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Case report

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Result of Bortezomib Induction Therapy Prior to Stem Cell Transplantation in Newly Diagnosed Multiple Myeloma Cases in Mongolia

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Objectives: For last 5 years, we have focused on establishing autologous stem cell transplantation (ASCT) in Mongolia. Herein, we report on three Mongolian multiple myeloma (MM) cases treated with bortezomib and dexamethasone (VD) prior to ASCT. **Methods:** The MM diagnosis was confirmed by bone marrow aspiration, urine protein electrophoresis, and serum protein electrophoresis. **Results:** Circulating white blood cells appeared 8-10 days after ASCT. Platelet levels recovered 10 -15 days after ASCT. **Conclusion:** In our MM cases, the VD regimen prior to ASCT obtained good response rates without the impairment of stem cells.

Keywords: Stem Cell, Transplantation, Bortezomib, Multiple Myeloma

Introduction

Multiple myeloma (MM) is a neoplastic disorder that is characterized by clonal proliferation of plasma cells in the bone marrow, monoclonal protein in the blood or urine, and is associated organ dysfunction. It accounts for approximately 1% of neoplastic diseases, 13% of hematologic cancers, and 2% of cancer related mortality. The median age at diagnosis is approximately 70 years, but 37% of patients are younger than 65 years [1, 2].

MM remains an incurable disease previously treated with conventional combination of melphalan and prednisone, the combination of vincristine, doxorubicin, and dexamethasone (VAD). Fortunately, clinical outcomes have significantly improved over the past two decades due to the use of novel therapy and autologous stem cell transplantation (ASCT). [3, 4]. An induction regimen that includes bortezomib and dexamethasone (VD) prior to ASCT is very effective and currently considered the gold standard for treating patients younger than 65 years. Randomized studies have been shown that, compare to conventional chemotherapy, VD prior to ASCT significantly improves a MM patient's quality of life, including overall survival (OS), disease free survival (DFS), and progression free survival (PFS) [5, 6].

An effective treatment strategy for patients diagnosed with MM has not yet been established in Mongolia. Therefore, our focus was to establish a proper method for ASCT in Mongolia and document its use in newly diagnosed MM cases.

Subjects and Methods

A total of 25 newly diagnosed MM patients were registered at the Center of Hematology and Bone Marrow Transplantation (BMT), First Central Hospital of Mongolia from 2012 to 2015. The MM diagnosis was confirmed by plasmocytes greater than 15% in the bone marrow (BM); elevation of serum or urine free light chain; and bone lesions shown by X-ray, CT, and/or MRI imaging. Of the 25 patients, 3 patients were permitted to undergo ASCT in Mongolia.

Induction chemotherapy, stem cell mobilization and autografting

The VD induction therapy consisted of 3 – 4 week cycles. For all cycles, 1.3 mg/m^2 of bortezomib was administered intravenously on days 1, 4, 8, and 11. Additionally, 40 mg of dexamethasone was administered intravenously on days 1–4 and days 9-12 during all cycles. After completion of the last induction cycle, stem cells were mobilized using intravenous cyclophosphamide (1500m g/m^2 per day) for 2 days, and granulocyte colony-stimulating factor (G-CSF) (10 mg/ kg per day) was injected subcutaneously to increase the absolute neutrophil count (ANC) for collection. 100 mg/kg melphalan was used for the conditioning regimen. Response was assessed according to the International Myeloma Working Group (IMWG) Response Criteria [7].

Case Report

Our three patients, 1 male (case 1) and 2 females (case 2 and 3), were 37–50 years old and had symptomatic MM. Clinical characteristics of these patients were very similar. They were evaluated to be at Durie-Salmon stage III. In case 2, renal failure had occurred at the time of diagnosis. No changes were observed in the peripherhal blood at diagnosis. Serum lactate dehydrogenase (LDH) and serum LCPs, including kappa and

Table 1. Baseline characteristics of patients with MM

	Case1		Case2		Case3	
Treatment with VD	**Before**	**After**	**Before**	**After**	**Before**	**After**
Age at diagnosis	50		46		37	
Sex	Male		Female		Female	
Durie-Salmon stage at diagnosis	IIIA		IIIA		IIIA	
Plasmocytes (%) in BM at diagnosis	46	5.6	Normal	Normal	27.6	
Plasmocytes (%) in BM at ASCT		3.6				
LDH (u/L)	312	146	486	147	1274	326
Serum creatinine (mg/dl)	0.49	0.5	2.27	1.2	0.6	0.5
Kappa (gr/L)	625	2.14	428	3.45	455	3.85
Lambda (gr/L)	28	2.18	87	3.28	75	3.59
Serum calcium (mg/dl)	2.19	1.08	2.2	2.26	2.02	2.14

