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REVIEW

Pomalidomide therapy for multiple myeloma and myelofibrosis: an update

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Abstract
Thalidomide possesses potent anti-inflammatory, immunomodulatory, and antiangiogenic properties. Thalidomide combined with corticosteroids is therapeutically active in multiple myeloma and myelofibrosis (MF). Lenalidomide and pomalidomide are second-generation immunomodulatory drugs (IMiDs) that were created by chemical modification of thalidomide with the intent to reduce toxicity and enhance therapeutic activity. Both drugs have also been shown to be active in the treatment of myeloma and MF. Thalidomide is US Food and Drug Administration (FDA)-approved for use in acute erythema nodosum leprosum and, in combination with dexamethasone, in newly diagnosed myeloma. Lenalidomide is approved for use in low/intermediate-1 risk myelodysplastic syndromes associated with transfusion-dependent anemia and a deletion 5q cytogenetic abnormality and, in combination with dexamethasone, in relapsed myeloma. Pomalidomide is currently not FDA-approved. Herein, we summarize what is currently known about the biologic and therapeutic effects of pomalidomide.

Keywords: *Pomalidomide, multiple myeloma, myelofibrosis*

Pomalidomide therapy in multiple myeloma

Multiple myeloma is a malignant plasma cell proliferative disorder that affects 1–5 per 100 000 individuals each year. In the United States alone, there are 20 000 new cases of myeloma and 11 000 myeloma-related deaths per year [1]. The introduction of thalidomide represented a major turning point in the treatment of myeloma [2]. The subsequent availability of its analog lenalidomide and the proteasome inhibitor bortezomib has revolutionized the therapeutic options for myeloma. It is currently believed that these and other novel therapeutic agents have favorably affected the survival of patients with myeloma [3].

Thalidomide was initially used for the treatment of myeloma because of its antiangiogenic properties. Promising clinical results led to the development of a class of thalidomide analogs termed immunomodulatory drugs (IMiDs), including lenalidomide and pomalidomide. In relapsed myeloma, thalidomide combined with dexamethasone produces response rates, including partial (PR), very good partial (VGPR), and complete (CR) remissions, of 40–50% [4]. The corresponding figure for lenalidomide combined with dexamethasone is 55–60% [5,6]. Bortezomib, a proteosome inhibitor, is another new drug shown to be active in relapsed myeloma and induces response rates of approximately 38%, when used as a single agent [7]. Combination drug therapy that includes IMiDs or bortezomib, along with other cytotoxic drugs such as pegylated doxorubicin or cyclophosphamide, has further improved response rates in relapsed myeloma to 55–82% [8–12].

The mechanisms of action for IMiDs are incompletely understood [13]. Thalidomide was first shown to be an inhibitor of angiogenesis induced by basic fibroblast growth factor, in a rabbit cornea micropocket assay [13]. Subsequent *in vitro* studies that included thalidomide analogs revealed that

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thalidomide's antiangiogenic activity correlated with its teratogenic but not sedative or immunosuppressive properties. More recent evidence suggests that IMiDs, including pomalidomide and lenalidomide, are in addition directly cytotoxic, and this might be mediated by their inhibitory effect on nuclear factor-kappa B (NF-κB) signaling and induction of apoptosis via the caspase-8/death receptor pathway [14,15]. Pomalidomide also causes p53-independent cell cycle arrest via p21 WAF activation, which suggests potential value in the treatment of p53 mutated/deleted disease [16].

The anti-cytokine and immunomodulatory effects of IMiDs includes augmentation of natural killer cell activity [17,18] and stimulation of cytotoxic T-cells [19,20]. In this regard, pomalidomide is the most potent of the currently available IMiDs [21–24. Pomalidomide also affects inflammation via transcriptional inhibition of cyclooxygenase-2 (COX-2) production, which is associated with increased prostaglandins in human lipopolysaccharide (LPS)-stimulated monocytes [25]. COX-2 is highly expressed in patients with myeloma, and is associated with poor outcome. Pomalidomide might also have a role in preventing or treating myeloma bone disease via its effects on osteoclasts [21]; the drug inhibits lineage commitment required for early differentiation and the resulting down-regulation of PU.1 inhibits osteoclast production and function.

