albumin (g/L)** | 30.5 (24.2 100% 35.3) | 31.6 (26.0 100% 37.1) | 0.74 |
| **Protein (g/L)** | 104.5 (84.5 100% 129.4) | 100.5 (88.0 100% 108.8) | 0.67 |
| **M-protein** | | | |
| **IgA, n (%)** | 10 (43.5) | 9 (13.7) | 0.54 |
| **IgG, n (%)** | 11 (47.8) | 13 (59.1) | |
| **Light chain** | 2 (8.7) | 0 (0.0) | |
| **R-ISS** | | | |
| **I** | 4 (17.4) | 1 (4.6) | 0.39 |
| **II** | 14 (60.9) | 17 (77.2) | |
| **III** | 5 (21.7) | 4 (18.2) | |
| **Cytogenetic risk category** | | | |
| **Standard risk** | 12 (52.2) | 12 (54.5) | 0.873 |
| **High risk** | 11 (47.8) | 10 (45.5) | |

From June 2019 to June 2023 (**Table 1**), our center had 53 newly diagnosed multiple myeloma patients treated with the bortezomib, lenalidomide, dexamethasone regimen; during the induction phase, 2 cases (3.7%) died of pneumonia, 3 cases (5.7%) had severe toxicity and had to stop treatment, 1 case (1.9%) was resistant to treatment, and 2 cases (3.7%) only achieved minimal response and were then switched to another multiple myeloma treatment regimen after considering the benefits and costs of continuing treatment with the bortezomib, lenalidomide, dexamethasone regimen. The remaining 48 cases completed the bortezomib, lenalidomide, dexamethasone treatment regimen, of which 23 cases (47.9%) were combined with autologous stem cell transplantation. The mean age of the autologous stem cell transplantation group was significantly younger than that of the non-autologous stem cell transplantation group, 55.1 ± 9.6 years old compared to 62.3 ± 8.2 years old ($p = 0.01$). The age group ≥ 65 years old in the autologous stem cell transplantation group accounted for only 8.7% ($n = 2$), while in the non-autologous stem cell transplantation group it was 50% ($n = 11$), a significant difference with $p = 0.005$. The remaining factors at diagnosis included biochemical values, M-protein type, R-ISS stage, or genetic risk subgroup, none of which were significantly different between the two groups with and without autologous stem cell transplantation.

**Clinical outcomes**

**Table 2. Treatment efficacy of the group with autologous stem cell transplantation and the group with bortezomib, lenalidomide, and dexamethasone alone.**

| | Transplantation (n = 23) | Borte, lena, dexam alone (n = 22) | p-value |
|---|---|---|---|
| **Response rate after completion of treatment** | | | |
| **PR, n (%)** | 3 (13.0) | 5 (22.7) | 0.46 |
| **VGPR, n (%)** | 20 (86.9) | 17 (77.3) | |
| **Long-term outcomes** | | | |
| **PFS 100% 2 years (%)** | 78.3% | 72.1% | 0.68 |
| **PFS- 3 years (%)** | 58.7% | 53.6% | 0.73 |
| **OS- 3 years (%)** | 91.7% | 88.8% | 0.52 |

Assessing the response rate achieved after completing treatment, the VGPR rate in the autologous stem cell transplantation group was higher than that in the non-autologous stem cell transplantation group; however, this difference was not statistically significant, specifically 86.9% compared to 77.3% (p = 0.459 > 0.05).

