A Case Report of a 58-Year-Old Woman with a Diagnosis of High-Risk Myeloma Refractory to Multiple Line of Therapy and Treated with Selinexor, Bortezomib, and Dexamethasone Prior to Allogeneic Stem Cell Transplantation

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Patient: Female, 40-year-old
Final Diagnosis: Multiple myeloma
Symptoms: Anaemia
Medication: —
Clinical Procedure: —
Specialty: Hematology • Oncology • Transplantology

Objective: Unusual clinical course

Background: Approximately 10% to 15% of patients with multiple myeloma (MM) are diagnosed with high-risk disease and have poor prognosis. Clinical trial data supports the combined use of selinexor, bortezomib, and dexamethasone (XVd) for treatment of patients with MM who have received at least 1 prior therapy. Information on the efficacy of XVd and of subsequent allogeneic stem cell transplantation (SCT) in heavily pretreated patients with high-risk MM is limited.

Case Report: We present a case of a 58-year-old woman with high-risk MM (revised International Staging System Stage III; serum β₂-microglobulin; 8.0 mg/L; and presence of del[17p]) who had received 8 prior treatment lines, and whose disease was refractory to ixazomib, bortezomib, and all immunomodulatory agents. Before initiating XVd (once weekly 1.3 mg/m² bortezomib subcutaneously, 80 mg selinexor per os, and 40 mg dexamethasone per os), the patient had severely hypoplastic bone marrow and was transfusion dependent. After 1 cycle of XVd, she achieved a partial response, and after 4 cycles, a very good partial response (VGPR). No adverse reactions to selinexor were observed. Because of the VGPR, a haploidentical transplant was planned. At posttransplant week 4, the patient had become transfusion independent. She remained relapse-free for 13 months after initiating XVd. Maintenance treatment with lenalidomide was initiated, and following receipt of donor lymphocyte infusions due to loss of donor chimerism, the patient’s light chain levels improved.

Conclusions: This report presents the cytogenetics and management of a heavily pretreated patient with high-risk MM treated with SVd followed by SCT.

Keywords: Cytogenetics • Hematopoietic Stem Cell Transplantation • Multiple Myeloma • Selinexor

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Background

The prognosis of patients with multiple myeloma (MM) has improved in the last 2 decades with the progress of high-dose therapy with stem cell transplantation (SCT), the development of proteasome inhibitors, immunomodulatory drugs (iMiDs), and monoclonal antibodies, and the use of combination therapies [1]. Nevertheless, MM remains incurable, with inevitable cycles of remission and relapse, and with the disease becoming refractory to some or all previous treatments, highlighting the need for class switching and the introduction of treatments with novel mechanisms of action [1]. Furthermore, according to the revised International Staging System (R-ISS) criteria, 10% to 15% of patients are diagnosed with high-risk MM, defined as disease with β₂-microglobulin levels ≥5.5 mg/L, presence of high-risk cytogenetics ([t(4;14), [t(14;16), and/or del[17p] cytogenetic abnormalities) by fluorescence in situ hybridization (FISH), or elevated lactate dehydrogenase (LDH) levels [2,3].

Selinexor is a novel, first-in-class, oral selective inhibitor of nuclear export compounds, which blocks exportin 1, forcing the nuclear retention and activation of tumor suppressors, ultimately causing selective apoptosis of cancer cells. In 2019, based on the results of the phase 2b STORM trial [4], the US Food and Drug Administration (FDA) granted accelerated approval of the combination of selinexor with dexamethasone (Dex) for patients with relapsed refractory MM who have received at least 4 prior therapies and whose disease is penta-refractory [5]. Moreover, in 2020, the triplet combination of once weekly selinexor (100 mg) per os (p.o.), once weekly subcutaneous bortezomib (1.3 mg/m²), and twice weekly p.o. Dex (20 mg) (XVd) received FDA approval for patients with MM with at least 1 prior therapy, based on the results of the phase 3 BOSTON trial [6].

This report describes the case of a 58-year-old woman with high-risk MM who was heavily pretreated and transfusion dependent and was successfully treated with XVd prior to allogeneic SCT.

Case Report

Our patient was a 58-year-old woman first diagnosed with light-chain MM at 40 years of age. The patient was initially treated with 6 cycles of vincristine/doxorubicin/Dex in 2002. She remained in complete remission for 12 years, after which the results of the phase 2b STORM trial [4], the US Food and Drug Administration (FDA) granted accelerated approval of the combination of selinexor with dexamethasone (Dex) for patients with relapsed refractory MM who have received at least 4 prior therapies and whose disease is penta-refractory [5]. Moreover, in 2020, the triplet combination of once weekly selinexor (100 mg) per os (p.o.), once weekly subcutaneous bortezomib (1.3 mg/m²), and twice weekly p.o. Dex (20 mg) (XVd) received FDA approval for patients with MM with at least 1 prior therapy, based on the results of the phase 3 BOSTON trial [6].