Phase I trials

An open label dose escalation (1, 2, 5, and 10 mg/day orally) phase I trial in relapsed myeloma established pomalidomide as being well tolerated in doses ranging from 1 to 5 mg/day, continuously [26] or on alternate days [27]. The overall response rates (≥PR) exceeded 50% despite the fact that the study populations were exposed to multiple prior therapies, including thalidomide therapy, and a substantial proportion had previously received an autologous stem cell transplant (Table I). These early phase I trials were conducted before lenalidomide and bortezomib were routinely available. The MM-002 pomalidomide trial is a phase I/II trial conducted in the era of novel agents, and established a maximum tolerated dose of 4 mg/day, for 21 of 28 days, in a heavily pretreated population of patients with relapsed, refractory myeloma (Table I) [28].

Phase II trials

The first phase II study using pomalidomide and dexamethasone (Pom-Dex) for myeloma was conducted in patients with relapsed disease after 1–3 prior regimens [29]. Pomalidomide was given orally at 2 mg/day, continuously, along with dexamethasone (40 mg) given weekly. The study included 60 patients and showed an overall response rate (≥PR by International Myeloma Working Group criteria) of 63%, including 33% who achieved VGPR or CR (Table I). Additionally 82% had at least a 25% decrease in their M-spike. Importantly, the study showed responses among 40% of patients who were lenalidomide-refractory, suggesting non-cross-resistance with other IMiDs. Responses were seen in 74% of patients with high-risk cytogenetic or molecular

Table I. Activity of pomalidomide in myeloma.

	Regimen	*n*	No. of prior regimens, median	Schema	Doses	≥PR	PFS/DOR/OS (months)
Phase I trials							
Schey *et al.*, JCO 2004	Pom	24	3	28/28	MTD 2 mg	54%	9.7/—/2.5
Streetly *et al.*, BJH 2008	Pom	20	4	28/28	MTD 5 mg QOD	50%	10.5/—/33
Richardson *et al.*, Blood 2010	Pom ± Dex	38	6	21/28	MTD 4 mg	25%	5/5/20
Phase II trials							
Lacy *et al.*, JCO 2009	Pom/Dex	60	2	28/28	2 mg	63%	11.6/97% at 6 months/94% at 6 months
Lacy *et al.**, Leuk 2010	Pom/Dex	34	4	28/28	2 mg	32%	9.1/4.8/13.9
Leleu *et al.*, Blood 2010	Pom/Dex	43	4	21/28	4 mg	42%	7.3/4/88% at 4 months
		41	4	28/28	4 mg	39%	5/4/85% at 5 months
Richardson *et al.*, Blood 2010	Pom ± Dex	120	5	21/28	4 mg	25%	NA
Lacy et al.†, Blood 2010	Pom/Dex	35	6	28/28	2 mg	26%	6.5/12/78% at 6 months
		35	6		4 mg	26%	3.3/NA/69% at 6 months

*Lenalidomide-refractory patients.

†Refractory to both lenalidomide and bortezomib.

PFS, progression-free survival; DOR, duration of response; OS, overall survival; JCO, *J Clin Oncol*; BJH, *Br J Haematol*; Leuk, *Leukemia*; Pom, pomalidomide; Dex, dexamethasone; MTD, maximum tolerated dose; QOD, every other day; NA, not available.

markers. The median progression-free survival was 11.6 months, and was not significantly different in the patients with high-risk disease compared to those with standard-risk disease.

Pomalidomide is active in the treatment of myeloma that is refractory to both lenalidomide and bortezomib

Follow-up trials have focused on developing pomalidomide as salvage therapy for patients with relapsed myeloma that is refractory to novel agents. Mayo Clinic investigators have recently reported results with Pom-Dex in a cohort of lenalidomide-refractory patients [30]. Thirty-four patients were enrolled. Responses of $\geq$PR were seen in 31% of patients. The median time to response was 2 months and response duration was 9.1 months. The median overall survival was 13.9 months.

