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Selinexor, Carfilzomib, Pomalidomide, and Dexamethasone as a Salvage Regimen for Refractory and Relapsed Multiple Myeloma with Plasma-Cell Leukemia Transformation: A Case Report and Literature Review

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Abstract

Refractory and relapsed multiple myeloma (RRMM) with plasma-cell leukemia (PCL) transformation is highly aggressive and resistant to conventional therapy. Novel therapeutics are needed for RRMM-transformed PCL. Selinexor [an oral exportin 1 (XPO1) inhibitor], carfilzomib (a second-in-class proteasome inhibitor), pomalidomide (third generation of immunomodulatory drug) are usually used for RRMM, but there are no reports on their application in PCL transformation. We describe a 62-year-old male initially diagnosed with MM IgD-lambda type with complex karyotype and extramedullary plasmacytoma in 2020, and relapsed after five months of autologous stem cell transplantation. Despite the use of various therapies, the patient rapidly developed into PCL over a 4-month period. The patient was started on selinexor, carfilzomib, pomalidomide, and dexamethasone (XKPd) combination as a salvage regimen in July 2021. He achieved fast response in first cycle. Then, he fulfilled third cycle of consolidation treatment and got four-month remission. The success of XKPd therapy in achieving a good response suggests its utility in RRMM transformed-PCL patients, who have exhausted various combinations of drug regimens and have historically poor survival outcomes.

Keywords

Selinexor, Carfilzomib, Multiple Myeloma, Plasma Cell Leukemia

1. Introduction

Multiple myeloma (MM) has witnessed significant advances due to the approval of many novel agents such as proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies (mAbs), which have profoundly improved the prognosis of MM. Despite all these new developments, multiple myeloma remained an incurable hematological malignancy, and most patients would eventually relapse [1]. The patients who had received several treatments would have poorer outcomes as resistance emerges, especially the disease transformed into plasma-cell leukemia (PCL), which was the most aggressive form of MM. Treatment options for RRMM with PCL were limited [2]. While the advance of novel agents to treat MM in recent years have likely prolonged the survival of PCL. The following case report described a patient with RRMM who had stubborn to PIs, IMiDs, daratumumab and finally progressed into PCL, who demonstrated an excellent response to selinexor, carfilzomib, pomalidomide, and dexamethasone combination treatment. To our knowledge, this is the rare case report of combination treatment in an RRMM-transformed PCL.

2. Case Report

A 62-year-old man was admitted to our hospital in March 2020 due to lumbar pain. The MRI examination suggested anterior spinal neoplastic lesions in the posterior mediastinum (**Figure 1**), and postoperative pathology revealed extramedullary myeloma involvement. The blood routine test revealed anemia with hemoglobin 87 g/L. He was transferred to our department. The patient had 10-year diabetes history. Laboratory examinations revealed serum calcium, albumin, globulin levels, and renal function test results were normal. The β2 microglobulin level was 8.57 mg/l (normal 0.70 - 1.3 mg/l). Immunoelectrophoresis

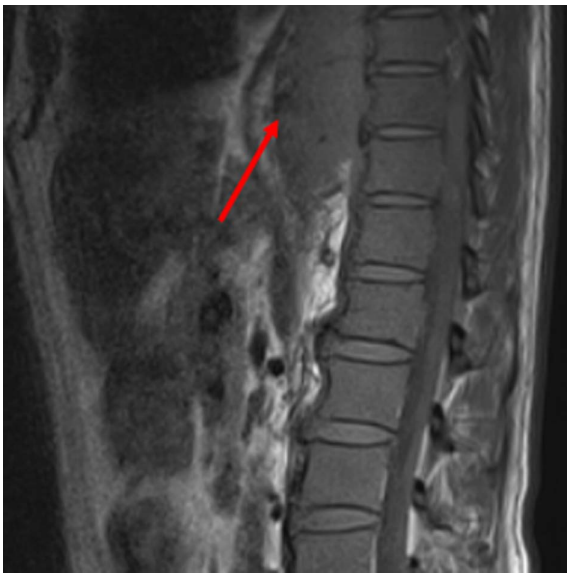

Figure 1. The MRI examination showed anterior spinal neoplastic lesions in the posterior mediastinum.