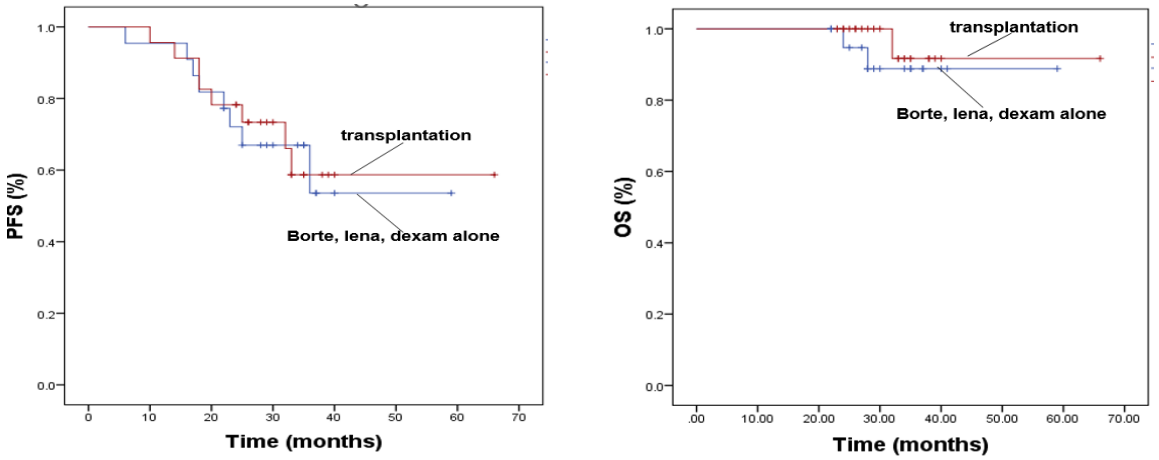


**Figure 1. Kaplan-Meier Curves for Progression-free Survival (PFS) and Overall Survival (OS)**

Regarding long-term outcomes, with a median follow-up of 36 months (0 months-66 months), the median PFS time was not reached at the end of the study (**Table 2**), the 2-year PFS probability of the group with and without autologous stem cell transplantation was 78.3% and 72.1%, respectively, the difference was not statistically significant with p= 0.68. The 3-year PFS probability of the group with combined stem cell transplantation was also not significantly different from that of the group treated with bortezomib, lenalidomide, and dexamethasone alone, 58.7% and 53.6%, respectively with p = 0.73. With a median follow-up time of 36 months (0 months 100% 66 months), the median OS time was not reached at the end of the study, the 3-year OS probability of the two groups was also not significantly different, 91.7% for the transplantation group and 88.8% for the non-transplantation group, respectively (p = 0.52).

**Adverse Events**

**Table 3. Adverse events of the group with autologous stem cell transplantation and the group with bortezomib, lenalidomide, and dexamethasone alone [n(%)]**

| | **Transplantation (n = 23)** | **Borte, lena, dexam alone (n = 22)** | **p value** |
|---|---|---|---|
| **Neutropenia**<br>**Neutropenia grade III/IV** | 7 (30.4)<br>3 (13.0) | 5 (22.7)<br>0 (0.0) | 0.55<br>**0.23** |
| **Thrombocytopenia** | 17 (73.9) | 11 (50) | **0.10** |
| **Thrombocytopenia grade III/IV** | 9 (39.1) | 3 (13.6) | **0.05** |
| **Cytopenia grade III/IV** | 12 (26.1) | 3 (6.8) | **0.014** |
| **Treatment-related mortality** | 0 (0.0) | 0 (0.0) | - |

In terms of safety, the rate of thrombocytopenia and the rate of grade 3 and grade 4 thrombocytopenia in the group with autologous stem cell transplantation was higher than in the group without transplantation; however, the difference was not significant, 73.9% vs. 50% ($p = 0.098 > 0.05$) and 39.1% vs. 13.6% ($p = 0.053 > 0.05$) (**Table 3**). Similarly, the rate of grade 3 and grade 4 neutropenia between the two groups was not significantly different ($p = 0.233 > 0.05$). However, all 3 cases of grade 3 and grade 4 neutropenia were in the autologous stem cell transplantation group. When comparing the total cases of grade 3 and grade 4 complications of thrombocytopenia and neutropenia, the group with autologous stem cell transplantation had a significantly higher rate of complications than the group without transplantation. There were no deaths in either group, including those ≥ 65 years old (n = 13), with the oldest case being 68 years old in the autologous stem cell transplantation group and 78 years old in the non-autologous stem cell transplantation group.

## 4. RESULTS OF STEM CELL COLLECTION FROM PERIPHERAL BLOOD

**Table 4. Results of stem cell collection from peripheral**

| | **$CD34^+$/kg (x $10^6$)** | **After 3 cycles (n = 7)** | **After 4 cycles (n = 21)** | **p (t-test)** |
|---|---|---|---|---|
| **1st time with G-CSF alone** | **$CD34^+$/kg (*)** | **10.2 ± 4.8** | **5.9 ± 4.4** | **0.036** |
| | ≥ 10 $CD34^+$/kg, n (%) | 3 (42.9) | 6 (28.6) | |
| | 5 - < 10 $CD34^+$/kg, n (%) | 4 (57.1) | 3 (14.3) | |
| | 2 - < 5 $CD34^+$/kg, n (%) | 0 | 7 (33.3) | |
| | Failure (< 2 $CD34^+$/kg), n (%) | 0 | 5 (24.0) | |
| **2nd with G-CSF and plerixafor** | Number of cases, n(%) | 0 | 2 (9.5) | |
| | $CD34^+$/kg (*) | - | 2.45 ± 0.50 | |

**Note** (*): Mean ± standard deviation

There were 28 cases of stem cell mobilization performed with G-CSF alone, 21 cases (75.0%) collected after completing 4 cycles and 7 cases (25.0%) collected after completing 3 cycles (**Table 4**). Notably, of the 21 cases of stem cell collection after 4 cycles, 5 cases (24.0%) failed with G-CSF alone, then 2 patients were collected a second time with G-CSF combined with plerixafor, and 3 patients decided not to undergo stem cell transplantation. The average number of CD34+/kg collected after 4 cycles was (5.9 ± 4.4) x $10^6$, lower than (10.2 ± 4.8) x $10^6$ collected after 3 treatment cycles, the difference was statistically significant with $p = 0.036$. Collecting stem cell after 3 cycles, there was no case where the stem cell amount reached < 5 x $10^6$ CD34+/kg and 42.4% of cases achieved ≥ 10 x $10^6$ CD34+/kg, this rate was 1.5 times higher than that collected after 4 cycles. Meanwhile, 1/3 of cases collected after 4 cycles only achieved the stem cell amount from (2 - < 5) x $10^6$ CD34+/kg.