A recent study reported that patients with relapsed myeloma refractory to bortezomib and thalidomide or lenalidomide have poor prognosis, with a median survival of 9 months and an event-free survival of 5 months [31]. The aforementioned phase I/II study (MM-002) included patients who had previously been treated with both bortezomib and lenalidomide and were refractory to their most recent regimen. Thirty-eight patients were enrolled in the phase I portion of MM-002. Responses of PR or better were seen in 25% [32]. The phase II portion of MM-002 randomized patients to receive pomalidomide alone or with dexamethasone. A total of 221 patients were enrolled, and data regarding efficacy has been reported for the first 120 patients. Responses of PR or better were seen in 25% [32].

The French Intergroup reported the IFM 2009-02 pomalidomide study which included myeloma patients who were symptomatic and progressing following at least two cycles of lenalidomide and two cycles of bortezomib (either separately or in combination) [33]. Pomalidomide was given orally either at 4 mg/day on days 1–21 of each 28-day cycle (arm A) or continuously on days 1–28 of each 28-day cycle (arm B). Dexamethasone was given orally at 40 mg daily on days 1, 8, 15, and 22 of each cycle. Among 92 patients enrolled, responses of PR or better were seen in 42% (arm A) and 39% (arm B).

Mayo Clinic investigators have recently reported results of pomalidomide therapy comparing two different dosing strategies in sequential phase II trials for patients with relapsed myeloma that was refractory to both lenalidomide and bortezomib [34]. Pomalidomide was given orally 2 mg/day or 4 mg/day, on days 1–28 of a 28-day cycle, with oral dexamethasone given 40 mg daily on days 1, 8, 15, and 22. Responses of PR or better were seen in 26% in both cohorts. The 2 mg cohort showed responses of minor response (MR) or better in 49% versus 40% in the 4 mg cohort. The median duration of response in the 2 mg cohort was 12 months. Toxicity consisted primarily of neutropenia, with grade 3 or 4 neutropenia seen in 49% of the patients treated with 2 mg daily and 66% of those treated with 4 mg daily. These data suggest that there is not a dose-response for pomalidomide, and that there is no distinct advantage for 4 mg over the 2 mg per day dose.

Pomalidomide is active in the treatment of myeloma-associated extramedullary disease

Myeloma is sometimes associated with extramedullary disease (EMD), which occurs in soft tissue, lymph nodes, muscle, skin, and other organs. Myeloma-associated EMD is uncommon at the time of initial presentation and is more often seen with relapsed or refractory disease, and may be associated with decreased overall survival and poor response to novel drug therapy. In the Mayo Clinic Pom-Dex study of 174 consecutive patients with relapsed/refractory myeloma [35], EMD was present at the time of trial entry in 7.5% (13 of 174 patients). Among the 13 patients with myeloma-associated EMD, two complete and two partial responses were documented for an overall response rate of 31%.

Pomalidomide toxicity in the context of myeloma therapy

Neutropenia is the major toxicity seen in patients with relapsed/refractory myeloma treated with pomalidomide. Grade 3 and 4 neutropenia has been seen in 26–66% of patients, and the higher incidence rates are seen with higher drug doses and in heavily pretreated patients [29,30,34]. Thromboembolic complications occurred with a frequency similar to that reported with other IMiDs. Neuropathy is infrequent in patients who are not heavily pretreated. Worsening of neuropathy was sometimes reported by previously heavily pretreated patients. Non-infectious acute lung injury is a rare but serious drug complication [36]. Fortunately it responds well to the use of corticosteroids. Following resolution of this particular drug toxicity, pomalidomide has been successfully reintroduced.

