JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Bone Marrow and Stem Cell Research

Case Report

Pomalidomide as Consolidation Therapy after Salvage Autologous Stem Cell Transplant

Mary Steinbach[1*], Tim Luetkens[1], Kristen Vinik[2], Sabarinath Venniyil Radhakrishanan[1], Djordje Atanackovic[1]

[1]*Hematology and Hematologic Malignancies, University of Utah, Huntsman Cancer Institute, Salt Lake City, UT, USA*

[2]*University of Utah, Department of Pharmacy, Hematology/Oncology, Salt Lake City, UT, USA*

**Corresponding author: Dr. Mary Steinbach, DNP, APRN, Division of Hematology and Hematologic, Malignancies University of Utah/Huntsman Cancer Institute, Room 2880 2000 Circle of Hope Drive, Salt Lake City, UT 84112,*

Email: mary.steinbach@hsc.utah.edu

Received: 08-01-2018

Accepted: 09-04-2018

Published: 09-10-2018

Abstract

Recent advancements in the treatment multiple myeloma (MM) have improved patient outcomes in both the first-line as well as the relapsed/refractory settings. High-dose chemotherapy plus autologous stem cell transplant followed by maintenance therapy remains the standard of care as a front-line treatment for eligible patients. Unfortunately, most patients still evidence minimal residual disease after their initial transplant and almost all patients eventually relapse. In the setting of relapsed MM, salvage autologous stem cell transplant should be considered in patients who showed a good and durable response to their initial transplant. However, it is currently unknown whether patients will receive a similar benefit from maintenance therapy after salvage autologous transplant, as they do in the first-line setting. Here we describe the clinical course of four patients who received consolidation/maintenance treatment with pomalidomide after salvage therapy with high-dose melphalan plus autologous stem cell rescue and in whom this combination resulted in excellent clinical outcomes.

Keywords: Pomalidomide; Consolidation Therapy; Salvage Transplant; Multiple Myeloma; Maintenance

Introduction

Over the past decade there have been many advances in the treatment of multiple myeloma (MM). However, in the first-line setting, induction treatment followed by high-dose chemotherapy plus autologous stem cell transplant (ASCT) is still considered the standard of care for eligible patients. Regardless of previous treatment and progression history, maintenance therapy has become a mainstay in myeloma treatment. Accordingly, a recent study showed that in both transplant-eligible and –ineligible patients, maintenance treatment with the immunomodulatory drug (IMiD) lenalidomide led to an improved progression-free survival [1].

Regardless what type of induction, consolidation, and maintenance treatment the individual patient receives, the vast majority of myeloma patients will eventually suffer a relapse or progression of their disease. Novel therapies such as pomalidomide, a next-generation IMiD approved for patients with relapsed / refractory myeloma, and carfilzomib have expanded treatment options and increased progression-free survival [2, 3]. However, despite the role of new therapies, salvage ASCT remains an effective and useful tool for many patients. Reinduction therapy followed by salvage ASCT should be considered in patients who have responded well to their initial transplant and have had a progression-free interval of at least 12-18 months [7]. It is an open question, however, whether patients will derive a similar benefit from consolidation/maintenance treatment after salvage ASCT as they do in the first-line setting.

In this report, we describe the clinical course of 4 consecutive patients who received consolidation/maintenance treatment with pomalidomide after salvage therapy with high-dose melphalan followed by ASCT.

Case Reports

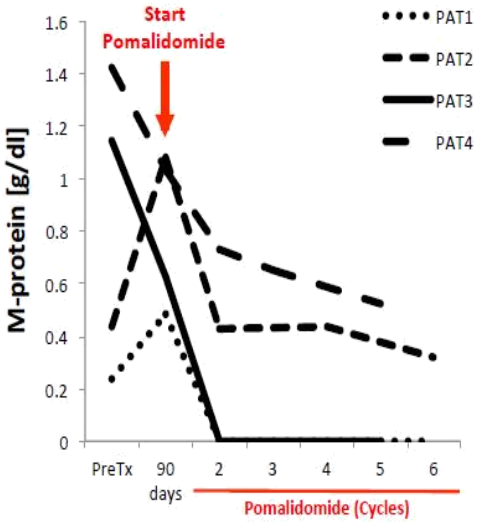
Patient 1:

The first patient (Table 1) is a 49-year-old woman with normal cytogenetics who had initially been treated with tandem ASCT. She had received induction with dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide (DPACE) chemotherapy, followed by the collection of stem cells. Her conditioning regimen prior to her first ASCT was bortezomib, thalidomide, dexamethasone and high-dose melphalan (VTD-Mel). Post-transplant she was bridged with bortezomib plus dexamethasone.