Table 2. Cycles of VD induction therapy and mobilization of stem cells

Case	Bortezomib (1.3mg/kg)	Dexamethasone (40mg)	Cycles	Response rate	Time between end of IT and start of ASCT	Cytoxan dose, days (1500mg/m^2) for 2 days	G-CSF dose, days (10mg/kg)	SC collection time	SC counts (x10^6/k gl)	Toxicity
Case 1	2.5	40	4	CR	5 months	2940 days	750 days	once	7.7 x10^6 /k gl	Peripheral neuropathy (moderate)
Case 2	2.25	40	4	CR	8 months	2594 days	690 days	once	13.73 x10^6 /k gl	Peripheral neuropathy (moderate)
Case 2	2.34	40	4	PR	1 month	2700 days	675 days	once	7.08 x10^6 /k gl	No side effects

Note: CR-complete response, PR-partial response, IT-induction therapy

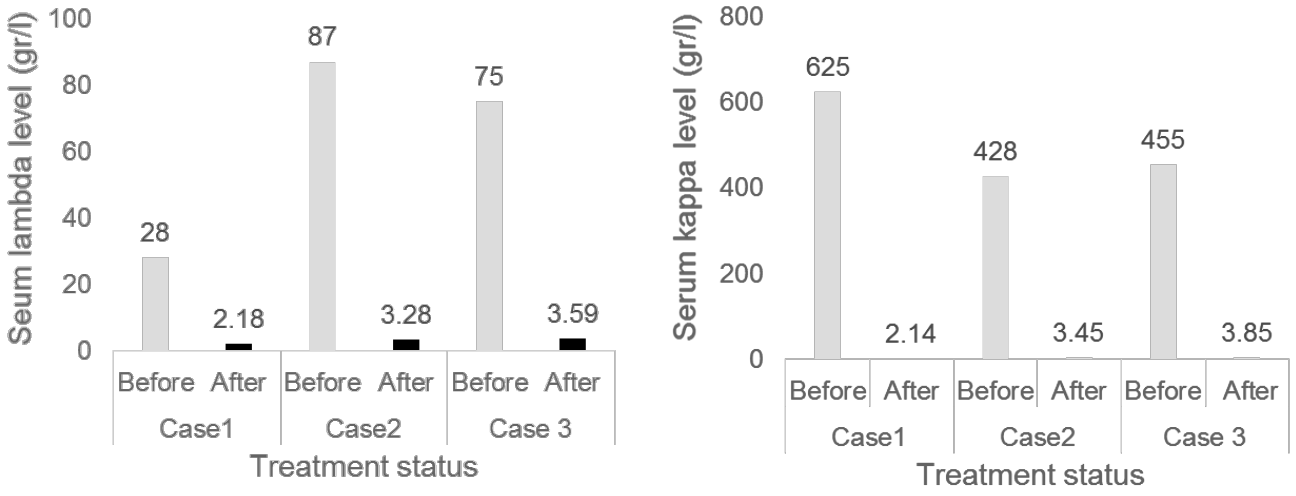

Figure 1. Serum paraprotein levels in patients with MM

Note: Serum paraproteins, including lambda and kappa, completely disappeared as a result of VD treatment.

lambda, was high in all 3 cases. At the time of diagnosis, plasmocytes were increased in the BM for case 1 and 3, but not for case 2 (Table 1).

The VD regimen did not cause peripheral cytopenia. As a result of the treatment, renal failure disappeared in case 2, and BM plasmocytes were decreased to normal values in case 1 and 3. Serum LCPs were significantly downregulated in all three cases (Table 1, Figure 1). Our results show there was complete response (CR) in case 1 and 2 and partial response (PR) in case 3 after the use of the VD regimen. Additionally, there was no toxicity, with the exception of moderate peripheral neuropathy (Table 2).

After VD induction therapy, CD34+ cells were mobilized using cyclophosphamide combined with G-CSF. The number of collected peripheral mononuclear cells via aphaeresis at ASCT day 0 was 7.7; 13.73; and 7.08 x 10^6/kg in cases 1, 2 and 3, respectively (Table 2). Circulating white blood count (WBC) reappeared at day 8-10 after ASCT (Figure 2A). A similar tendency was observed for increasing ANC (Figure 2B). Platelets recovered 10-15 days after ASCT (Figure 2C).