Pomalidomide therapy in myelofibrosis

Myelofibrosis (MF) is a myeloproliferative neoplasm (MPN) that develops either *de novo* (primary MF) or in the setting of antecedent polycythemia vera (post-PV MF) or essential thrombocythemia (post-ET MF) [37]. MF represents a stem cell-derived clonal

process, but the precise pathogenetic contribution of currently known MF-associated mutations has not been clarified [38]. The clinical phenotype of MF includes anemia, marked splenomegaly, profound constitutional symptoms, cachexia, extramedullary hematopoiesis (EMH), and progression into blast phase disease [39]. Prognosis in primary MF (PMF) is reliably predicted by application of the recently established Dynamic International Prognostic Scoring System (DIPSS)-plus model that uses eight risk factors (age >60 years, hemoglobin <10 g/dL, red cell transfusion dependency, leukocyte count $>25 \times 10^9$/L, circulating blasts $\geq 1\%$, platelet count $<100 \times 10^9$/L, constitutional symptoms, and unfavorable karyotype) to define low (no risk factors), intermediate-1 (one risk factor), intermediate-2 (two or three risk factors), and high (four or more risk factors) risk groups with respective median survivals of 15.4, 6.5, 2.9, and 1.3 years [40].

Treatment in MF is currently suboptimal. Allogeneic stem cell transplant (allo-SCT) offers the chance for long-term disease-free remission, but treatment is complicated by more than 50% risk of death or chronic morbidity [41]. Drug therapy has not been shown to improve survival but definitely has palliative value. Conventional treatment options for MF-associated anemia include erythropoiesis stimulating agents (ESAs), androgens, danazol, corticosteroids, thalidomide, and lenalidomide [42]. MF-associated splenomegaly is usually treated with hydroxyurea, splenectomy, or radiotherapy [43]. Radiotherapy is also used to manage non-hepatosplenic EMH [43]. Investigational drugs used in MF include JAK inhibitors, which have been shown to have activity in reducing spleen size and alleviating constitutional symptoms [44,45], and pomalidomide, which is the focus of the current paper.

Rationale for IMiD therapy in myelofibrosis

It is generally believed that inflammation accompanies clonal myeloproliferation in MF and contributes to disease-associated bone marrow stromal changes and abnormal cytokine expression [46]. Also, increased bone marrow angiogenesis is a characteristic feature of MF [47]. More recent studies have confirmed the presence of excess plasma cytokines in MF and their potential contribution to clinical phenotype and prognosis [44,48]. Therefore, it is reasonable to consider the use of novel drugs in MF where mechanism of action includes anti-cytokine, anti-inflammatory, and antiangiogenic effects. Proof-of-principle in this regard was recently demonstrated in the context of JAK inhibitor therapy for MF [44].

Thalidomide and lenalidomide therapy in myelofibrosis

Thalidomide (50 mg/day) $\pm$ prednisone (0.25 mg/day) [49,50] or lenalidomide (10 mg/day) $\pm$ prednisone [51–53] have both been shown to alleviate anemia, thrombocytopenia, and, in some instances, splenomegaly in MF. In one of the first thalidomide treatment studies in MF ($n=15$) [54], the 200 mg/day dose was poorly tolerated, and the respective anemia and spleen response rates were approximately 20% and 25%, using response criteria that were less stringent than those of the International Working Group (IWG) criteria [55]. A higher proportion of patients experienced an increase in platelet count. Subsequently, both lower drug doses of thalidomide (50 mg/day) [56] and the combination of low-dose thalidomide (50 mg/day) and prednisone (a tapering schedule starting at 30 mg/day) [49] were shown to be better tolerated as well as more effective in terms of anemia response. A recent update of 50 Mayo Clinic patients with MF who received thalidomide (50 mg/day) in combination with prednisone $\pm$ cyclophosphamide or etanercept revealed an IWG-consistent response rate of 22% for anemia and 8% for splenomegaly [57]. The median response duration was 8.5 months (range 3–42). A substantial proportion of patients develop thalidomide-associated peripheral neuropathy after 1–2 years of therapy.

