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Blood Spotlight

Pomalidomide

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This spotlight review focuses on the second-generation immunomodulatory drug pomalidomide, which was recently approved by the US Food and Drug Administration. This drug was approved for patients with multiple myeloma who have received at least 2 prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy. This review focuses on the clinical trial data that led to approval and provides advice for treating physicians who are now prescribing this drug for patients. (*Blood*. 2013;122(14):2305-2309)

Introduction

Therapy for multiple myeloma (MM) is evolving. Thalidomide and lenalidomide have proven roles in the treatment of both newly diagnosed and relapsed MM.[1-5] The introduction of novel agents has resulted in improvement in median survival.[6] However, once patients are no longer responsive to immunomodulatory drugs (IMiDs) and bortezomib, prognosis is poor.[7] Consequently, new agents are needed. Pomalidomide, the newest IMiD, was designed to be more potent and less toxic than thalidomide and lenalidomide. The US Food and Drug Administration approved the drug in February 2013 for patients with MM who have received at least 2 prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression. In this review, we discuss the clinical experience to date with pomalidomide in MM (Table 1).

Mechanism of action

Although the antiangiogenic effects are what generated the initial interest in IMiDs,[8] it is not clear how much this contributes to their antimyeloma effects.[9] IMiDs exert their anticancer effects in several other ways, including impeding cytokine production, immunomodulation, and interaction with the bone marrow and tumor microenvironment. Direct cytotoxic effects have also been shown by IMiDs, including the inhibition of nuclear factor κ-B and apoptosis induction via the caspase 8/death receptor pathway.[10] Immunomodulatory mechanisms include cytotoxic T-cell stimulation[11,12] and increased natural killer cell activity.[13,14] The antiinflammatory effects of pomalidomide have been demonstrated by its ability to inhibit cyclooxygenase-2 production and prostaglandin generation in lipopolysaccharide-stimulated monocytes.[15]

The proliferation and survival of myeloma cells is largely unaffected by thalidomide, whereas lenalidomide and pomalidomide cause both cell-cycle arrest and apoptosis.[16] Specifically, they induce cell-cycle arrest by P21 WAF (cyclin-dependent kinase inhibitor 1) activation independently of P53.[17] This suggests the possibility of using these agents to treat P53-mutated malignancies.

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.[18]

Recently, the protein cereblon was identified as a target of thalidomide,[19] and its presence appears to be important for IMiD response.[16,20] Cereblon is a highly conserved E3 ligase protein, [21] and IMiD activity in myeloma may depend on its expression. It has been shown to be a binding target for thalidomide,[19] lenalidomide, and pomalidomide.[21] Decreased cereblon mRNA expression has been correlated with lenalidomide resistance. Interestingly, pomalidomide appears to remain effective in lenalidomide-resistant cells.[21] Cereblon expression by gene-expression profiling was evaluated in 53 patients with relapsed/refractory MM treated with pomalidomide and dexamethasone.[22] Cereblon expression predicted both progression-free survival and overall survival. The mechanism of resistance to IMiDs is not known; however, this study suggests a threshold level of cereblon expression is required for response to IMiD therapy.

Phase 1 studies

An open-label dose-escalation (1, 2, 5, and 10 mg) phase 1 trial established pomalidomide as being well tolerated in doses ranging from 1 to 5 mg/d continuously[23] or on alternate days[24] with response rates (> partial response [PR]) of 51%. The MM-002 trial was a phase 1, dose-escalation study to determine the maximum tolerated dose (MTD) of pomalidomide given for 21 of 28 days per cycle in patients with relapsed and refractory myeloma.[25] The patient population was heavily pretreated with a median of 6 prior regimens, including bortezomib and lenalidomide. Dexamethasone was added in 22 patients for suboptimal responses. Among the 38 patients treated, responses of PR or better were seen in 21% and minor response or better in 42%. Because there were 4 dose-limiting toxicities (grade 4 neutropenia) at 5 mg/d, the MTD was 4 mg/d. This study determined the dose of 4 mg daily for 21 of 28 days as the recommended dose.

Phase 2 studies

A series of phase 2 studies conducted at the Mayo Clinics (Phoenix/Scottsdale AZ, Jacksonville FL, and Rochester MN) used doses of 2 mg and 4 mg continuously for 28 days with dexamethasone 40 mg

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Table 1. Pomalidomide trials in multiple myeloma

Trials by Reference	Patient population	N	Regimen/dose	ORR (%)
Phase 1 trials				
23	Relapsed	24	Pom dose escalation MTD 2 mg 28/28	54
24	Relapsed	20	Pom ± dex MTD 5 mg QOD 28/28	50
25	RR/MM	38	Pom ± dex MTD 4 mg 21/28	25
Phase 2 trials				
31	Len/Btz ref	120	Pom ± dex, 4 mg, 21/28	25
26	Rel, 1-3 reg	60	Pom/dex 2 mg, 28/28	63
28	Len ref	34	Pom/dex 2 mg, 28/28	47
30	Len/Btz ref	43	Pom/dex 4 mg, 21/28	30
		40	Pom/dex 4 mg, 28/28	47
29	Len/Btz ref	35	Pom/dex 2 mg, 28/28	49
		35	Pom/dex 4 mg, 28/28	43
27	Len ref, 1-3 reg	60	Pom/dex 4 mg, 28/28	38
	Len ref	120	Pom/dex 4 mg, 21/28	23
32	RR/MM	52	Cla/ Pom ± dex, 4 mg, 21/28	60
Phase 3 trials				
34	RR/MM	302	Pom/dex 4 mg, 21/28	31
		153	HiDex 40 mg (≤75 y) 20 mg (>75 y) D 1-4, D 9-12, D 17-20	15
Combination regimens				
37	RR/MM	21	Pom 1-4 mg/d D 1-14 Btz 1-1.3 mg/m^2 D 1, 4, 8, 11 Dex 20 mg/d D 1 and 2, D 4 and 5, D 8 and 9, D 11 and 12	72
38	RR/MM	32	Pom and Car dose escalation MTD: carfilzomib 20/27 mg/m^2 Pom 4mg D 1-21 Dex 40 mg weekly	50
39	RR/MM	10	Pom 2, 3, or 4 mg for 21/28 D PLD 5 mg/m^2 IV on D 1, 4, 8, 11 Dex 40 mg IV weekly MTD: not reached	43
40	RR/MM		Pom dose escalation MTD 2.5 mg 28/28 Cyclophosphamide 50 mg QOD Prednisone 50 mg QOD	54

Abbreviations: 21/28, 21 days of a 28-day cycle; 28/28, 28 days of a 28-day cycle; Btz, bortezomib; D, days; dex, dexamethasone; HiDex, high-dose dexamethasone; Len ref, lenalidomide, refractory; Len/Btz ref, lenalidomide and bortezomib refractory; MTD, maximum tolerated dose; N, number of patients; ORR, overall response rate; PLD, pegylated doxorubicin; Pom, pomalidomide; QOD, every other day; Rel, 1-3 reg, relapsed with 1-3 prior regimens; RR/MM, relapsed refractory multiple myeloma.

once a week. In the first Mayo Clinic trial, responses of PR or better were seen in 63% of patients treated with 2 mg daily.[26] The median duration of response was 21 months, and median progression-free survival was 13 months.[27] This group of patients was less heavily pretreated than subsequent cohorts. Follow-up trials in lenalidomide-refractory patients using pomalidomide 2 mg[27] and 4 mg[28] daily showed responses of PR or better in 32% and 38% of patients, respectively. Among patients refractory to both lenalidomide and bortezomib,[29] responses of PR or better were seen in 26% of the patients treated with 2 mg daily and in 29% of those treated with 4 mg daily. A subsequent study used pomalidomide 4 mg for 21 of 28 days with weekly dexamethasone in a population of lenalidomide-refractory patients with a response rate of 23%.[27] An analysis of 345 patients enrolled in the Mayo Clinic studies suggested the strongest predictors of response and survival were the number and type of prior regimens.[27] Toxicity in all of these trials was manageable and consisted primarily of neutropenia and fatigue.

The IFM 2009-02 phase 2 pomalidomide study by the French Intergroup[30] is a randomized phase 2 study comparing different dosing schedules of pomalidomide and low-dose dexamethasone in dual refractory MM patients. Eighty-four patients with relapsed MM who were refractory to both bortezomib and lenalidomide were randomized to receive pomalidomide 4 mg for 21 of 28 days or 4 mg continuously with weekly dexamethasone. Overall response rates did not appear to be dose dependent, being 35% and 34%, respectively. They also found little difference in toxicity between the 2 dose schedules.

Results of the phase 2 portion of the MM-002 trial have been presented.[31] Patients were randomized to receive pomalidomide alone (4 mg/d, days 1–21 of 28-day cycle) or pomalidomide with low-dose dexamethasone (40 mg/wk). Two hundred and twenty-one 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 in 15% of the

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pomalidomide-alone arm, with median progression-free survival of 4.6 months and 2.5 months.

At least 1 study suggests that the addition of clarithromycin may enhance antimyeloma activity of pomalidomide and dexamethasone.[32] The ClaPD trial is a phase 2 study of 100 patients with heavily pretreated relapsed myeloma who were treated with clarithromycin 500 mg twice daily, pomalidomide 4 mg on days 1-21 of a 28-day cycle, and dexamethasone 40 mg weekly.[32] The overall response rate (≥PR) was 53.6%, with 21.6% of patients achieving very good partial response. Median progression-free survival was 82 months.

Phase 3 study

The MM-003 trial is a large multicenter randomized phase 3 trial that compares pomalidomide and low-dose dexamethasone with high-dose (HD) dexamethasone in 455 patients with MM refractory to lenalidomide and bortezomib.[33] Patients were randomized to receive pomalidomide 4 mg daily for 21 of 28 days and dexamethasone 40 mg weekly vs 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 3.6 months in the pomalidomide–dexamethasone arm vs 1.8 months[34] with dexamethasone alone. There was a trend toward improved overall survival, with median overall survival not reached (11.1-NE) in the pomalidomide–dexamethasone arm vs 7.8 (5.4-9.2) months, $P = .53$, in the HD arm.[34] Overall responses rates (>PR) were seen in 31% of those in the pomalidomide–dexamethasone arm vs 15% of those in the HD arm.[34] This benefit was seen even in patients with high-risk cytogenetics.[35] Poor renal function (baseline creatinine clearance <60 mL/min) did not impact efficacy or safety of the regimen.[36]

Combination regimens

The MM-005 trial is a phase 1 trial of a combination of pomalidomide, bortezomib, and dexamethasone in patients with relapsed and/or refractory MM.[37] Each cohort received 21-day cycles of pomalidomide 1-4 mg/d on days 1-14; bortezomib 1-1.3 mg/m^2 on days 1, 4, 8, and 11; and dexamethasone 20 mg/d on days 1 and 2, days 4 and 5, days 8 and 9, and days 11 and 12. An expansion cohort was enrolled at the MTD; 21 patients were enrolled. Among the 18 evaluable patients, the overall response rate (>PR) was 72%.[37] The maximum planned dose of pomalidomide 4 mg/d on days 1-14; bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11; and dexamethasone 20 mg on days 1 and 2, days 4 and 5, days 8 and 9, and days 11 and 12 of a 21-day cycle has now been incorporated into the MM-007 phase 3 trial that is comparing pomalidomide, bortezomib, and dexamethasone with bortezomib and dexamethasone in relapsed, refractory MM.

The combination of carfilzomib and pomalidomide with dexamethasone was studied in a multicenter phase 1/2 trial.[38] Treatment consisted of 28-day cycles of oral pomalidomide once daily on days 1-21; intravenous (IV) carfilzomib over 30 minutes on days 1, 2, 8, 9, 15, and 16; and oral or IV dexamethasone 40 mg on days 1, 8, 15, and 22. Carfilzomib was initiated at 20 mg/m^2 for cycle 1, days 1 and 2 at all dose levels. The MTD was established as the starting dose level (carfilzomib 20/27 mg/m^2, pomalidomide 4 mg, dexamethasone 40 mg). Among 30 evaluable patients, responses of PR or better were seen in 50%.

The combination of pomalidomide, dexamethasone, and pegylated liposomal doxorubicin is currently being evaluated in a phase 1/2 study of patients with relapsed or refractory MM. Pomalidomide was given at doses of 2, 3, or 4 mg in 3 cohorts of 3 patients for 21/28 days. Pegylated liposomal doxorubicin was given at 5 mg/m^2 IV on days 1, 4, 8, and 11. Dexamethasone 40 mg IV was also given on days 1, 4, 8, and 11. MTD has not been reached, with no dose-limiting toxicities after the first 10 patients. Seven patients were evaluable for efficacy, with 3 patients reaching PR, 2 reaching minor response, 1 reaching stable disease, and 1 reaching progressive disease.[39]

Pomalidomide has been combined with cyclophosphamide and prednisone in a phase 1 study. Pomalidomide was given at doses from 1 to 2.5 mg daily on days 1-28, with cyclophosphamide 50 mg every other day and prednisone 50 mg every other day for days 1-28 for 6 cycles, with subsequent pomalidomide–prednisone maintenance. Fifty-two patients were enrolled at the MTD level of 2.5 mg. Responses of PR or better were seen in 54%.[40]

Pomalidomide therapy in myelofibrosis

Three studies involving the use of pomalidomide in myelofibrosis have been reported.[41-43] The first was a multicenter phase 2 randomized study in which 84 patients were assigned to treatment in 1 of 4 treatment arms: pomalidomide (2 mg/d) plus placebo, pomalidomide (2 mg/d) plus prednisone, pomalidomide (0.5 mg/d) plus prednisone, and prednisone plus placebo. Response was assessed using International Working Group criteria.[43] Twenty patients met criteria for response in anemia, including 15 who became transfusion independent. There were no responses in splenomegaly.

The second study used low-dose pomalidomide (0.5 mg/d) alone in 58 Mayo Clinic patients.[41] In this study, anemia response was documented only in the presence of JAK2V617F (24% vs 0%). As was the case in the aforementioned multicenter study, pomalidomide had limited activity in reducing spleen size.[41] The third study tested the safety and efficacy of doses larger than 2 mg/d in 19 subjects[42] Dose-limiting toxicity was myelosuppression at 3.5 mg/d, and the MTD was established at 3 mg/d.

Pomalidomide in special populations

The MM-003 trial established that pomalidomide is safe and well tolerated in myeloma patients with moderate renal failure (clearance <60 mL/min),[36] but no data are available for patients with severe renal failure. The MM-008 trial is currently accruing and should address these questions in this population. No data are available regarding dosing, safety, or efficacy in patients with liver failure. There are no data regarding pomalidomide use in pediatric patients.

Toxicity

The major toxicity described in pomalidomide myeloma trials is neutropenia. Grade 3-4 neutropenia is reported in 26%-66% of patients and is affected by dose (2 mg or 4 mg) as well as the number of prior treatment regimens.[26-29] Thrombocytopenia and anemia are also common side effects of therapy. However, grade 3

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toxicity is seen in only 13% of patients and grade 4 is seen in 17% of patients.[27]

Nonhematologic toxicities are uncommon.[27] Fatigue is the most commonly reported adverse effect, with 62% of patients experiencing any fatigue and 8% experiencing fatigue of grade 3 or higher.[27] The incidence of thromboembolic events in patients treated with pomalidomide is similar to that in patients treated with the other IMiDs. Venous thromboembolism occurred at a rate of 3% in the 345 patients studied at the Mayo Clinic[27] and in 2% of the 221 patients in the MM-002 trial.[31] Prophylactic treatment with aspirin is a reasonable strategy for preventing thromboembolic complications in these patients and has been successfully used in pomalidomide clinical trials to date.[26,28,29] The risk of neuropathy has varied from zero to 33%,[25,27,30] but these data are confounded by preexisting neuropathy in these heavily pretreated populations. Infections were seen in 12% of patients,[27] primarily pneumonia, which was seen in 10% of patients.[27] Acute noninfectious pulmonary toxicity has been described in 2 patients.[44] This injury seems to respond to corticosteroids, and reintroduction of pomalidomide has been successful. Among the trials reported to date, a second primary malignancy has only been reported in 3 of the 345 patients enrolled in the Mayo Clinic trials,[27] a rate that is not higher than would be expected in this population.

Although similar, there are important differences between pomalidomide and the other IMiDs. Like thalidomide and lenalidomide, pomalidomide is oral and responses occur rapidly. Although lenalidomide is less myelosuppressive than many chemotherapeutic agents, there is a subset of myeloma patients who are sensitive to the myelosuppressive effects of lenalidomide and have trouble tolerating even very low doses. Such patients tend to respond well to pomalidomide, suggesting less myelosuppressive effects. Pomalidomide induces less constipation, asthenia, and neuropathy than thalidomide. Finally, skin rash is commonly seen with lenalidomide and thalidomide but rarely seen with pomalidomide.

Conclusions

Pomalidomide is the third immunomodulatory agent to have significant activity in MM. Available data suggest that efficacy and toxicity are similar at the 2-mg and 4-mg dose levels. Pomalidomide is well tolerated, with minimal toxicity, features important for a drug that is targeted for heavily treated, multiply relapsed patients. It has shown impressive results in patients who are refractory to lenalidomide and bortezomib. Studies using pomalidomide in combination with other active drugs are ongoing.

Authorship

Contribution: M.Q.L. wrote the manuscript; and A.R.M. edited the manuscript.

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