Pomalidomide and its clinical potential for relapsed or refractory multiple myeloma: an update for the hematologist

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Abstract: Multiple myeloma is a common plasma cell neoplasm that is incurable with conventional therapy. The treatment paradigm of multiple myeloma is not standardized and is evolving. The advent of novel drugs, including the proteasome inhibitor bortezomib and the immunomodulatory agents, has resulted in increased median survival. Unfortunately, all patients eventually relapse and require further therapy. Pomalidomide is the newest immunomodulatory drug, created by chemical modification of thalidomide with the intention of increasing therapeutic activity while limiting toxicity. Its mechanism of action is incompletely understood but involves anti-angiogenic effects, immunomodulation, an effect on the myeloma tumor microenvironment, and the protein cereblon. It is more potent than thalidomide and lenalidomide. In phase II studies, it has shown significant activity in patients with relapsed and refractory multiple myeloma, including patients who are heavily pretreated, have disease refractory to lenalidomide and bortezomib, and those with high-risk cytogenetic or molecular markers. It is generally well tolerated, with adverse effects including fatigue, neutropenia, neuropathy, and thromboembolic disease. Pomalidomide is a promising new agent in the expanding arsenal of antimyeloma drugs. In this review, we discuss the clinical experience to date with pomalidomide in multiple myeloma.

Keywords: multiple myeloma, pomalidomide, treatment

Introduction

Multiple myeloma (MM) is a plasma cell neoplasm affecting 1 to 5 per 100,000 individuals, with a higher incidence in the developed world [Jemal *et al.* 2011]. In 2012 in the United States, it is expected that 21,700 people will be diagnosed with MM and 10,710 will die of the disease [Siegel *et al.* 2012].

Therapy for MM is evolving. The advent of novel agents including the immunomodulatory drugs (IMiDs) thalidomide and lenalidomide, and the proteasome inhibitor bortezomib has resulted in a 50% improvement in median survival [Kumar *et al.* 2008]. Unfortunately, in spite of these improvements, MM remains incurable with conventional therapy and relapse is inevitable in all patients.

Thalidomide was the first immunomodulatory agent to show activity in MM [Singhal *et al.* 1999]. Angiogenic cytokines and bone marrow vascularization, prominent features in MM, were potential targets to exploit the anti-angiogenic properties of thalidomide [Singhal *et al.* 1999]. The combination of thalidomide and dexamethasone results in response rates of 40–50% in relapsed MM [von Lilienfeld-Toal *et al.* 2008]. Favorable clinical results prompted development of the thalidomide analogs lenalidomide and pomalidomide, collectively known as the IMiDs. These agents were designed to improve the therapeutic activity of thalidomide while reducing toxicity. Indeed, response rates of 55–60% to lenalidomide and dexamethasone have been seen in relapsed MM [Dimopoulos *et al.* 2007; Weber *et al.* 2007].

Pomalidomide, the newest IMiD, has shown significant activity in MM. In this review, we discuss the clinical experience to date with pomalidomide for the treatment of MM.

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Mechanism of action

The IMiDs exert their anticancer effects in several ways including angiogenesis inhibition, immunomodulation, impeding cytokine production, and interaction with the bone marrow and tumor microenvironment. Recently, the protein cereblon has been identified as a target of thalidomide [Ito *et al.* 2010], and its presence appears to be important for IMiD response [Zhu *et al.* 2012].

The anti-angiogenic effect of thalidomide was first demonstrated by its ability to inhibit angiogenesis induced by basic fibroblast growth factor in a rabbit cornea micropocket assay [D'Amato *et al.* 1994]. This was felt to be independent of tumor necrosis factor alpha (TNF-α) production [D'Amato *et al.* 1994]. Immunomodulatory mechanisms, including cytotoxic T-cell stimulation [Corral *et al.* 1999; Haslett *et al.* 1998] and increased natural killer (NK) cell activity [Davies *et al.* 2001; Reddy *et al.* 2008] have been illustrated with IMiD exposure. Direct cytotoxic effects have also been shown by the IMiDs, including the inhibition of nuclear factor kappa-B (NF- κB) and apoptosis induction via the caspase 8/death receptor pathway [Keifer *et al.* 2001; Mitsiades *et al.* 2002]. The anti-inflammatory effects of pomalidomide have been demonstrated by its ability to inhibit COX-2 production and prostaglandin generation in lipopolysaccharide (LPS)-stimulated monocytes [Ferguson *et al.* 2007]. Lytic bone disease is a major cause of morbidity in patients with MM, and most patients will have bone involvement at some point in their disease course. Importantly, pomalidomide downregulates the transcription factor PU.1, resulting in reduced osteoclast production and differentiation [Anderson *et al.* 2006].