In the very first study of lenalidomide in MF ($n=68$) [51], an IWG-consistent response in anemia was documented in 22% of patients, splenomegaly in 5%, and thrombocytopenia in 50%. The hemoglobin level normalized in eight of 46 patients (17%), with a baseline hemoglobin level of below 10 g/dL [51]. Four of these patients also displayed resolution of leukoerythroblastosis and two of the four experienced a post-treatment reduction in bone marrow fibrosis. The benefit of lenalidomide in MF is most remarkable in the presence of del(5q), where both del(5q) cytogenetic and *JAK2*V617F molecular remissions were demonstrated [58]. Side effects of lenalidomide included grade 3 or 4 neutropenia in 31% of the patients and thrombocytopenia in 19%. Thrombotic complications were infrequent. Two subsequent studies [52,53] used lenalidomide (10 mg/day) in combination with prednisone. In the first multicenter study of 48 patients [53], the IWG response rate was 19% for anemia and 10% for splenomegaly; most patients (88%) experienced grade 3 or 4 myelosuppression. In the second single-center study of 40 patients [52], the reported response rates were better, at 30% for anemia and 42% for splenomegaly. In the latter but not the former study, treatment-induced reductions in bone marrow fibrosis and *JAK2*V617F allele burden were also reported. Grade 3 or 4

neutropenia or thrombocytopenia occurred in 58% and 13% of patients, respectively.

Pomalidomide therapy in myelofibrosis

To date, three studies involving the use of pomalidomide in MF have been reported [59–61]. The first was a phase II randomized study ($n = 84$) where patients were assigned to treatment with pomalidomide alone (2 mg/day), pomalidomide (0.5 or 2 mg/day) combined with prednisone, or prednisone alone [59]. Twenty patients met IWG criteria for response in anemia, whereas there were no responses in splenomegaly. Fifteen of the 20 anemia-responders became red cell transfusion-independent. Response rates were 23% for pomalidomide 2 mg/day, 16% for pomalidomide 2 mg/day + prednisone, 36% for pomalidomide 0.5 mg/day + prednisone, and 19% for prednisone alone. Median time to response was 2 months. The median response duration in the 16 patients who responded to pomalidomide ± prednisone was 7.8 months (range 3.2–16.9), and two had relapsed during this period. A leukocyte count $>10 \times 10^9$/L or palpable spleen size $\geq$10 cm correlated with lower response rate. A >50% increase in platelet count was recorded in six (43%) of 14 patients who received pomalidomide (0.5 or 2 mg/day) ± prednisone and had baseline platelet counts in the range of 50–100 $\times 10^9$/L. Bone marrow histology or *JAK2*V617F allele burden was largely unaffected by treatment. Grade 3 or 4 adverse events were infrequent and included neutropenia (8%), thrombocytopenia (11%), pneumonia/sepsis (11%), and venous thrombosis (4%). Most patients experienced drug-induced eosinophilia or basophilia, and marked thrombocytosis was attributed to protocol therapy in two patients.

The second study used low-dose pomalidomide (0.5 mg/day) alone in 58 Mayo Clinic patients [61]. In this study, anemia response was documented only in the presence of *JAK2*V617F (24% vs. 0%). In addition, response was predicted by the presence of pomalidomide-induced basophilia (38% vs. 6%) or absence of marked splenomegaly (38% vs. 11%). A platelet response was seen in 58% of patients with baseline platelet count of 50–100 $\times 10^9$/L. As was the case in the aforementioned multicenter study, pomalidomide had limited activity in reducing spleen size [61]. Drug-associated neuropathy and myelosuppression were infrequent. The third study tested the safety and efficacy of higher than 2 mg/day doses of pomalidomide (phase I/II design) in 19 subjects [60]. Dose-limiting toxicity was myelosuppression at 3.5 mg/day, and the maximum tolerated dose (MTD) was established at 3 mg/day. However, drug-induced myelosuppression was still evident at the MTD, without any evidence to suggest improved efficacy [60].

Conclusions

It is reasonable to conclude that pomalidomide is well tolerated in patients with either myeloma or MF. In addition, the drug has measurable activity in the treatment of both diseases; in myeloma, pomalidomide appears to overcome resistance to both lenalidomide and bortezomib, and in *JAK2*V617F-positive MF, the drug alleviates anemia in about a quarter of patients. In both myeloma and MF, pomalidomide's activity does not appear to be undermined by the presence of unfavorable karyotype. Future clinical trials should consider the use of pomalidomide in newly diagnosed myeloma and the combination of pomalidomide with hydroxyurea or JAK inhibitors in MF. The latter strategy stems from the observation that pomalidomide had limited value for the treatment of MF-associated splenomegaly.

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