Patient #	Cytogenetics at diagnosis & relapse	Initial Treatment	Reinduction Regimen
1	normal/normal	DPACE, VTD-Mel	VRD
2	normal/normal	RD	CyBorD, DPACE
3	normal/normal	DPACE, VTD-Mel	VRD
4	15q22 gain/1q21 gain	DPACE, VTD-Mel	CRD, DPACE

Table 1. Patient Characteristics.
DPACE = dexamethasone / cisplatin / doxorubicin / cyclophosphamide / etoposide;
VTD = velcade / thalidomide / dexamethasone;
Mel = Melphalan
VRD= bortezomib/lenalidomide/dexamethasone
CyBorD= cyclophosphamide/bortezomib/dexamethasone
RD= revlimid/dexamethasone
CRD= carfilzomib, lenalidomide, dexamethasone

Her second transplant preparative regimen of bortezomib, thalidomide, dexamethasone, carmustine, etoposide, cytarabine, melphalan (VTD-BEAM) resulted in a complete response. She received a total of 1 year of maintenance therapy with bortezomib, thalidomide, and dexamethasone (VTD), with thalidomide being switched to lenalidomide after 9 cycles. She then received an additional year 1 year of single agent bortezomib. She then had a serological relapse with an increased number of aberrant plasma cells in the bone marrow and new bony lesions, her cytogenetics remained normal. She was reinduced with 2 cycles of bortezomib, lenalidomide, and dexamethasone (VRD), and obtained a partial remission. Following this remission, she proceeded with high-dose melphalan (200 mg/m^2) followed by ASCT. At day 90 post transplant she showed a serum M-protein level unchanged from her pre-transplant level and was started on consolidation therapy with pomalidomide at 4 mg on days 1-21 of a 28-day cycle combined with 40mg dexamethasone weekly. After 2 cycles of pomalidomide consolidation, the patient had achieved a complete response (CR) with a negative serum immunofixation (IFE). Remarkably, she recently completed 16 months of pomalidomide consolidation/maintenance therapy with a continued CR (Figure 1).



Patient 2:

Our 60-year-old patient with normal cytogenetics (Table 1) was initially treated outside of our institution with 12 cycles of lenalidomide plus dexamethasone with less than a partial response. When we first saw him he had developed the refractory disease and was started on reinduction treatment with cyclophosphamide, bortezomib, and dexamethasone (CyBorD). After 2 cycles he had only achieved a minimal response and went on to one cycle of chemotherapy with DPACE prior to stem cell collection. He then received high-dose melphalan at (200 mg/m^2) followed by ASCT. Unfortunately, at 90 days post-transplant the patient had not even achieved a partial response compared to his pre-transplant serum M-protein levels (Figure 1). His cytogenetics remained normal. He was started on consolidation treatment with pomalidomide and dexamethasone. The patient has currently received 4 cycles of treatment and he shows an ongoing response with his serum M-protein having decreased by 50%.

Patient 3:

Patient 3 is a 67-year-old male (Table 1) with normal cytogenetics who was initially induced by DPACE chemotherapy and received tandem transplant with a VTD-Mel conditioning regimen for his first transplant. He was bridged with thalidomide and dexamethasone and the preparative regimen for the second transplant was VD-Mel, carmustine, and gemcitabine, followed by one year of maintenance with VRD. He remained in a durable partial remission for 3 years. At his relapse, his cytogenetics remained normal. He received 8 cycles of reinduction treatment with VRD resulting in a partial remission before proceeding with high-dose melphalan (200 mg/m^2) followed by ASCT. At 90 days post-transplant the patient showed more than a 50% increase in his serum M-protein compared to his pre-transplant levels. He was started on pomalidomide and dexamethasone and after a total of 4 cycles, this consolidation regimen has resulted in a greater than 70% reduction in his

serum M-protein (Figure 1), despite the fact that multiple dose reductions had to be performed due to chemotherapy-related toxicity.