The proliferation and survival of myeloma cells is largely unaffected by thalidomide, whereas lenalidomide and pomalidomide cause both cell cycle arrest and apoptosis [Zhu *et al.* 2012]. Specifically, they induce cell cycle arrest by P21 WAF activation independently of P53 [Escoubet-Lozach *et al.* 2009]. This highlights the possibility in using these agents to treat P53 mutated malignancies [Escoubet-Lozach *et al.* 2009].

Cereblon is a highly conserved E3 ligase protein [Lopez-Girona *et al.* 2012]. IMiD activity in myeloma may depend on its expression. It has been shown to be a binding target for thalidomide [Ito *et al.* 2010], and more recently for lenalidomide and pomalidomide [Lopez-Girona *et al.* 2012]. Decreased cereblon mRNA expression has been correlated with lenalidomide resistance [Zhu *et al.* 2011; Lopez-Girona *et al.* 2012]. Interestingly, pomalidomide appears to remain effective in lenalidomide resistant cells [Lopez-Girona *et al.* 2012]. Pomalidomide is felt to be the most potent IMiD: 100 times strength of thalidomide and 10 times that of lenalidomide [Gertz, 2013].

Cereblon expression by gene expression profiling was recently evaluated in 53 patients with relapsed/refractory MM treated with pomalidomide and dexamethasone [Schuster *et al.* 2012]. In this study, cereblon expression was shown to predict both progression-free survival and overall survival. When patients in the lowest quartile of cereblon expression were compared with the highest quartile, progression-free survival was 3.0 months *versus* 8.9 months and overall survival was 9.1 months *versus* 27.2 months.

Phase I studies

A total of 24 patients with relapsed or refractory MM were studied in a phase I open-label dose escalation (1, 2, 5, and 10 mg) study [Schey *et al.* 2004]. Despite a median of three lines of previous therapy including thalidomide (53%) and autologous stem cell transplant (40%), 54% of patients achieved at least a partial response (PR) with 17% achieving complete remission (CR) [Schey *et al.* 2004]. This was confirmed in a second phase I study of 20 heavily pretreated patients using an alternate day regimen, with 50% of patients achieving at least a PR and 10% achieving CR [Streetly *et al.* 2008]. These two studies were conducted prior to the novel agents bortezomib and lenalidomide being readily available, potentially partially explaining the response rates seen in these pretreated patients. MM-002 is a randomized phase I/II open-label dose escalation study of heavily treated patients refractory to both lenalidomide and bortezomib. This study established a maximum tolerated dose of 4 mg for 21 of 28 days in this patient population. Efficacy results of the 38 patients in the phase I study showed 21% achieving at least a PR; in patients refractory to both lenalidomide and dexamethasone, 25% had a response [Richardson *et al.* 2012].

Phase II studies

The first phase II study of pomalidomide and dexamethasone evaluated 60 patients with relapsed or refractory MM with 1–3 prior treatments [Lacy *et al.* 2009]. Pomalidomide was administered at a dose of 2 mg daily continuously (28 day cycles),

with dexamethasone 40 mg weekly. Response was seen in 63% of patients, with 5% achieving CR, 28% achieving very good partial response (VGPR), and 30% achieving PR according to the International Myeloma Working Group criteria. Importantly, responses were seen in 40% of lenalidomide-refractory patients, 37% of thalidomide-refractory patients, and 60% of bortezomib-refractory patients. Responses were seen in 74% of patients with high-risk cytogenetic or molecular markers including a plasma cell labeling index ≥3%, deletion 17p, t(4;14) or t(14;16) by fluorescent *in situ* hybridization, or deletion 13 on conventional cytogenetics. Median progression-free survival was 11.6 months.