Both hemoglobin and red blood cell (RBC) levels were only slightly affected by the high dose melphalan conditioning regimen. Levels slowly increased and reached normal values 30 days after ASCT (Figure 3A, 3B). BM engraftments occurred on 14 days after ASCT.

We followed these cases for 23 – 59 months after the

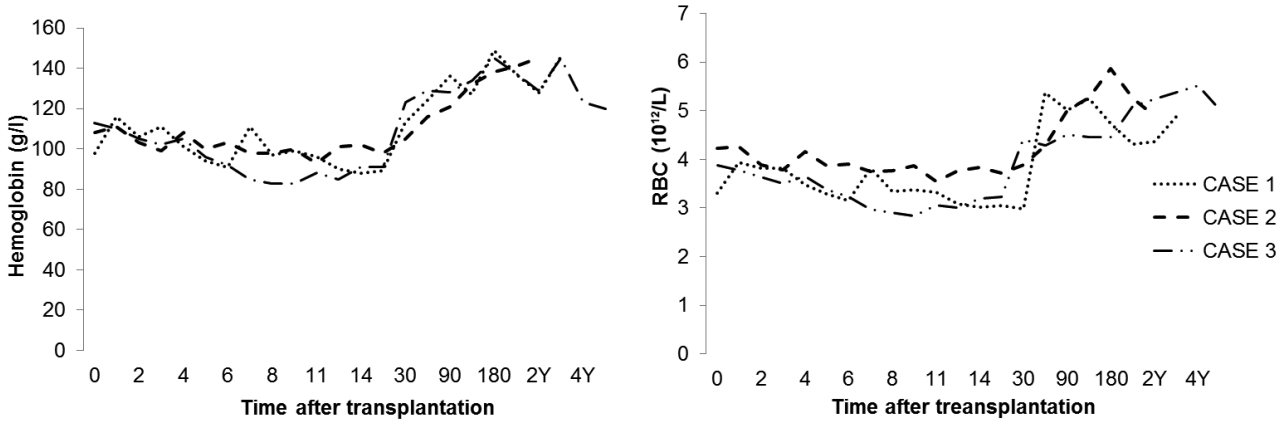

Figure 2. Engraftment of WBC and platelets after ASCT in MM patients

Note: (A) Circulating WBC reappeared at day 8-10 after ASCT. (B) ANC increased starting from day 10. (C) Platelets increased 10-15 days after ASCT.

ASCT. DFS was over 3 years in case 1 and over 2 years in case 2. PFS was almost 5 years in case 3. Continuous follow up is necessary for these patients, and additional maintenance therapy may also be required.

Discussion

Over the last 4 years, our team has established a proper method for the use of ASCT in Mongolia. Herein, we described the first three cases of MM who were treated with VD induction therapy followed by ASCT and achieved CR and very good PR. In previous studies, ASCT has showed a 12-month improvement in OS compared with nontransplant patients [8].

Stem cell mobilization remains a key factor for ASCT [9]. The goal of CD34+ cell mobilization is to collect enough cells to achieve a rapid and sustained hematopoietic recovery after high-dose chemotherapy, since delayed hematopoietic recovery correlates with increased toxicity and transplant-related mortality [10]. IMWG has suggested a minimum target of 4 × 10^6, and it has been demonstrated that high CD34+ cell doses (>3- 5 × 10^6/kg) are associated with faster hematological recovery and lower incidence of infectious and bleeding complications [11]. Mobilization is usually achieved with hematopoietic stem cell-sparing chemotherapy and growth factors [10]. The median yield of stem cells collected after VD is greater when using the combination of cyclophosphamide and G-CSF compared with G-CSF alone [10, 12-14]. In our subjects, we found via aphaeresis that 7.7; 13.73; 7.08 x 10^6/kg cells were mobilized in cases 1, 2, and 3, respectively, by a combination of cyclophosphamide and G-CSF after VD induction therapy. Poor peripheral blood stem cell mobilization have worse outcomes [15, 16].

Similar to the MM response criteria, the IMWG has introduced criteria for serum and urine assessment of monoclonal proteins and plasmocytes in BM [7]. CR is defined as negative immunofixation on the serum and urine, the disappearance of any soft tissue plasmacytomas, and ≤5% plasma cells in BM. PR is defined as a minimum 50% reduction of M protein in serum, and a minimum 90% reduction of M protein in urine or urine M protein levels at <200 mg per 24 hour. According to the above criteria, case 1 and 2 achieved CR and case 3 achieved PR after the VD regimen.