Patient 4:

Our fourth patient was a 72-year-old man with a 15q22 gain (Table 1) who had initially received treatment with DPACE followed by VTD-Mel and ASCT. The patient then received maintenance therapy with bortezomib for one year. When he showed signs of progression, his therapy was escalated with the addition of lenalidomide, which resulted in stable disease for another year. When he finally had progression of his disease, his cytogenetics had changed to include a 1q21gain. He received carfilzomib, lenalidomide, and dexamethasone (CRD) for a total of 7 cycles. While he initially responded, his disease eventually progressed again and he received another cycle of DPACE chemotherapy prior to single agent melphalan (140 mg/m^2) followed by ASCT. At day 90 post transplant his serum M-protein level had only decreased by less than 50% compared to his pre-transplant levels. At this time he was started on consolidation treatment with pomalidomide and dexamethasone and has achieved a complete response after only 2 cycles (Figure 1).

Conclusions

Since pomalidomide has received FDA-approval for the treatment of patients with relapsed/refractory myeloma, we have placed 4 patients on consolidation/maintenance treatment with pomalidomide following salvage ASCT. Our observations indicate that pomalidomide consolidation treatment is safe and highly effective in this particular clinical setting. In fact, all of our patients achieved a deepening of their transplant-induced response, with two of the patients achieving a complete response.

It has been shown in the setting of relapsed/refractory myeloma that treatment with pomalidomide plus dexamethasone will result in a median progression-free survival of about 4 months. Overall response rates are approximately 30%, and in those patients who respond, responses will last for 7 months [2, 8]. More recently, it was shown that novel approaches such as monoclonal antibodies are significantly more effective when used in combination with an IMiD such as lenalidomide [4-6]. Our data indicate that the same is the case if high-dose chemotherapy and salvage transplant are combined with the next-generation IMiD pomalidomide, possibly based on a synergistic effect. Controlled clinical trials should examine whether this combination is as promising as suggested by our observations.

Consent

Written informed consent was obtained from the patient for publication of this Case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Authorship and Disclosures

MS and DA and were the primary authors of the paper. KV and SR assisted in the gathering of data. TL and SR assisted with preparation of the manuscript, graph, and table formatting. DA is a consultant for Celgene, MS is on the speakers bureau for Celgene. The authors declare that there is no conflict of interest regarding the publication of this article.

References

1. Palumbo A, Cavallo F, Gay F, Di Raimondo F, Ben Yehuda D et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med. 2014, 371(10): 895-905.

2. San Miguel J, Weisel K, Moreau P, Lacy M, Song K et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013, 14(11): 1055-1066.

3. Siegel DS, Martin T, Wang M, Vij R, Jakubowiak AJ et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood. 2012, 120(14): 2817-2825.

4. Atanackovic D, Schilling G. Second autologous transplant as salvage therapy in multiple myeloma. Br J Haematol. 2013, 163(5): 565-572.

5. Leleu X, Attal M, Arnulf B, Moreau P, Traulle C et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myelome 2009-02. Blood. 2013, 121(11): 1968-1975.

6. Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med. 2015, 373(7): 621-31.

7. van der Veer MS, de Weers M, van Kessel B, Bakker JM, Wittebol S et al. Towards effective immunotherapy of myeloma: enhanced elimination of myeloma cells by combination of lenalidomide with the human CD38 monoclonal antibody daratumumab. Haematologica. 2011, 96(2): 284-290.

8. Moreau P, Masszi T, Grzasko N, Bahlis NJ, Hansson M et al. Ixazomib, an Investigational Oral Proteasome Inhibitor(-PI), in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival (PFS) for Patients (Pts) with Relapsed and/ or Refractory Multiple Myeloma (RRMM): The Phase 3 Tourmaline- MM1 Study (NCT01564537). 2015.