fixation revealed abnormal IgD-lambda immunoglobulin in the serum. Bone marrow smear (BMs) showed 59% of plasma cells (PCs), and flow cytometry (FCM) revealed 52.29% abnormal PCs with restrictive lambda light chain expression. Fluorescence in situ hybridization (FISH) analysis had a complex karyotype, including gain1q, deletion 13q, deletion 16q, and deletion 17p. Accordingly, the patient was diagnosed with IgD-lambda type MM (Internatinoal Staging System stage III) having a complex karyotype.

The patient was initially treated with bortezomib, thalidomide, cyclophosphamid, dexamethasone (VTCd) for a total of four cycles, and achieved a complete remission (CR). He underwent autologous hematopoietic stem cell transplant (ASCT) with 200 mg/m^2 melphalanin in October 2020. After ASCT, lenalidomide was given as maintenance treatment. After 5 months, he experienced morphological recurrence, with 20% of PCs in BMs in March 2021. He subsequently started daratumumab, ixazomib, dexamethasone (DId) therapy. After 5 weeks, his platelet count rapidly declined to less than 20 × 10^9/L, BMs showed 28% of PCs, and FISH test remained the same as that the disease diagnosed. The patient proceeded to liposome doxorubicin, pomalidomide, ixazomib, dexamethasone (PIDd) regimen, the disease was still progressing. Taken the nature of the disease and resistance to conventional therapy, he initiated selinexor [an oral exportin 1 (XPO1) inhibitor], pomalidomide, dexamethasone (XPd) regimen, selinexor 60 mg once a week, in combination with pomalidomide 2 mg days 1 - 21, and dexamethasone 20 mg once a week. During the first course of XPd therapy, the PCs rapidly disappeared from the PB. Soon after, the treatment regimen failed to achieve control, with approximately 35% monoclonal PCs in PB (**Figure 2**), 72% of bone marrow PCs and secondary myelofibrosis. It appeared that MM had progressed to PCL.

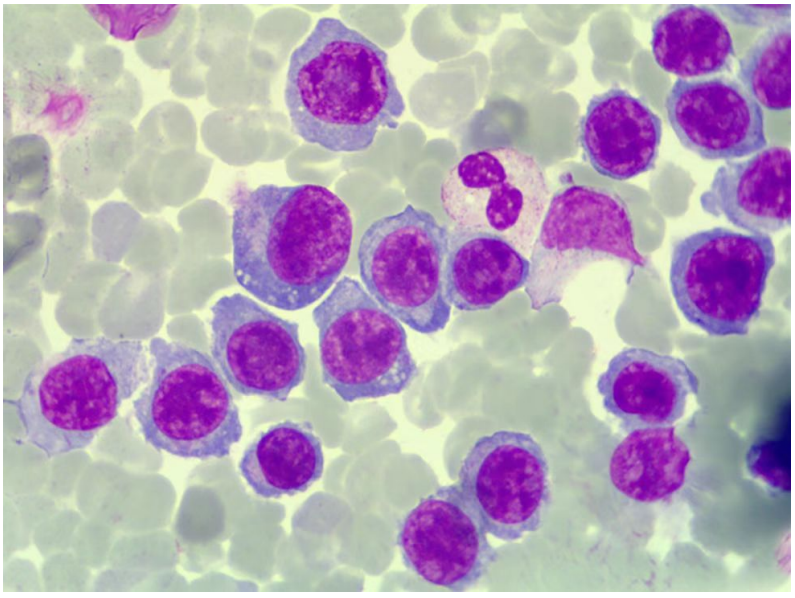

Figure 2. Circulating plasma cells as evident on the peripheral smear (1000×) in June 2021.