## 5. DISCUSSION

This study evaluated the characteristics of patients in the treatment group combined with autologous stem cell transplantation

(n = 23) and the group treated with bortezomib, lenalidomide, and dexamethasone alone (n = 22) (excluding 3 cases achieving a response < PR after the induction phase, 3 cases discontinued treatment due to severe toxicity, and 2 deaths during the induction phase). The mean age of the autologous stem cell transplantation group was significantly younger than that of the non-autologous stem cell transplantation group, 55.1 ± 9.6 years old versus 62.3 ± 8.2 years old (p = 0.01). This difference was due to the fact that our study was retrospective and encountered selection bias regarding age in the autologous stem cell transplantation group. The treatment plan for autologous stem cell transplantation at our center is only applied to the group of subjects < 65 years old and will be expanded to the group from 65 to under 70 years old with good general condition by 2023. This is clearly shown in our study, when only 2 cases in the autologous stem cell transplantation group were ≥ 65 years old. In contrast, in the group without autologous stem cell transplantation, the treatment regimen with bortezomib, lenalidomide, and dexamethasone was not limited by age. Specifically, the group without autologous stem cell transplantation had a total of 11 cases ≥ 65 years old, accounting for 50%, with the oldest case being 78 years old.

When examining biochemical factors, M-protein type, R-ISS stage, or genetic risk grouping, no factor was different between the two treatment groups. The results from Table 1 show that except for the significant difference in age, other factors examined at diagnosis were similar between the two treatment groups. From there, we compared the treatment effectiveness between the group with and without autologous stem cell transplantation. Regarding the response rate achieved after completing treatment, the rate of VGPR in the group with autologous stem cell transplantation was higher than that in the group without autologous stem cell transplantation; however, this difference was not statistically significant, specifically 86.9% compared to 77.3% (p = 0.459 > 0.05). This result is similar to the study of author Richardson5; the response rate ≥ VGPR in the autologous stem cell transplantation and non-transplantation groups was 87.7% compared to 79.6% (p = 0.99).

Regarding long-term outcomes, with a median follow-up of 36 months (0 months-66 months), the median PFS time was not reached at the end of the study, the 2-year PFS probability of the group with and without autologous stem cell transplantation was 78.3% and 72.1%, respectively, the difference was not statistically significant with p= 0.68. The 3-year PFS probability of the two groups was also not significantly different, 58.7% and 53.6%, respectively with p =0.73. With a median follow-up time of 36 months (0 months 100% 66 months), the median OS time was not reached at the end of the study, the 3-year OS probability of the two groups was also not significantly different, 91.7% for the transplantation group and 88.8% for the non-transplantation group, respectively (p = 0.52 > 0.05).

Therefore, in our study, the effect of autologous stem cell transplantation in patients with multiple myeloma on long-term outcomes is unclear, including the probability of PFS - 2 years, EFS - 3 years, OS - 3 years. Therefore, in elderly patients (≥ 70 years old) or those who are not eligible for autologous stem cell transplantation, treatment with bortezomib, lenalidomide, dexamethasone alone also brings high treatment efficacy and good survival prognosis. However, our study had a small sample size in both groups and did not have enough follow-up time to assess median PFS and OS, so the benefit of autologous stem cell transplantation may not be assessed.

In terms of safety, the rate of thrombocytopenia and the rate of grade 3 and grade 4 thrombocytopenia in the autologous stem cell transplantation group were higher than in the non-transplantation group, however, the difference was not statistically significant, 73.9% vs. 50% (p = 0.098 > 0.05) and 39.1% vs. 13.6% (p = 0.053 > 0.05). Similarly, the rate of grade 3 and grade 4 neutropenia between the two groups was not significantly different (p = 0.233 > 0.05). However, all 3 cases of grade 3 and grade 4 neutropenia were in the autologous stem cell transplantation group. In addition, when comparing the total cases of grade 3 and grade 4 complications of thrombocytopenia and neutropenia, the autologous stem cell transplantation group had a significantly higher rate of complications than the non-transplantation group.