Results of the phase II study of the aforementioned MM-002 trial have been presented [Jagannath *et al.* 2012]. Patients were randomized to receive pomalidomide alone (4 mg/day, days 1–21 of 28-day cycle), or pomalidomide with low-dose dexamethasone (40 mg/week). A total of 221 patients were randomized, 108 to the pomalidomide alone arm and 113 to pomalidomide and dexamethasone. Responses (≥PR) were seen in 34% of the combination group and 15% in the pomalidomide alone arm, with median progression-free survival of 4.6 months and 2.5 months.

The ClaPD trial is a randomized phase II study of 100 patients treated with clarithromycin 500 mg twice daily, pomalidomide 4 mg on days 1–21 of a 28-day cycle, and dexamethasone 40 mg weekly [Mark *et al.* 2012]. Of note, this cohort of patients was highly refractory with 73%, 70%, and 64% being refractory to lenalidomide, bortezomib, or both, respectively. The overall response rate (≥PR) was 53.6% with 21.6% of patients achieving VGPR. Median progression free survival was 82 months. At last follow up, median overall survival has not been reached with 72 patients (74%) alive.

Pomalidomide in patients refractory to IMiDs and bortezomib

Patients with relapsed MM that is refractory to bortezomib and the IMiDs thalidomide and lenalidomide have a poor prognosis: median survival is 9 months, and event-free survival of just 5 months [Kumar *et al.* 2009]. Much of the subsequent work with pomalidomide has focused on these patients who require salvage therapy.

The Mayo Clinic group treated a cohort of 34 patients with lenalidomide refractory disease with continuous pomalidomide (2 mg/day) and weekly dexamethasone (40 mg/week) [Lacy *et al.* 2010]. The overall response rate was 47%, with 31% achieving at least a PR. The median time to response was 2 months, response duration was 9.1 months, and median overall survival was 13.9 months. The MM-002 trial discussed above included patients treated with lenalidomide and bortezomib [Richardson *et al.* 2011]. In patients refractory to both agents, 30% of patients treated with pomalidomide and dexamethasone and 16% of those on pomalidomide alone achieved PR.

The IFM 2009-02 phase II pomalidomide study by the French Intergroup evaluated patients with symptomatic progressive disease following at least two cycles of bortezomib and two cycles of lenalidomide in combination or separately [Leleu *et al.* 2011]. These were heavily pretreated patients, with median time from diagnosis to enrollment of 70.5 months and median number of five prior therapies. Two schedules of pomalidomide were evaluated: 4 mg daily on days 1–21 of a 28-day cycle (arm A) and 4 mg continuously on days 1–28 of a 28-day cycle (arm B). Both regimens included dexamethasone 40 mg weekly. Median follow up was 10.4 months. A total of 84 patients were enrolled, 43 in arm A and 41 in arm B. There was no significant difference between the two arms. The overall response rate was 34.9% in arm A and 34.1% in arm B. Stable disease was reported in 40 patients (47.6%) overall. Median progression-free survival was 6.3 months overall, with median duration of response of 11.4 months in arm A and 7.9 months in arm B.

The Mayo Clinic Group compared two dosing strategies from two sequential phase II studies of patients refractory to both bortezomib and lenalidomide [Lacy *et al.* 2011]. Pomalidomide was administered at 2 mg daily or 4 mg daily with dexamethasone 40 mg weekly for 28 day cycles. With 35 evaluable patients in each cohort, the 2 mg cohort had an overall response rate (MR or better) of 49% while the 4 mg group had an overall response rate of 43%. In both cohorts, 26% of patients achieved at least a PR. While nonrandomized, these results suggest that 4 mg daily dosing does not yield superior responses than 2 mg daily dosing. Recently, long-term follow up of 345 patients treated with pomalidomide and low dose dexamethasone at Mayo Clinic were presented showing similar efficacy between the 2 and 4 mg dose levels [Lacy *et al.* 2012]. In contrast, a trend towards a dose-dependent response was seen in

the 38 patients studied in the recently published phase I MM-002 study previously mentioned [Richardson *et al.* 2012].