This report describes the case of a 58-year-old woman with high-risk MM who was heavily pretreated and transfusion dependent and was successfully treated with XVd prior to allogeneic SCT.
her disease relapsed (Figure 1). She presented with a paraprotein level of 17.6 g/L (evaluated by serum protein electrophoresis), anemia, extensive bone marrow plasmacytosis, and lytic lesions in her skull. Her Eastern Cooperative Oncology Group (ECOG) performance status was 1. FISH analysis revealed 4 copies of the MAF oncogene, and 4 copies of wild type p53. FISH was negative for t(4;14), t(4;16), and p53 deletion.

In the 6 years between her referral for relapsed disease and commencement of treatment in March 2020 with XVd (80 mg p.o. selinexor, 1.3 mg/m² subcutaneous bortezomib, and 40 mg p.o. Dex weekly over 28-day cycles), the patient received 7 additional lines of therapy (Figure 1). Following her eighth treatment line, she had exhausted all treatment options available to her. She was not eligible for any clinical trial, her disease was refractory to ixazomib, bortezomib, and all IMiDs, and she did not have access to carfilzomib and/or daratumumab. Based on preclinical and clinical evidence [6-9], we reasoned that selinexor treatment would overcome the patient’s MR refractoriness to bortezomib, resulting in a significant response.

At XVd initiation, her ECOG performance status was 0. She had normal liver function, moderate renal impairment (estimated creatinine clearance, 62 mL/min), and mild mitral regurgitation on cardiac echocardiography. She had high-risk disease [3]: R-ISS stage III MM (serum β₂-microglobulin, 8.0 mg/L; LDH, 299 U/L; and presence of del[17p]). Other cytogenetic abnormalities included trisomy 1q, del(14q), and del(13q). The patient had an empty marrow, with 10% cellularity, most likely due to multiple prior treatment lines. She exhibited leukopenia (white blood cell count, 1.79×10⁹/L); severe neutropenia (absolute neutrophil count, 0.19×10⁹/L); anemia (hemoglobin, 8.1 g/dL); and severe thrombocytopenia (platelet count, 9×10⁹/L). As a result, she required 2 units of red blood cells (RBC) and 1 unit of platelets every 14 days. No hematopoietic growth factor support was administered.

Prior to XVd treatment, the patient had no measurable monoclonal protein by serum protein electrophoresis, and the serum free light chain (FLC) assay was considered to be more reproducible and reliable for follow-up than urine protein electrophoresis. Her serum lambda FLC levels were 297.0 mg/L (reference range, 8.3-27.0 mg/L), and her kappa/lambda ratio was 0.018. After 1 treatment cycle, she achieved a partial response (PR), with lambda FLC levels of 133.0 mg/L, kappa/lambda ratio of 0.49 (Figure 2), and with a 56% decrease in the difference between involved and uninvolved FLC levels. The patient achieved a very good PR (VGPR) [10] by cycle 4; her lambda FLC levels were 59.0 mg/L, kappa/lambda ratio of 0.09, and with a 93% decrease in the difference between involved and uninvolved FLC levels.
levels. With the administration of prophylactic granisetron and metoclopramide, the patient did not exhibit adverse reactions to selinexor. After 2 cycles of Xvd, the patient’s hematopoietic function improved substantially, and she required only 1 unit of RBC every 2 weeks and 1 unit of platelets every 4 weeks, about 50% of her requirement prior to treatment.

In light of the significant response achieved, and as the patient had already received 2 autologous transplants and had a severely hypoplastic marrow, we planned an allogeneic transplant. As there were no matched sibling donors or unrelated donor options, a haploidentical transplant was planned (the donor was her son, with a matched ABO blood group; matched cytomegalovirus status; and the patient had no donor-specific antibodies). Her hematopoietic cell transplantation-specific comorbidity index (HCT-CI) showed no comorbidities (HCT-CI: 0) [11]. The patient’s pretransplant bone marrow biopsy demonstrated a morphological complete response, with minimal residual disease positivity at a level of 1.45% (by immunophenotyping). The patient underwent Baltimore reduced-intensity conditioning followed by the haploidential transplant in August 2020. Transplant-related complications included an episode of cytokine release syndrome (grade 3) on day 3 after transplant, manifesting as fever and hypotension, which responded rapidly to tocilizumab without requiring inotrope support, and an episode of neutropenic sepsis on day 5 after transplant, which responded to antibiotics.

The patient was discharged from our transplant unit 20 days after transplant. At her week 4 posttransplant follow-up visit, she had the most robust full blood count in 2 years (hemoglobin level, 10.1 g/dL; platelet count, 94×10^9/L; neutrophil count, 3.08×10^9/L) and was transfusion independent. Bone marrow biopsies at posttransplant weeks 6 and 11 demonstrated morphological remission and trilineage engraftment. The patient was unable to receive reimbursement for maintenance treatment until posttransplant week 36, at which time generic lenalidomide became available. At lenalidomide initiation, her lambda FLC levels had risen to 144 mg/L and briefly declined to 106 mg/L 1 month after lenalidomide initiation at posttransplant week 39, but increased to 253 mg/L at posttransplant week 43, confirming a biochemical relapse (Figure 2).

