Long-Term Disease Control by Pomalidomide-/Dexamethasone-Based Therapy in a Patient with Advanced Multiple Myeloma: A Case Report and Review of the Literature

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Key Words
Multiple myeloma · Combination therapy · Pomalidomide · Hepatitis B virus reactivation

Abstract

Background: Therapy for multiple myeloma (MM) has substantially improved in the era of immunomodulatory drugs and bortezomib. However, the prognosis of patients with progressive disease despite treatment with these ‘novel agents’ remains poor. Recently, pomalidomide was approved in this setting, but a median progression-free survival of <4 months still leaves room for improvement. Pomalidomide-based combination therapies are currently under investigation, but data on long-term treatment are lacking. Case Report: We present the case of a 68-year-old woman with refractory MM who received pomalidomide in combination with various drugs including anthracyclines, alkylators and proteasome inhibitors. Initially, major hematological toxicities and infectious complications including a hepatitis B virus reactivation were encountered. With careful dose adjustments and selection of combination partners, pomalidomide treatment was maintained for over 4 years and led to a sustained partial remission. In particular, the well-tolerated regimen of bortezomib, cyclophosphamide and dexamethasone together with pomalidomide was administered for >30 cycles. Conclusion: This case illustrates the value of an individualized approach to myeloma care given an increasing availability of ‘novel agents’. Tailored treatment using these drugs as a backbone is essential to achieve long-lasting responses and minimize side effects.

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Introduction

Immunomodulatory drugs (IMiDs) are a distinct group of oral antineoplastic drugs that have gained therapeutic relevance for the treatment of multiple myeloma (MM) since the turn of the millennium [1]. For myeloma patients, the introduction of IMiDs has fundamentally changed treatment options and has significantly improved clinical outcomes [2]. However, in patients failing to respond to treatment with novel agents – including thalidomide and lenalidomide as well as bortezomib – treatment options are limited and survival rates are poor [3].

Pomalidomide (CC-4047), the most recent IMiD, has shown substantial clinical activity in this setting. A randomized phase 2 study showed that the efficacy of pomalidomide is significantly enhanced by concomitant administration of dexamethasone and, moreover, continuous administration of the drug is well tolerated [4]. The MM-003 trial [5] demonstrated a significant increase in progression-free survival for patients receiving pomalidomide plus low-dose dexamethasone compared to patients treated with high-dose dexamethasone alone. The trial eventually led to the approval of pomalidomide for the treatment of patients with refractory and/or relapsed myeloma by the European Medicines Agency (EMA) in August 2013. Combination protocols with bortezomib, carfilzomib, doxorubicin and oral cyclophosphamide are currently under investigation, but data on the long-term treatment with such regimens are lacking.

In this report, we discuss the case of a heavily pretreated female patient with refractory MM who received >30 cycles of an experimental combination of pomalidomide, bortezomib, cyclophosphamide and dexamethasone as ninth-line therapy, resulting in a long-lasting partial remission (PR) and in a good quality of life.

Case Presentation

A 59-year-old woman was diagnosed with IgG kappa MM in May 2002, when she presented with Durie-Salmon stage III A disease with lytic destruction of the pelvis. Fluorescence in situ hybridization (FISH) performed on a bone marrow aspirate in 2006 did not reveal any high-risk cytogenetic abnormalities. Induction therapy with vincristine/doxorubicin/dexamethasone was followed by double autologous stem cell transplantation after conditioning with high-dose melphalan (200 mg/m²), resulting in a PR that lasted for 2 years. At first relapse, 4 cycles of bortezomib and subsequent bortezomib maintenance were administered and led to a PR for further 3 years. Third-line treatment with lenalidomide, bendamustine and dexamethasone produced only a short-lived response. Therapeutic attempts with the Hsp-90 inhibitor AUY-922 (phase I-Ib/II study) and bortezomib/dexamethasone resulted in disease progression. Salvage treatment using multidrug combinations of two novel agents (bortezomib plus lenalidomide), alkylating agents (cyclophosphamide or melphalan) and dexamethasone also failed to induce a durable response. With high-grade plasma cell infiltration of the bone marrow (fig. 1), increasingly severe pancytopenia developed, causing chronic fatigue and impaired quality of life and eventually led to treatment discontinuation.