The MM-003 trial is a large multicenter randomized phase III trial comparing pomalidomide and low-dose dexamethasone to high-dose dexamethasone (HD) in 455 patients with MM refractory to lenalidomide and bortezomib [Dimopoulos *et al.* 2012]. Patients were randomized to receive pomalidomide 4 mg daily for 21 of 28 days and dexamethasone 40 mg weekly *versus* dexamethasone 40 mg on days 1–4, 9–12, and 17–20 of a 28-day cycle. Benefit was seen in progression-free survival, with a median of 15.7 weeks in the pomalidomide–dexamethasone arm *versus* 8.0 weeks with dexamethasone alone. Overall survival advantage was also reported, with median overall survival not reached in the pomalidomide–dexamethasone arm *versus* 34 weeks in the HD arm.

Extramedullary disease

Extramedullary disease (EMD) is very common in patients with end-stage MM and can occur in lymph nodes, soft tissues, skin, muscles, and other organs. It has been associated with a poor response to treatment and shortened overall survival. EMD was present at diagnosis in 13/174 patients (7.5%) in the aforementioned initial phase II Mayo Clinic study of 174 patients with relapsed/refractory MM [Short *et al.* 2011]. Response rate for EMD was 31%, with two patients achieving CR and two patients achieving PR. This illustrates that pomalidomide is active and effective in EMD.

Toxicity

The major toxicity described in patients with relapsed/refractory MM treated with pomalidomide is neutropenia. Grade 3–4 neutropenia is reported in 26–66% of patients, with heavily treated patients and higher doses leading to higher incidence [Lacy *et al.* 2009, 2010, 2011]. Thrombocytopenia and anemia are also common side effects of therapy, however grade 3–4 toxicity is seen in 13% and 17% of patients, respectively [Lacy *et al.* 2012].

Nonhematologic toxicities are seen in 5% of patients [Lacy *et al.* 2012]. Fatigue is the most commonly reported adverse effect, with 62% of patients experiencing fatigue and 8% of those patients with grade 3–4 fatigue [Lacy *et al.* 2012]. Thromboembolic events are a well-known complication of IMiD therapy, occurring in approximately 2–4% of patients with IMiDs alone and up to 12–26% in patients treated with an IMiD/dexamethasone combination [Carrier *et al.* 2011]. The incidence in pomalidomide-treated patients is similar to patients treated with the other IMiDs. Venous thromboembolism occurred at a rate of 3% in the 345 patients studied at the Mayo Clinic [Lacy *et al.* 2012], and in 2% of the 221 patients in the MM-002 trial [Jagannath *et al.* 2012]. Prophylactic treatment with acetylsalicylic acid at doses of 325 mg daily is a reasonable strategy to prevent thromboembolic complications in these patients and has been successfully used in pomalidomide clinical trials to date [Lacy *et al.* 2009, 2010]. In the Mayo Clinic trials, neuropathy has been reported in up to 33% of patients, many of who have pre-existing neuropathy that worsens [Lacy *et al.* 2012]. However, in the MM-002 trial, grade 1–2 peripheral neuropathy was seen in 13% of patients [Jagannath *et al.* 2012], whereas no neuropathy was reported in the IFM 2009-02 trial [Leleu *et al.* 2010]. Acute noninfectious pulmonary toxicity has been described in two patients [Geyer *et al.* 2011], and grade 3+ pneumonitis was reported in 1% of patients in the Mayo Clinic series [Lacy *et al.* 2012]. This injury seems to respond to corticosteroids, and re-introduction of pomalidomide has been successful.

Conclusions

Pomalidomide is a third-generation immunomodulatory agent with significant activity in MM. It has shown impressive results in patients who are refractory to lenalidomide, suggesting non-cross-resistance. It also has activity in patients refractory to both lenalidomide and bortezomib, with 26% of patients achieving at least a PR and remission duration of 12 months [Lacy *et al.* 2011]. Response rates of 74% in patients with high risk cytogenetic or molecular markers provide a viable option in this group of patients who are often challenging to treat at relapse [Lacy *et al.* 2009]. No prospective randomized studies have delineated optimal dose, however, available data suggests that efficacy and toxicity are similar at the 2 and 4 mg dose levels. Pomalidomide is well tolerated, minimally toxic, and easy to use, which are important features of a drug used in heavily treated, multiply relapsed patients.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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