IMMUNOMODULATORY COMPOUNDS (IMIDS®) IN THE TREATMENT OF MULTIPLE MYELOMA

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Abstract

The design of innovative, more effective, less toxic therapy of multiple myeloma (MM) is emerging in parallel to a better understanding of the underlying pathophysiology of this common hematologic malignancy. Thalidomide has changed the treatment paradigm of patients with MM. Its efficacy, however, has been compromised by significant side effects. IMiDs® (immunodulatory compounds) are structural and functional analogs of thalidomide that were specifically designed to create new agents with enhanced immunomodulatory and anticancer properties and better tolerability profiles. In this article, we review the clinical trial development of the second-generation IMiDs®, lenalidomide and pomalidomide. Both agents demonstrate potent activity and are highly effective and well tolerated treatment options for patients with MM.

KEY WORDS: lenalidomide, thalidomide, multiple myeloma, pomalidomide, IMiDs®

Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy and is invariably fatal (1, 2). Each year, 19,920 new cases of MM are diagnosed, resulting in nearly 11,000 deaths annually (2). Despite available therapies such as high-dose chemotherapy and autologous stem cell transplantation (ASCT), MM remains an incurable disease with a median survival of 3 to 5 years depending on disease stage (3), and a 5-year relative survival rate of approximately 35% (4). The role of high-dose chemotherapy and ASCT continues to be controversial, with overall survival (OS) only minimally improved if any (5, 6). Patients with progressive disease can achieve a 50-75% response rate to salvage regimens such as vincristine, doxorubicin, and dexamethasone (VAD) (7, 8); however, these responses are often short-lived. Therefore, the need for novel agents and therapeutic modalities in MM remains critical. The introduction of the IMiDs®, such as lenalidomide and pomalidomide, for the treatment of various malignancies has gained momentum, especially in the management of MM (9). The re-discovery of thalidomide not only improved response rates and provided a new class of agents for MM patients, but also instigated a wide range of bench and clinical research activities that enriched the understanding of MM pathophysiology (10).

Thalidomide

The discovery that thalidomide had anti-angiogenic (11) and T-cell co-stimulatory (12) activity led to the clinical investigation of thalidomide for therapy in MM. In relapsed and refractory MM, thalidomide produced response rates of approximately 30% as a single agent (9). In newly diagnosed patients, thalidomide achieved response rates of 36% alone and 64-72% in combination with dexamethasone (13, 14). As a result, thalidomide in combination with dexamethasone received United States Food and Drug Administration (US FDA) approval for the treatment of newly diagnosed MM in 2006. In addition, recent phase III studies have investigated various thalidomide-containing regimens and reported improvements in quality of response with: thalidomide, adriamycine and dexamethasone compared to VAD (15); bortezomib, melphalan, prednisone and thalidomide (VMPT) compared to bortezomib, melphalan and prednisone (VMP) (16), melphalan, prednisone and thalidomide (MPT) compared to melphalan and prednisone (MP) (17), and bortezomib, thalidomide and dexamethasone (VTD) compared to thalidomide and dexamethasone (TD) (18). However, the encouraging effects of thalidomide are hampered by toxicity, which often compromises the dose or leads to discontinuation of therapy. Common adverse events include fatigue, somnolence, constipation, fluid retention, peripheral neuropathy, venous thromboembolism (VTE), and rash (9, 19). Given the promising activity of thalidomide, synthetic analogs were developed and introduced in an effort to provide equal or greater immunomodulation, but a better tolerability profile. Clinical data indicate that the incidence of peripheral neuropathy, which is common with thalidomide, is low with lenalidomide and pomalidomide, (20-24).

Lenalidomide and pomalidomide

The IMiDs® are a group of unique, orally bioavailable agents that have been refined, using thalidomide as a structural template (Figure 1).

Modification of the thalidomide structure through removal of a carbonyl on the ring formed lenalidomide (CC-5013, Revlimid®), and addition of an amino group at the 4 position of the phthaloyl ring formed pomalidomide (CC-4047). These IMiDs® were specifically designed to enhance immunomodulatory and anticancer properties of thalidomide with fewer side effects. Preclinical studies have shown that lenalidomide and pomalidomide are 50 000 times more potent, in vitro, than thalidomide at inhibiting tumor necrosis factor alpha (TNF-α) (25, 26).