In August 2010, at the age of 68 and 8 years after primary diagnosis (fig. 2), we started treatment with pomalidomide (4 mg days 1–21 of a 28-day cycle) and low-dose dexamethasone (40 mg weekly) in combination with doxorubicin (4 mg days 1–4 by continuous infusion). Due to grade 3 thrombocytopenia, the pomalidomide dose was reduced to 2 mg from cycle 2 onwards, resulting in improved tolerability, serological PR and hematological
improvement. However, myeloma therapy had to be stopped after six cycles due to the reac-
tivation of a hepatitis B virus (HBV) infection \(11.7 \times 10^6\) copies/ml, which the patient sup-
posedly acquired in 1945 and which had never emerged during therapy before. Antiviral
treatment with entecavir was initiated, which led to a sufficient drop in viral load \(9.7 \times 10^2\)
copies/ml.

Five months after the interruption of antmyeloma treatment, the patient suffered from
serological disease progression and a pathological humeral fracture requiring surgical
treatment (fig. 3). To prevent further disease progression, one more cycle of pomali-
domide/doxorubicin/dexamethasone was administered. For the subsequent cycles, doxorubi-
cin was replaced by bendamustine \((40 \text{ mg/m}^2 \text{ days 1–2})\) in light of the published data re-
porting an increased risk of HBV reactivation in patients receiving anthracyclines. However,
two cycles of the new combination regimen resulted in transfusion-dependent anemia and
grade 3 neutropenia, and only stable disease was observed.

Since the patient was not eligible for treatment within one of the active clinical trials at
our institution, individualized therapy was initiated, whereby pomalidomide \((2 \text{ mg on days}
1–21 of a 28-day cycle) was combined with bortezomib \((1.3 \text{ mg/m}^2 \text{ day 1, 4)}\), cyclophos-
phamide \((250 \text{ mg days 1–3})\) and dexamethasone \((10 \text{ mg days 1–3, weekly thereafter})\). As
nine-line therapy, this individualized combination regimen inhibited the progression of the
bone lesions, and the patient continued to experience a good quality of life. When the symp-
toms of sensory polyneuropathy worsened after 18 cycles, bortezomib was reduced to 1.0
\text{ mg/m}^2\) and the cycle length was extended to 43 days. Neuropathy improved gradually; how-
ever, we observed a steady rise in serologic disease activity. For the subsequent cycles, the
pomalidomide dose was increased to 3 mg days 1–21 and the cycles were repeated on day
29, resulting in sustained PR. Due to an extended treatment-free interval after 34 cycles of
pomalidomide + VCD (bortezomib/cyclophosphamide/dexamethasone), we observed an
increase of serologic markers. More than 12 years after primary diagnosis and 4 years and 4
months after the first treatment with pomalidomide, regrettably, our patient succumbed to a
fulminant pneumogenic septicemia in grade 1 neutropenia.

**Discussion**

Recently, pomalidomide was approved by the EMA for treatment of advanced MM in
conjunction with low-dose dexamethasone based on favorable results of a phase III trial [5].
Even though this combination results in further disease control in heavily pretreated mye-
loma patients, the median gain in the overall survival of roughly 4 months is modest. Triplets
of IMiDs, corticosteroids and the first-in-class proteasome inhibitor bortezomib have proven
to be effective in various myeloma settings. Therefore, it is tempting to speculate that co-
bining pomalidomide with bortezomib and dexamethasone might be more efficacious than
pomalidomide and dexamethasone alone.