Despite responses to various therapies, the patient continued to experience relapses and exhausted options of many novel agents seen in MM treatment. He was not eligible for CAR-T clinical research. After detailed communication with the patient and his family, they accepted the treating doctor advice to receive the salvage therapy including selinexor, carfilzomib, pomalidonide and dexamethasone (XKPd) in July 2021. The dose of carfilzomib was 20 mg/m^2 twice a week, selinexor was 60 mg once a week, pomalidomide was 2 mg on days 1 - 21, and dexamethasone 20 mg on twice a week. After the first week of treatment PB plasma cells disappeared remarkably. Only one cycle of therapy finished we evaluate the efficacy revealed BMs had no PCs, bone marrow MRD was 0.0%, and immunoelectrophoresis fixation revealed IgD immunoglobulin was negative and the serum FLC ratio returned to normal range. The PET-CT scan showed extramedullary myeloma was disappeared (**Figure 3**). He achieved CR. The treatment-related adverse events including slight fatigue and grade 3/4 myelosuppression, which were managed with appropriate supportive care and dose modifications. Then, he fulfilled three cycles of XKPd consolidation and got four-month remission. The patient refused to undergo allogeneic hematopoietic stem cell transplantation. XKPd therapy was continued, and his condition was evaluated as very good response with negative MRD tests after three cycles of chemotherapy. A summary report of clinical and treatment assessments is presented in **Table 1**. However the patient eventually died of severe pneumonia during the fourth cycle.

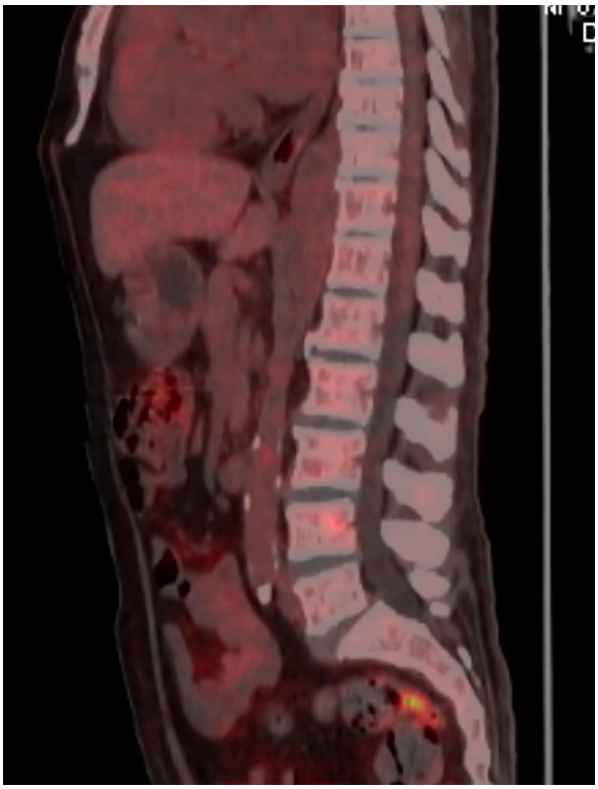

Figure 3. The PET-CT scan showed extramedullary myeloma was disappeared.

Table 1. Evolution of therapy in our patient.

Regimen	Duration of therapy (month range)	Best response	Reason for stopping
Bortezomib/thalidomide/cyclophosphamide/dexamethasone (VTCD)	5 (May-Oct 2020)	CR	Started ASCT
ASCT	Oct 2020	CR	Started maintenance
Lenalidomide	5 (Oct 2020-Mar 2021)	CR	PD
Daratumumab/ixazomib/dexamethasone (DId)	1 (Mar-Apr 2021)	PD	PD
liposome doxorubicin/pomalidomide/ixazomib/dexamethasone (PIDd)	2 (Apr-Jun 2021)	PD	PD
Selinexor/pomalidomide/dexamethasone (XPd)	1 (Jun-Jul 2021)	PD	PCL
Selinexor/carfizomib/pomalidonide/dexamethasone (XKPd)	4 (Jul-Nov 2021)	CR	Died

Abbreviations: CR: complete remission; ASCT: autologous hematopoietic stem cell transplant; PD: progressive disease; PCL: plasma-cell leukemia.