Protein electrophoresis, which allows us to differentiate the types and stage of MM, was introduced in our clinical practice in 2012. Response to the induction therapy and the ASCT treatment was assessed using the IMWG criteria.

The VD regimen has been found to be effective and has become an important part of standard induction therapy [17, 18]. However, there is limited information regarding its efficacy, adverse effects, and long term complications of this induction regimen. It has been found that bortezomib toxicity is mainly due to peripheral neuropathy and thrombocytopenia [21]. In two of three of our cases (case 1 and case 2), moderate peripheral neuropathy was observed.

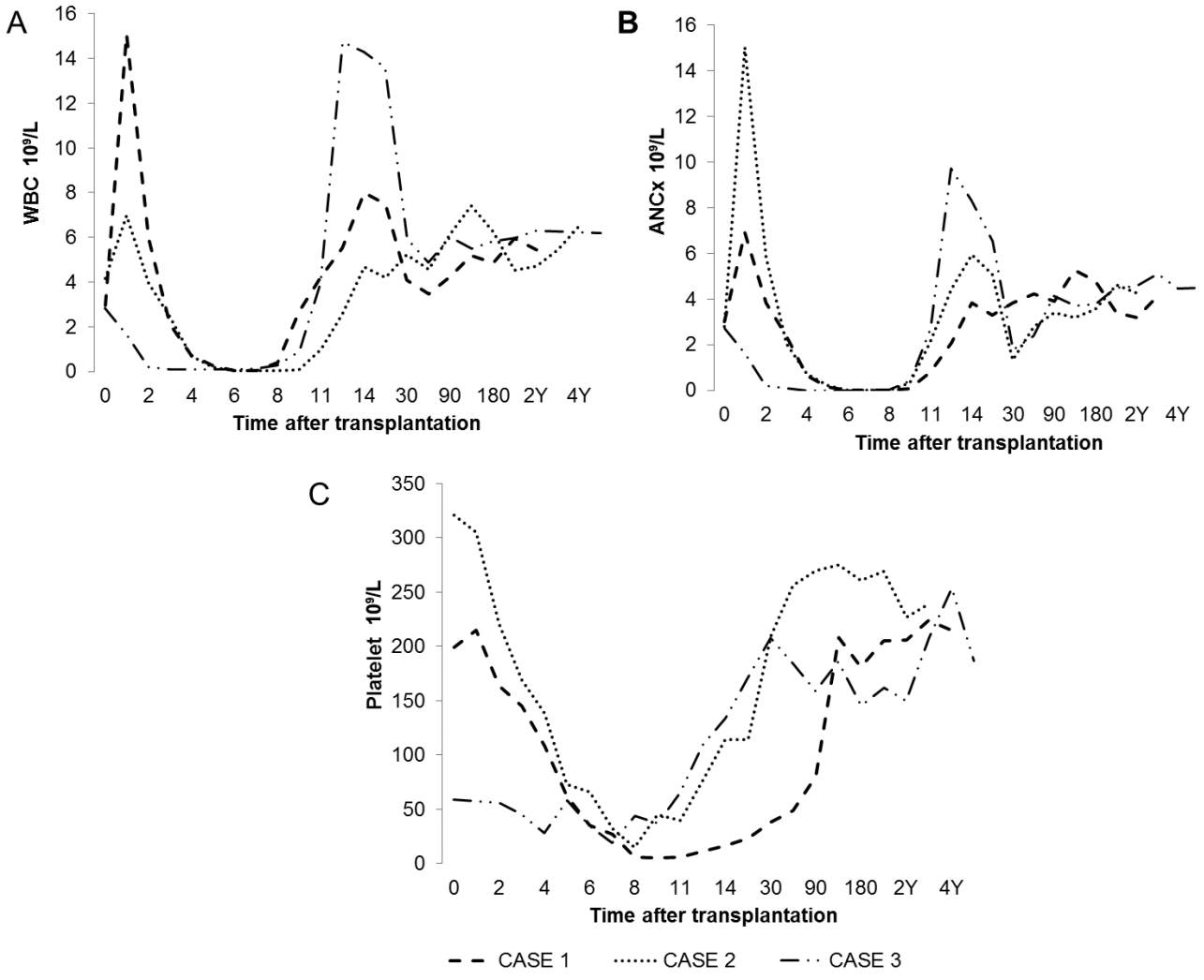

Figure 3. Engraftment of RBC after ASCT in patients with MM

Note: Both hemoglobin (A) and RBC (B) were only slightly affected by the high dose melphalan.