Eight years after initial diagnosis and following five lines of treatment, the patient in this
report had been refractory to multidrug regimens containing both bortezomib and lenali-
domide in combination with alkylating agents and dexamethasone. Having exhausted ther-
apeutic options and with an increasing need for treatment, the idea of re-intensification using
pomalidomide and dexamethasone as a backbone was intriguing.

Combinations of IMiDs and doxorubicin have previously shown promising clinical activi-
ty with an acceptable toxicity profile in advanced MM [6]. Preliminary results from an ongo-
ing phase I/II study suggest that using pomalidomide together with anthracyclines and dex-
amethasone is feasible but carries the risk of substantial hematotoxicity [7]. Similarly, in our
patient, grade 3 thrombocytopenia was observed after treatment with pomalidomide at
4 mg together with doxorubicin and dexamethasone. Following a pomalidomide dose reduc-
tion to 2 mg, the combination was well tolerated and resulted in a rapid serological response
and hematologic improvement.

Interestingly, a HBV reactivation occurred after six cycles of pomalidomide/doxor-
ubicin/dexamethasone treatment in our patient with an initially unknown HBV carrier sta-
tus. This had not been observed after previous administration of highly immunosuppressive
high-dose melphalan prior to autologous stem cell transplantation [8]. Whilst there are cli-
cal [9] and preclinical [10] data indicating an increased risk of HBV reactivation for doxor-
ubicin-containing treatments, the role of IMiDs remains unclear [11]. Furthermore, severe
immune dysfunction associated with advanced myeloma might also have predisposed our
patient to virus reactivation [12].

With MM being a disease characterized by intraclonal heterogeneity [13] and with novel
agents generally having bearable side effects, the use of combination regimens of three or
more drugs, even in the advanced disease setting, becomes more and more enticing. There-
fore, we combined pomalidomide/dexamethasone with bortezomib and cyclophosphamide
instead of doxorubicin and were able to elicit a long-lasting partial response in this heavily
pre-treated refractory patient. Thus, it is tempting to speculate that in a progressive disease
setting, substituting various drugs within combination treatments might help in regaining
disease control.

Besides the known hematological toxicities [14] that were observed at the maximum
tolerated dose (MTD) of 4 mg, pomalidomide proved to be well tolerated in our patient for
more than 4 years of therapy. This is in line with recently published data from a French trial
[15] in which 12% of the patients were still on treatment with pomalidomide/dexa-
methasone after 30 months. Similarly, pomalidomide-based combination regimens appear
to be suitable for long-term continuous application as illustrated in our case study. Tailored
treatment approaches including careful dose adaptations are essential to control side effects
and allow a good quality of life.

Unfortunately, the fact of an insufficient disease control after a prolonged treatment-free
interval made our patient more susceptible to formerly well-controlled hematological side
effects, resulting in neutropenia and a fulminant pneumogenic septicemia. Despite intensive
antiinfective treatment, the patient succumbed to the generalized infection shortly after
hospitalization.

Results from systematic trials of combination regimens containing pomalidomide are
expected in the near future, further helping to guide therapeutic decisions in the setting of
advanced MM. In the meantime, the use of pomalidomide/dexamethasone as a backbone in
antimyeloma combination treatment has proven to be effective in a heavily pretreated re-
fractory patient and has demonstrated a good long-term tolerability.

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References

Fig. 1. Cytomorphology of a bone marrow aspirate smear (×63) performed in August 2010 showing high-grade diffuse infiltration with atypical plasma cells.

Fig. 2. Disease course based on M protein levels indicated in months after primary diagnosis (DX). Benda = Bendamustine; Len = lenalidomide; Dex = dexamethasone; Bort = bortezomib; Cyclo = cyclophosphamide; Mel = melphalan; Poma = pomalidomide; VCD = bortezomib/cyclophosphamide/dexamethasone.
Fig. 3. Radiograph of a pathological humeral fracture corresponding to serological disease progression in June 2011. Imaging after osteosynthesis with a proximally and distally fixed intramedullary nail.