At posttransplant week 45, donor chimerism was documented to be 44.97%. One week later, the patient received a first donor lymphocyte infusion (DLI) with a CD34 dose of 1×10^5/kg, followed by a second DLI 10 days later with a CD34 dose of 1×10^5/kg. Improvement in chimerism was paralleled with improvements in the patient’s serum FLC levels (Figure 2). In particular, her lambda FLC levels declined to 229 mg/L at posttransplant week 52 and donor chimerism improved to 66.73% at posttransplant week 54. At the time of this report, the patient was scheduled to receive a third DLI during posttransplant week 56.

Discussion

We report the use of Xvd in a heavily pre-treated patient with high-risk MM refractory to all IMiDs, bortezomib, and ixazomib. The patient showed a rapid and deep response to Xvd (VGPR by Cycle 4), with improvement in transfusion requirements that enabled her to receive haploidential allogeneic SCT. The patient was heavily transfusion dependent prior to initiating selinexor treatment. The low counts can be attributed to the aggressive disease and multiple prior therapies. However, the platelet and RBC counts improved after she was started on selinexor. The frequency of transfusion was reduced and eventually the counts returned close to normal range. This also supports the rapid clinical response to the selinexor-based regimen. Selinexor has been shown to overcome acquired bortezomib resistance in MM in pre-clinical and clinical settings [8,9]. Sixty-nine percent of the patients who received Xvd in the BOSTON trial were previously exposed to bortezomib. The overall response rate (ORR) for this subgroup was 77.6% [6].

The patient had a VGPR after transplant but experienced a biochemical relapse 13 months after starting selinexor 80 mg once weekly in combination with bortezomib and Dex. This relapse appeared to be related to a loss of donor chimerism, since receipt of DLIs was accompanied by improvement not only in chimerism but also in serum FLC levels. The improvement observed following receipt of DLI may have been enhanced by lenalidomide [10,11]. Lenalidomide contributes to the elimination of MM cells by potentiating T cell and natural killer cell functions [12,13]. This may lead to a synergistic effect with DLI when the 2 are used as combination treatment in patients with high-risk MM [11], although further studies supporting such an association are warranted.

Our patient had received 8 prior treatment lines (including bortezomib) as opposed to a maximum of 3 allowed for the population enrolled in the BOSTON trial [4], and yet, the time to response in our patient was 1 month, similar to that of the BOSTON trial findings, in which the median time to response in the Xvd arm was 1.1 (interquartile range, 0.8-1.6) months. A sub-analysis of patients in the BOSTON trial with high-risk cytogenetics demonstrated that Xvd compared to bortezomib + dexamethasone (Vd) conferred benefits on ORR (78.6% vs 57.7%; odds ratio, 2.68; 95% confidence interval [CI], 1.28-5.62; \(P=0.004\)), and time-to-next-treatment (14.0 vs 8.6 months; hazard ratio, 0.64; 95% CI, 0.42-0.97; \(P=0.018\)). Moreover, when each of the high-risk cytogenetic abnormalities were examined separately, patients with del(17p) (as in our case) receiving the Xvd regimen were found to have a median progression-free survival of 12.2 months compared with 5.9 months for those treated with Vd (hazard ratio, 0.38; 95% CI, 0.16-0.86; 1-sided \(P=0.008\)) and an ORR of 76.2% vs 37.5% (1-sided \(P=0.010\)). Additionally, the median time to next therapy was significantly
improved in patients with del(17p) receiving the XVd regimen compared with those on Vd (14.8 vs 7.6 months; hazard ratio, 0.30; 95% CI, 0.12-0.75; P=0.003), with a not statistically significant trend toward improved duration of response (14.8 vs 6.8 months; P=0.008) [16]. Notably, due to transfusion-dependent thrombocytopenia, our patient was treated with a selinexor dose lower than the initial dose used in the XVd combination in the BOSTON trial [6]. The BOSTON trial excluded patients with platelet counts lower than 75 × 109/L. Our patient did not experience any adverse events with this regimen, owing to a proactive supportive care strategy. Prevention of nausea may be explained by the fact that according to the selinexor best clinical practice recommendations [17], the patient received 2 prophylactic anti-emetics: granisetron and metoclopramide.

Conclusions

This report has presented the cytogenetics and management of a patient with high-risk MM that was refractory to multiple lines of therapy and was treated with XVd followed by autologous SCT. It would be of interest to further study the potential use of selinexor prior to SCT in patients with MM who are heavily pretreated.

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Institution Where Work Was Done

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Declaration of Figures’ Authenticity

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