3. Discussion

In MM, the triple cytogenetic abnormalities combined with del17p, IGH translocation and gain (1q) were associated with particularly inferior prognosis and a median OS is only 9.1 months [3]. Bortezomib and carfilzomib treatment appear to abrogate the negative impact of del (17p), improve complete response [4]. In contrast, patients with multiple adverse cytogenetic abnormalities do not benefit from these agents [5]. PCL was the end stage of MM with high drug resistance, which highlights its aggressive and advanced stage, and historical median survival was only one month [6] [7]. A multicenter retrospective study including 101 patients with PCL revealed that over-all survival (OS) who received therapy was 4.2 months, 1-year OS only 19% [8]. Because PCL patients were often heavily pretreated, studies are minimal, only a few cases of successful treatment have been reported. Such as the venetoclax-based therapy in some cases of RRMM and transformed into PCL, harboring the (11; 14) translocation, had shown single-agent activity [9] [10]. Our patient did not have the t (11; 14) abnormity, so the venetoclax-based therapy may have limited effects.

As for the new upcoming studies, we focused on selinexor, a selective inhibitor of the nuclear export compound that blocks exportin 1 (XPO1), which is a novel potential treatment for RRMM [11] [12]. In STORM study utilized the selinexor with dexamethasone for RRMM, 68% of patients were penta-refractory, the overall response rate (ORR) was 26%, of note, response rates appeared to be consistent across subgroups, including patients with high-risk cytogenetics [13] [14]. In many studies, selinexor with dexamethasone as skeleton combined with various drugs such as ixazomib, liposomal doxorubicin, bortezomib, pomalidomide, carfilzomib, daratumumab, had shown modest activity in a heavily refractory patient population [15]. Carfilzomib is a new irreversible proteasome inhibitor targeting the chymotrypsin like activity of the 20 S proteasome [16]. An Phase IIb study PX-171-003-A1 evaluating carfilzomib in patients with

RRMM, demonstrated the ORR was 23.7%, with a median duration of response lasting 7.8 months and median OS was 15.6 months [17]. The common adverse effects of carfilzomib included fatigue (55.5%), anemia (46.8%), nausea (44.9%), and thrombocytopenia (36.3%) [17]. An phase 3 clinical trial ASPIRE showed carfilzomib combination with lenalidomide and dexamethasone in RRMM, the median progression-free survival (PFS) was 26.3 months, the median time to response was 1 month, duration of response was 28.6 months [18]. The combination of Selinexor, carfilzomib, pomalidomide and dexamethasone (XKPd) in the treatment of RRMM is rare, and the toxicity may greater.

Our patient's baseline characteristics and treatment experience were more complex and had all high-risk factors. Ultimately, the patient proceeded to a salvage regimen of XKPd, and achieved CR with only one cycle of treatment. Although the CR status lasted for only 4 months, the patient died of severe pneumonia eventually. This therapy still gave the patient 4-month follow-up treatment opportunities.

To our knowledge, this is the first case report describing the XKPd regimen usage in RRMM that has progressed to PCL. The above case highlights the refractory, aggressive nature of PCL and limited treatment options. Based on the successful outcome seen in this case, future clinical studies are warranted in exploring selinexor, carfilzomib, pomalidomide, in combination with other therapies for the treatment of RRMM and PCL.

The limitation of this case was that we failed to take effective consolidation measures after the PCL remission status, and the patient died of treatment complications finally.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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