High response rates have been observed with the VD induction therapy (overall response rate 81%, PFS 36 months) [1, 19]. We followed our three cases over 2-4 years after ASCT. Under our supervision, our patients have lived peacefully without any treatment. Our data suggests that PFS will be greater than 4 years for our patients, but we will need provide continuous follow up and additional maintenance therapy, if required.

In conclusion, the use of the VD regimen prior to ASCT obtained good response rates without impairment of stem cell collection. We also found that the positive responses to induction therapy was related to better results after ASCT.

Conflict of Interest

The authors declare that they have no competing interests.

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References

1. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med 2011; 364: 1046-1060.
2. Zweegman S, Palumbo A, Bringhen S, Sonneveld P. Age and aging in blood disorders: multiple myeloma. Haematologica 2014; 99: 1133-1137.
3. Ludwig H, Bolejack V, Crowley J, Bladé J, Miguel JS, Kyle RA, et al. Survival and years of life lost in different age cohorts of patients with multiple myeloma. J Clin Oncol 2010; 28: 1599-1605.
4. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008; 111: 2516-2520.
5. Mellqvist UH, Gimsing P, Hjertner O, Lenhoff S, Laane E, Remes K, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. Blood 2013; 121: 4647-4654.
6. McCarthy PL, Owzar K, Hofmeister CC, Hurd DD, Hassoun H, Richardson PG, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012; 366: 1770-1781.
7. Kumar S, Paiva B, Anderson KC, Durie B, Landgren O, Moreau P, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016; 17: e328-346.
8. Child JA, Morgan GJ, Davies FE, Owen RG, Bell SE, Hawkins K, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003; 348: 1875-1883.
9. Giralt S, Costa L, Schriber J, Dipersio J, Maziarz R, McCarty J, et al. Optimizing autologous stem cell mobilization strategies to improve patient outcomes: consensus guidelines and recommendations. Biol Blood Marrow Transplant 2014; 20: 295-308.
10. Cavallo F, Bringhen S, Milone G, Ben-Yehuda D, Nagler A, Calabrese E, et al. Stem cell mobilization in patients with newly diagnosed multiple myeloma after lenalidomide induction therapy. Leukemia 2011; 25: 1627-1631.
11. Demirer T, Buckner CD, Bensinger WI. Optimization of peripheral blood stem cell mobilization. Stem Cells 1996; 14: 106-116.
12. Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Gastineau DA, et al. Impact of lenalidomide therapy on stem cell mobilization and engraftment post-peripheral blood stem cell transplantation in patients with newly diagnosed myeloma. Leukemia 2007; 21: 2035-2042.
13. Gertz MA. Current status of stem cell mobilization. Br J Haematol 2010; 150: 647-662.
14. Milone G, Leotta S, Indelicato F, Mercurio S, Moschetti G, Di Raimondo F, et al. G-CSF alone vs cyclophosphamide plus G-CSF in PBPC mobilization of patients with lymphoma: results depend on degree of previous pretreatment. Bone Marrow Transplant 2003; 31: 747-754.
15. Sugrue MW, Williams K, Pollock BH, Khan S, Peracha S, Wingard JR, et al. Characterization and outcome of "hard to mobilize" lymphoma patients undergoing autologous stem cell transplantation. Leuk Lymphoma 2000; 39: 509-519.
16. Gordan LN,Sugrue MW, Lynch JW, Williams KD, Khan SA, Wingard JR, et al. Poor mobilization of peripheral blood stem cells is a risk factor for worse outcome in lymphoma patients undergoing autologous stem cell transplantation. Leuk Lymphoma 2003; 44: 815-820.
17. Moreau P, Attal M, Facon T. Frontline therapy of multiple myeloma. Blood 2015; 125: 3076-3084.
18. De Matteo M, Brunetti AE, Maiorano E, Cafforio P, Dammacco F, Silvestris F. Constitutive down-regulation of Osterix in osteoblasts from myeloma patients: in vitro effect of Bortezomib and Lenalidomide. Leuk Res 2010; 34: 243-249.
19. Kapoor P, Ramakrishnan V, Rajkumar SV. Bortezomib combination therapy in multiple myeloma. Semin Hematol 2012; 49: 228-242.