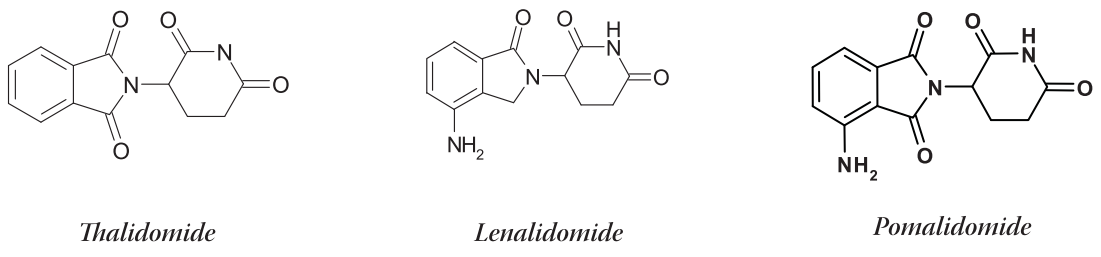

FIGURE 1. Molecular structure of thalidomide, lenalidomide and pomalidomide

	Thalidomide	Lenalidomide	Pomalidomide
Anti-angiogenic activity (human explant model)	++++	+++	++++
Anti-inflammatory activity against monocytes	+	++++	+++++
T cell/NK cell costimulation	+	++++	+++++
T regulatory cell inhibition	-	++++	+++++
Antibody-dependent Cellular Cytotoxicity (ADCC)	-	++++	++++

TABLE 1. Comparative table of IMiDs® activity in preclinical studies
+ = **potency factor of 10**

Studies have revealed that IMiDs® not only inhibit angiogenesis, but also stimulate T-cell proliferation and induce apoptosis and growth arrest in resistant myeloma cells (Table 1) (27-29). These compounds also prevent the adhesion of myeloma cells to bone marrow stromal cells, and thereby inhibit the enhanced secretion of migratory factors, such as interleukin (IL)-6, TNF-α, and vascular endothelial growth factor (VEGF) (30-35). Lenalidomide has more potent activity than thalidomide in the preclinical setting (25, 36), and has also demonstrated impressive clinical activity in both newly diagnosed and relapsed or refractory MM (23, 37-39). Pomalidomide also demonstrates potent activity against TNF-α in vitro, indicating greater synergy than lenalidomide with rituximab in vivo (40). It also promotes T-cell differentiation and cytokine production via the transcription factor T-bet (41), and has demonstrated promising activity in clinical trials (24, 42).

Studies among patients with relapsed or refractory MM have demonstrated that lenalidomide can overcome resistance to prior MM therapy, including thalidomide (43-45). In addition, time to progression (TTP) and progression-free survival (PFS) are superior when lenalidomide is given at first relapse rather than given later as salvage therapy (45). Two phase I trials of lenalidomide have demonstrated promising activity as well as decreased toxicity in heavily pretreated patients with relapsed or refractory MM [42, 43]. These studies established 25 mg/day as the maximum tolerated dose (MTD) for lenalidomide in relapsed or refractory MM, and provided a firm foundation for continuing trials with lenalidomide, either alone or in combination with other active agents in MM. Two large, randomized, phase III, double-blind, placebo-controlled clinical trials (North American MM-009 and European MM-010) have compared the efficacy and safety of lenalidomide plus dexamethasone (Len+Dex) with placebo plus dexamethasone in patients with relapsed or refractory MM (23, 37). In both trials, lenalidomide 25 mg/day or placebo was administered on days 1-21 of each 28-day cycle and oral dexamethasone 40 mg was administered on days 1-4, 9-12, 17-20 of each 28-day cycle. The MM-009 trial enrolled 353 patients (Len+Dex n=177; placebo+Dex n=176) and the MM-010 trial enrolled 351 patients (Len+Dex n=176; placebo+Dex n=175). The Len+Dex combination achieved a significantly higher overall response rate (ORR) (MM-009: 61% vs. 20%; MM-010: 60% vs. 24%; both p<0,001) and complete response (CR) rate (MM-009: 14,1% vs. 0,6%; MM-010: 15,9% vs. 3,4%; both p<0,001), (Figure 2). The median TTP was significantly prolonged by the addition of lenalidomide to dexamethasone (MM-009: 11,1 months vs. 4,7 months; MM-010: 11,3 months vs. 4,7 months; both p<0,001), (Figure 3) and the median OS was significantly longer in the Len+Dex arm (MM-009: 29,6 months vs. 20,2 months; p<0,001; MM-010: not reached vs. 20,6; p=0,03).

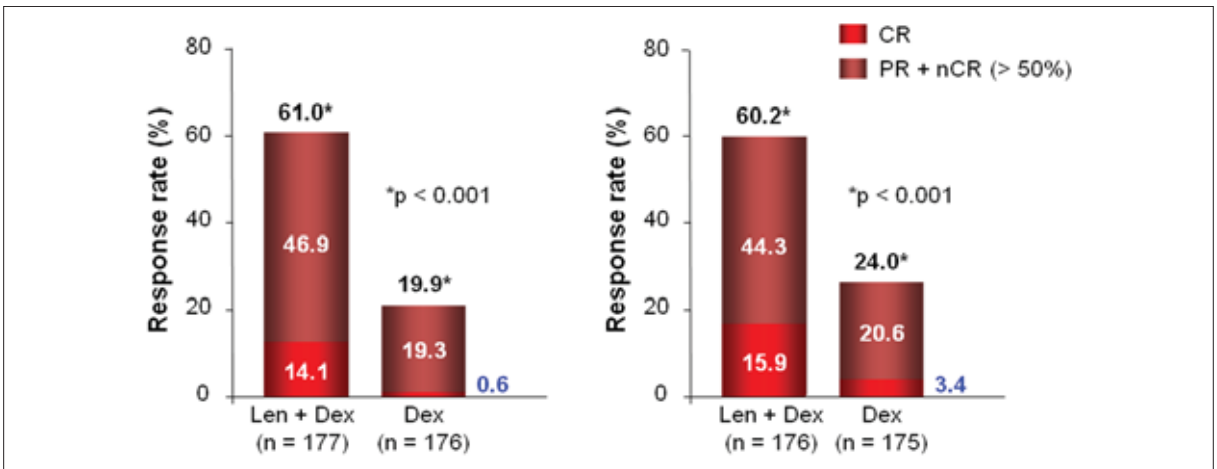

FIGURE 2. Response rates with Len+ Dex versus Dex alone in the pivotal phase III trials, MM-009 and MM-010.

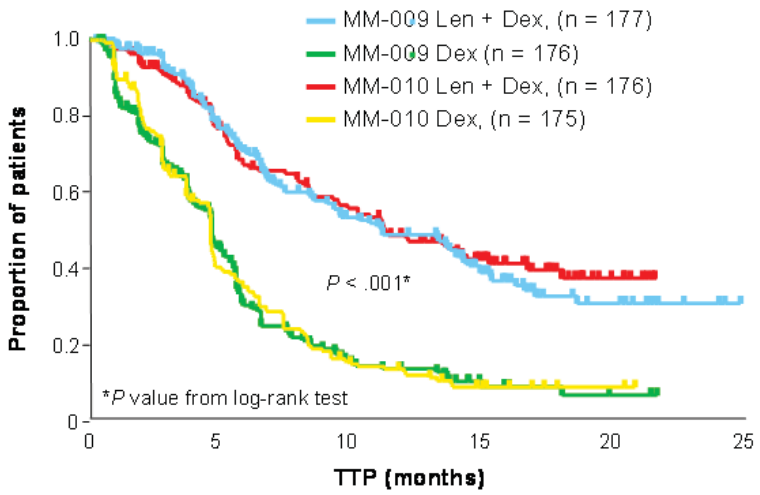

FIGURE 3. Time to progression with Len+ Dex versus Dex alone in in the pivotal phase III trials, MM-009 and MM-010.

In the MM-009 and MM-010 studies, grade 3/4 hematologic adverse events were more common with Len+Dex and included neutropenia (41,2% and 29,5% vs. 4,5% and 2,3%, respectively), anemia (13,0% and 8,6% vs. 5,1% and 6,9%), thrombocytopenia (14,7% and 11,4% vs. 6,9% and 5,7%), and febrile neutropenia (3,4% vs. 0%). Other common grade 3/4 adverse events included infection (21,4% and 11,3% vs. 12,0% and 6,2%, respectively), and fatigue (6,2% and 6,8% vs. 6,3% and 3,4%). The incidence of VTE in the MM-009 and MM-010 studies was higher in the Len+Dex arm (14,7% and 11,4% vs. 3,4% and 4,6%, respectively); however, it was comparable to the incidence of 10% observed for the general MM population in retrospective analyses (46). On the basis of these studies, lenalidomide was approved by the US FDA in June 2006 and by the European Medicines Agency in June 2007 for use in combination with dexamethasone in the treatment of MM in patients who have received at least one prior therapy. Due to encouraging results in the relapsed or refractory setting, a phase II trial was undertaken to assess the efficacy and safety of the Len+Dex combination therapy in the front-line setting (21). In this phase II trial, lenalidomide (25 mg/day orally on days 1-21 of each 28-day cycle) was combined with dexamethasone (40 mg/day orally on days 1-4, 9-12, and 17-20 of each 28-day cycle) in 34 newly diagnosed, previously untreated MM patients. The ORR was 91%, with CR in 6% and very good partial response (VGPR) and near CR in 32%. