Original Article

Pomalidomide: A novel imunomodulatory drug for the treatment of relapsed and refractory multiple myeloma

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ABSTRACT

Introduction: The novel agents bortezomib and lenalidomide have demonstrated improved clinical outcomes in multiple myeloma (MM), yet most relapsed MM patients will become refractory to therapy. **Methods:** Pomalidomide is a second generation immunomodulatory agent that has been recently approved in the USA for the treatment of relapsed and refractory MM after two prior therapies, including lenalidomide and bortezomib. **Results:** Pomalidomide has several potential mechanisms of action which include anti-angiogenic effects, immunomodulation, an effect on the myeloma tumor microenvironment and the protein cereblon. **Discussion:** Several trials demonstrate the efficacy and safety of this novel compound in relapsed and refractory MM, including subjects refractory to lenalidomide and bortezomib. In the following review article, we discuss the role of pomalidomide as a new clinical treatment option for MM.

Key words: Immunomodulatory drugs, multiple myeloma, pomalidomide

INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy with clonal proliferation of plasma cells in the bone marrow leading to organ dysfunction. It accounts for 13% of the hematological malignancies with highest incidence in developed countries and African Americans.[1-3] As per 2012 statistics, MM affected 21,700 adults with a mortality of about 50%.[3]

For several decades, the treatment for MM has included various combinations of chemotherapeutic agents with steroids followed by autologous stem-cell transplantation. The therapy is still evolving as researchers are developing a better understanding of the biology and molecular basis of MM.

Prominent bone marrow vascularization and elevated angiogenic cytokines like interleukin-6 (IL-6) are key features of the pathogenesis of this disease entity. These are also suitable targets for the anti-angiogenic effects of anti-myeloma agents like thalidomide, in addition to activation of apoptotic pathways through caspase-8 mediated cell death and activation of T-cells to produce IL-2 to augment the natural killer (NK) cell-mediated cytotoxicity.[4,5]

Thalidomide was first introduced as an antiemetic (1950s) and later withdrawn in early 1960s due to the increased risk of teratogenicity. Subsequent clinical research and trials showed its potent angio-inhibitory, anti-neoplastic and immunomodulatory effect. In 2006, thalidomide, in combination with dexamethasone, was approved by the United Stated Food and Drug Administration (USFDA) for the treatment of newly diagnosed MM.[6]

During that same year, Celgene Corporation initiated the research program into immunomodulatory drugs (IMiDs), i.e., immunomodulatory derivatives of thalidomide and their structural analogs, which displayed a higher potency and better safety profile. This resulted in the emergence of novel agents such as lenalidomide, which improved the clinical outcome and median survival by about 50%.[7] However, in spite of such advances, MM had only transient clinical responses and remains incurable. There

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remained an imperative necessity for further research into the development of newer and more potent agents. Since then, two more anti-myeloma drugs were approved by the USFDA; Kyprolis (carfilzomib) (July 2012) and pomalidomide (February 2013).[8,9]

Pomalidomide is a highly potent third-generation IMiD with very promising activity in MM and myelofibrosis.[10] This article will review the pharmacological properties and all available safety and efficacy data from reported clinical studies of pomalidomide (CC-4047) and its role in relapsed and refractory MM.

PHARMACOKINETICS

A study by Hoffman *et al*. extensively studied and described the absorption, metabolism and excretion of pomalidomide (November 2012).[11] The chemical name of pomalidomide is 4-amino-2-(2,6-dioxopiperidin-3-yl) isoindoline-1,3-dione and its empirical formula is $C_{13}H_{11}N_3O_4$, with a molecular weight of 273.24 Da. It is structurally different from thalidomide and lenalidomide due to the presence of an additional carbonyl and amino group in the phthaloyl ring.[12]

A single-dose oral administration of radiolabeled pomalidomide 2 mg suspension was administered to healthy male volunteers and the mean maximum plasma concentration (Cmax) of 13 ng/mL was attained after a time (tmax) of 3.0 h. The area under the plasma concentration-time curve from time 0 to ∞ (area under the curve [AUC∞]) was 189 ng h/mL.[13] There was also good bioavailability as evidenced by the mean total recovery of radioactivity was 88%. In patients with MM receiving pomalidomide 4 mg once daily, the steady-state Cmax was 75 ng/mL and the AUC at steady-state AUCs was 400 ng h/mL.

The mean apparent volume of distribution in patients was 62-138 L.[11-13]

Pomalidomide was extensively metabolized, but unchanged pomalidomide accounted for 70% of the circulating radioactivity and the exposure AUC to metabolites ranged from only 1.7% to 6.3% of total radioactivity. However, unchanged pomalidomide in the urine accounted for < 3% of the dose, whereas three of the metabolites in urine together accounted for 52% of the dose. The elimination half-life ($t^{½}$) of pomalidomide was 8.9 h and the mean recovery of radioactivity was 73% in urine and 15% in feces. More than 80% of the radioactivity was recovered in the first 48 h after administration. The tmax and $t^{½}$ values for the metabolites were similar to those for the parent drug.[11]

PHARMACODYNAMICS

The precise cellular targets and exact molecular mechanism of pomalidomide remains elusive. Several mechanisms [Figure 1] have been proposed including anti-angiogenic, anti-proliferative and immunomodulatory effects. Cereblon has been identified as a primary target for binding of IMiDs on myeloma cells. Although, its depletion was related to lenalidomide resistance, no cross-reactivity was seen with pomalidomide.[14] In fact, pomalidomide is shown to be 100 times more potent than thalidomide and 10 times more potent than lenalidomide. Pomalidomide enhances both NK cell cytotoxicity and antibody-dependent cellular cytotoxicity (antibody cell mediated toxicity) by triggering IL-2 production from T cells.[15] Induction of IL-2 and IF-gamma further down-regulates suppressor of cytokine signaling. It also inhibits proliferation of lenalidomide-resistant myeloma cell lines and acts synergistically with dexamethasone to induce apoptosis. Pomalidomide inhibits the production of IL-1 and IL-6 from peripheral blood mononuclear cells (PBMC). Reduction of the expression of IL-6 and vascular endothelial growth factor is responsible for its anti-angiogenic activity as seen in mouse models.[16,17] Studies show that IMiDs also exert augmented anti-tumor activity with Rituximab against B cell malignancies in mouse models.[13] IMiDs can interfere with actin cytoskeleton through activation of Rho GTPase, enhance actin polymerization and enhance formation of immune synapse and expression of IL-2 in T cells.[18]

In addition to anti-neoplastic and immunonodulatory effect, it exhibits anti-inflammatory effect by inhibiting cyclooxygenase-2 enzyme and prostaglandin production in lipopolysaccharide stimulated PBMCs.

Pomalidomide also inhibits MM-induced osteoclast formation through normalization of the receptor activator of NF-kappa-B ligand/osteoprotegerin (RANKL/OPG) ratio targeting the expression of adhesion molecules by MM cells. This is accomplished by blunting RANKL up-regulation by reducing CD49d expression. It down-regulates PU.1 resulting in reduced osteoclast formation and differentiation from CD 14+ progenitor cells.[12]

Recent studies are currently exploring the possible utilization of pomalidomide for other indications. A study was conducted in knockout transgenic mouse model of sickle cell anemia. After 8 weeks of pomalidomide administration, fetal hemoglobin expression was increased comparable to hydroxyurea without associated myelosuppression, thus reducing transfusion requirements.[19] Pomalidomide was also shown to improve erythropoiesis and enhance fetal hemoglobin in human CD34+ cells.[20] These results suggest that pomalidomide

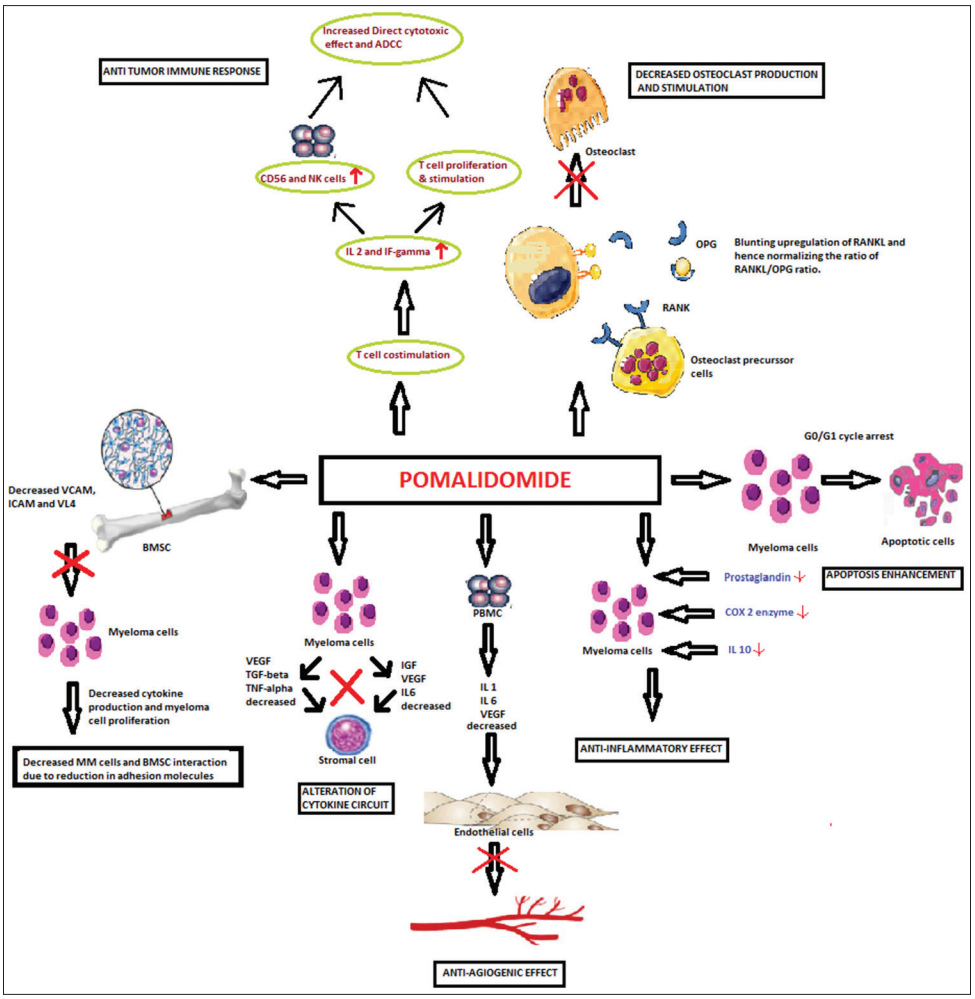

Figure 1: Demonstrating mode of action of pomalidomide

may prove useful in the treatment of sickle-cell disease and b-thalassaemia.

CLINICAL TRIALS

In the Phase III MM-003 trial [Figure 2], pomalidomide in combination with low-dose dexamethasone significantly improved progression-free survival (PFS) (primary endpoint) compared with high-dose dexamethasone (median 15.7 weeks vs. 8.0 weeks; hazard ratio [HR] 0.45; $P > 0.001$), in patients with relapsed or refractory MM.[21] This trial studied the efficacy and tolerability of pomalidomide in combination with low-dose dexamethasone versus high-dose dexamethasone alone in patients with relapsed or refractory MM who had received at least two prior therapies including both lenalidomide and bortezomib. A total of 455 patients were randomized (2:1) to receive oral pomalidomide 4 mg on days 1-21 of each 28 days cycle plus low-dose (40 mg weekly) oral dexamethasone (n = 302) or high-dose dexamethasone (40 mg on days 1-4, 9-12 and 17-20 of each 28 days cycle) alone (n = 153) until disease progression. Patients age > 75 years received 20 mg doses of dexamethasone instead of 40 mg doses within each arm according to the relevant schedules. Overall survival (OS) was also significantly better in the pomalidomide group at interim analysis (median OS not reached vs. 34 weeks; HR 0.53; $P < 0.001$). This analysis included 45 patients who received pomalidomide after progressing on high-dose dexamethasone.

The MM-002 Phase II trial showed that pomalidomide (4 mg once daily for days 1-21 of each 28 days cycle) plus low-dose dexamethasone (20-40 mg once daily on days 1, 8, 15 and 22 of each 28 days cycle) (n = 113) resulted in a partial response (PR) rate (or better) of 34%, compared with 13% for pomalidomide alone (n = 108) in heavily pretreated (including two or more cycles of lenalidomide and bortezomib separately or in combination) patients with relapsed or refractory MM.[22] The primary endpoint was PFS and after a median treatment duration of 5.0 months, median PFS was 4.6 months and 2.6 months in the two study groups, respectively. The comparison indicated that pomalidomide in combination with low-dose dexamethasone was associated with greater clinical benefit and no increased toxicity compared with pomalidomide alone,[22] and at progression, patients

PPPPPHASE	TRIAL/INVESTIGATOR	STUDY DESIGN	POPULATION	RESULT (ORR)
I	Richardson et al.	Pomalidomide + Bortezomib + low dose dex	Relapsed multiple myeloma/ refractory	73%
II	Lacey et al. (2009)	2mg/day+ low dose dexamethasone	n=60 prior thalidomide or lenalidomide	63%
II	Lacey et al. (2010)	2mg/day+ low dose dexamethasone	n=34 lenalidoide refractory	32%
II	IFM 2009-02 Leleu et al.	4mg/day+ low dose dexamethasone	n=84 Relapsed or refractory to lenalidoide or bortezomib	35%
II	Richardson et al.	4mg/day+ low dose dexamethasone	n=221 Refractory to Lenalidomide and bortezomib	34%
II	CC-4047-MM-002	Pomalidomide v/s Pomalidomide +low dose dexamethasone	n=221 Relapsed multiple myeloma/ refractory to Lenalidomide to Bortezomib	7.4%
II	NCT00558896	2 or 4 mg/day + low dose dexamethasone	n= 225 Relapsed/refractory to Bortezomib and lenalidomide multiple myeloma or amyloidosis	47%
III	MM-003	Pomalidomide +low dose dex v/s high dose dex alone	n=455 Relapsed multiple myeloma/ refractory to Lenalidomide to Bortezomib	31%
III	CC-4047-MM-007	Pomalidomide, Bortezomib + low dose dex v/s Bortezomib + low dose dex	Relapsed/refractory multiple myeloma	
	NCT01632826	Expanded access trial for Pomalidomide 4mg/day +low dose dex	Relapsed/refractory multiple myeloma	

Figure 2: Clinical trials

receiving pomalidomide alone could receive the addition of dexamethasone at the investigator's discretion.[23] In updated results from the end of March 2012 in patients receiving pomalidomide plus low-dose dexamethasone (n = 113), PFS and OS were 4.6 and 16.5 months, respectively,[23] and treatment was associated with improvement in clinically important end-organ functional parameters with potential prognostic significance.[24] The Phase I part of this trial had earlier discovered that 4 mg/day was the maximum tolerated dose (MTD) and the recommended dose for the Phase II trial.[25]

The sequential Phase II trial (NCT00558896) carried out by the Mayo Clinic investigated pomalidomide combined with low-dose dexamethasone in 225 patients with relapsed or refractory MM. Patients were grouped according to disease status: relapsed/refractory myeloma; lenalidomide refractory myeloma (2 mg dose); lenalidomide- and bortezomib-refractory myeloma (2 mg dose); lenalidomide- and bortezomib-refractory myeloma (4 mg dose); and lenalidomide-refractory myeloma, 1-3 prior regimens, (4 mg dose).[26] Pomalidomide was administered on days 1-28 of a 28 days cycle and oral dexamethasone 40 mg daily on days 1, 8, 15 and 22 of each cycle.[26-28] Responses were assessed using the criteria published by the International Myeloma Working Group.[29] Pomalidomide plus low-dose dexamethasone was highly active in the population with relapsed myeloma (n = 60) with 38 patients (63%) achieving

an objective response to therapy, including 3 (5%) patients with a complete response (CR), 17 patients (28%) with very good partial response (VGPR) and 18 (30%) with a PR.[9] Lack of cross resistance with lenalidomide was established in the cohort of 34 patients with lenalidomide-refractory disease receiving pomalidomide 2 mg daily, with an overall response rate (ORR) of 47%.[27] This included three patients (9%) with VGPR, 8 (23%) with PR and 5 (15%) with minor response (MR). The median duration of response was 9.1 months, median PFS was 4.8 months and the median OS 13.9 months.[27] Pomalidomide was shown to overcome resistance in myeloma refractory to both lenalidomide and bortezomib.[28] Pomalidomide 2 mg daily or 4 mg daily (both on days 1-28 of a 28 days cycle) were evaluated in two sequentially treated cohorts in patients who had failed both these agents. The ORR (MR or better) was 49% in the pomalidomide 2 mg cohort (n = 35) and 43% in the pomalidomide 4 mg cohort (n = 35). Event-free survival at 6 months was 78% and 67% in the 2 mg and 4 mg cohorts, respectively, suggesting no advantage for the 4 mg dose with the continuous regimen used in this study.[28] The confirmed response rate (CPR) was 37% for the cohort with lenalidomide-resistant myeloma (1-3 prior regimens) receiving the higher pomalidomide dose of 4 mg (n = 60), with the PFS 63% and OS 93% at 6 months.[26] A CPR of 21% was reported with pomalidomide 4 mg daily in an additional 6th cohort of 120 patients with lenalidomide resistant myeloma.[30] The 6-month PFS and OS were 34% and 74%, respectively.

A 31% response was seen in 13 patients with extramedullary disease (EMD) in a sub study of 174 patients in the Mayo Clinic Phase II trial.[31] This included one CR and two PRs (>50% reduction) in EMD.

The intermittent regimen of pomalidomide 4 mg/day on days 1-21/28 days cycle and the continuous regimen of pomalidomide 4 mg daily were similarly effective in 84 patients with MM refractory to lenalidomide and bortezomib. The ORR was 34.5% and 47% of patients had stable disease. Furthermore similar across groups were duration of response, time to progression and PFS of 7.3 (95% confidence intervals [CI]: 5-15), 5.4 (4-8) and 4.6 (4-7) months, respectively. OS at 18 months was 14.9 (95% CI: 11-20) months, with 44% of patients alive at 18 months. All patients received oral dexamethasone 40 mg/day in this Phase II trial conducted by the Intergroup Francophone du Myélome (IFM 2009-02; NCT01053949).[32]

PFS was 10.5 months and median OS was 33 months in 17 patients who continued pomalidomide 1 mg, 2 mg or 5 mg on alternate days after an expanded access extension of a 4-week Phase I dose-escalation study to determine the MTD. The MTD of pomalidomide 1 mg, 2 mg, 5 mg and 10 mg on alternate days was defined as 5 mg in this dose escalating Phase I trial in 20 patients with relapsed myeloma.[33] An earlier Phase I dose-escalating study of daily pomalidomide 1 mg, 2 mg, 5 mg and 10 mg for 4 weeks by these researchers had defined the MTD as 2 mg/day, with neutropenia the dose-limiting toxicity in 24 patients with relapsed or refractory myeloma.[34]

The ORR (CPR) was 53.6% and median PFS was 8.2 months in a Phase II trial of clarithromycin 500 mg twice a day with pomalidomide (4 mg on days 1-21 of a 28 days cycle) and low-dose dexamethasone in 100 patients with relapsed/refractory MM. Eligible patients had at least three prior lines of therapy, including lenalidomide. Median OS had not been reached after a mean follow-up of 10.1 months.[35]

The 1-year PFS and OS rates were 52% and 78%, respectively, after a median follow-up of 11 months in an early trial investigating alternate day cyclophosphamide in combination with pomalidomide and prednisone. Patients with MM relapsed/refractory to lenalidomide (n = 52) received pomalidomide 2.5 mg/day, cyclophosphamide 50 mg every other day and prednisone 50 mg every other day on days 1-28 for six cycles, followed by pomalidomide plus prednisone.[36]

Phase I studies to determine the MTD for pomalidomide in combination with low-dose dexamethasone plus bortezomib,[37] low-dose dexamethasone plus carfilzomib[38] and prednisone plus oral weekly cyclophosphamide[39] have been completed, with further trials of these combinations now underway or planned.

DOSAGE AND INDICATIONS

The recommended initial dosage is 4 mg orally once daily without food for days 1-21 of each 28 days cycle with 40 mg dexamethasone weekly until disease progression activity in patients with MM, pretreated with lenalidomide or bortezomib.[10] There is synergistic activity reported with dexamethasone to improve overall response and survival. As per a study by Lacy *et al*., no advantage was observed for dosage of pomalidomide of 4 mg over 2 mg daily with an ORR being 49% in the group with 2 mg daily dosage versus 43% with 4 mg daily dosage.[28] The French Intergroup, IFM 2009-02 Phase II demonstrated similar responses with pomalidomide given for 1-21 days of a 28 days cycle versus every day for 28 days.[32]

Pomalidomide as aforementioned has been USFDA approved only for MM in patients who have received at least 2 prior therapies (including lenalidomide and bortezomib) and progressed within 60 days after completion of last therapy.[10]

Due to the wide spectrum of clinical activity and effects on the human body, pomalidomide is under investigation in various Phases I and II clinical trials for utilization in other hematological and non-hematological indications such as myelofibrosis, waldenstrom's macroglobulinemia, immunoglobulin light chain amyloidosis, steroid resistant graft versus host disease, systemic sclerosis with interstitial lung disease, reduction of transfusion in sickle cell anemia, Kaposi sarcoma with or without human immunodeficiency, various solid tumors; hormone refractory prostate cancer, small cell lung cancer in combination with cisplatin and etoposide, metastatic pancreatic cancer in combination with gemcitabine, to name a few.[40-46]

DRUG SAFETY PROFILE

Pomalidomide is generally well-tolerated and its adverse effects include fatigue, neutropenia, thrombocytopenia, neuropathy and thromboembolic disease.

The most significant adverse effect seen in all clinical trials in patients with refractory or relapsed MM treated with pomalidomide was neutropenia of grades 3 or 4. It was shown to increase with dose escalation and depended upon the intensity of previous treatment with other agents.

In the landmark MM-002 study (n = 221), neutropenia was seen in 41%, with anemia in 22%, thrombocytopenia in 19% and leukopenia in 10% patients who were treated with pomalidomide plus low dose dexamethasone. Neutropenia was responsible for dose reduction in 4% individuals. Non-hematological side effects included pneumonia (22%), fatigue (14%), dyspnea (13%), peripheral neuropathy (13%), back pain (10%) and urinary tract infection (9%).[22]

MM-003 is a Phase III study that compared pomalidomide plus low dose dexamethasone versus high dose dexamethasone alone.[21] It illustrated an increase in adverse events with higher dose of steroids. Toxicities like neutropenia (42% vs. 15%), thrombocytopenia (21 vs. 24%), infections (24 vs. 23%), hemorrhage (2 vs. 3%) and glucose intolerance (3 vs. 7%) were seen in pomalidomide with dexamethasone versus high dose dexamethasone alone. Thromboembolism was only seen with pomalidomide group and peripheral neuropathy was seen equally (1%) in both groups.[21]

In Mayo Clinic Phase II trial, the most common side effect was myelosuppression, 31% neutropenia, 16% anemia, 12% thrombocytopenia, 8% pneumonia, 8% fatigue and 3% venous thromboembolism (VTE) where n = 345.[31] In this study, reversible grade-3 pneumonitis was seen in 1% patients, which responded to steroids. 33% exhibited peripheral neuropathy of grades 1-2, but many of them had existing neuropathy. Low dose aspirin was successfully used in the Mayo Clinic and MM-002 trials in order to prevent VTE.

CONCLUSION

Pomalidomide is a third generation immunomodulatory agent which represents a novel drug for the treatment of refractory/relapsed MM. It received its first global approval on the 8th of February 2013 in the USA for the treatment of patients with MM who have received at least two prior therapies, including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. It directly affects myeloma cells, as well as modulates the bone marrow microenvironment and these results in optimal clinical outcomes even in heavily pretreated patients. The encouraging results of Phase III trials provide the rationale for its use in combination with dexamethasone in patients who fail multiple lines of treatment, including bortezomib- and lenalidomide-based regimens. The adverse events are manageable. There is also the added advantage that the drug can be administered orally. Further clinical research and trials are needed to explore combinations with alkylating agents, proteasome inhibitors, or other novel compounds, which will probably further improve response rates.

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