The toxicity in the group with autologous stem cell transplantation was higher than that in the group without autologous stem cell transplantation, as also shown in the study of author Richardson5, the rate of grade 3 and grade 4 hematological complications in the autologous stem cell transplantation group was 89.9% compared to 60.5% in the non-transplantation group (p < 0.001). However, we found that the hematological side effects were transient and recovered when the treatment cycle ended or chemotherapy was temporarily stopped, except for one case of a decrease in two blood cell lines, hemoglobin and platelets, lasting 4 months after stem cell transplantation.

In our study, no autologous stem cell transplantation resulted in death, including those ≥ 65 years old (n = 2) (the oldest was 68 years old) with the melphalan dose reduced to 100 mg/m². This shows that combined treatment with autologous stem cell transplantation is safe for patients with multiple myeloma, even in the elderly (from 65 to 70 years old), who can consider autologous stem cell transplantation depending on their general condition and underlying pathology. This conclusion was also drawn in the study of author Badros6; with the median age of patients being 72 years old, the author found that elderly patients who are eligible for transplantation should not be excluded from autologous stem cell transplantation. Currently, the United States has agreed to perform autologous stem cell transplantation for patients up to 75 years old if eligible, while in Europe, autologous stem cell transplantation can be performed in people up to 70 years old.[7]

When conducting the study, in addition to evaluating the effectiveness of autologous stem cell transplantation, we examined the entire process from initial preparation to completion of the transplantation, including the process of harvesting stem cells from the patient. We noted this issue because some studies found that the more cycles of lenalidomide treatment the patient

received before stem cell collection, the lower the number of stem cells collected from peripheral blood, especially those who only mobilized stem cells with G-CSF alone.[8] To limit failure, the International Multiple Myeloma Study Group (IMWG) recommends early stem cell collection, after 3 or 4 cycles of lenalidomide treatment, as soon as a partial response (PR) is achieved.[8] At our center, the process of collecting stem cells from peripheral blood in patients with multiple myeloma treated with lenalidomide is also carried out after 3 or 4 cycles, as soon as the patient achieves a PR response..

In our study, 28 cases underwent stem cell mobilization with G-CSF alone, 21 cases (75.0%) were collected after completing 4 cycles of bortezomib, lenalidomide, and dexamethasone, and 7 cases (25.0%) were collected after completing 3 cycles. Notably, 5 cases, accounting for nearly ¼ of cases of stem cell mobilization after 4 cycles, failed with G-CSF alone. On the other hand, 7 cases of stem cell mobilization after 3 cycles with G-CSF alone did not fail. The number of CD34+/kg collected after 4 cycles was significantly lower than that collected after 3 cycles of treatment, specifically (5.9 ± 4.4) x $10^6$ vs (10.2 ± 4.8) x $10^6$ CD34+/kg (p = 0.036). Failed stem cell collection increased the economic burden on patients (2 patients subsequently had to undergo a second collection with G-CSF combined with plerixafor) and negatively affected patients' psychology (3 patients decided not to undergo autologous stem cell transplantation). In addition, the collection also aims to have enough stem cells for two autologous stem cell transplantations, especially in the young patient group. Therefore, the number of stem cells that should be collected should be as large as possible. According to our data, after 3 cycles of stem cell collection, there were no cases where the stem cell count was < 5 x $10^6$ CD34+/kg, and 42.4% of cases achieved ≥ 10 x $10^6$ CD34+/kg; this rate was 1.5 times higher than that after 4 cycles. Meanwhile, one-third of cases collected after 4 cycles only achieved stem cell counts from (2 - < 5) x $10^6$ CD34+/kg. Therefore, for patients receiving combined treatment with autologous stem cell transplantation, collection should be performed after 3 cycles instead of after 4 cycles of treatment, as soon as a partial response is achieved. This helps to limit failed collection as well as achieve optimal stem cell numbers and significantly save costs for patients.

## 6. CONCLUSIONS

Our study results show that the combination treatment regimen of bortezomib, lenalidomide, and dexamethasone is highly effective and safe in newly diagnosed multiple myeloma patients, including patients without transplantation and patients with autologous stem cell transplantation. In elderly patients (≥ 70 years old) or those who are not eligible for autologous stem cell transplantation, treatment with the regimen of bortezomib, lenalidomide, and dexamethasone alone also brings high treatment efficiency and good survival prognosis. Hematological toxicity is common and occurs more severely in patients with autologous stem cell transplantation. For patients with combined treatment with autologous stem cell transplantation, stem cell collection should be performed early, as soon as a PR response or higher is achieved, usually after 3 treatment cycles. Multicenter studies with larger sample sizes and long enough follow-up are needed to accurately evaluate the effectiveness of autologous stem cell transplantation when combined with bortezomib, lenalidomide, and dexamethasone regimens in the treatment of newly diagnosed multiple myeloma patients.

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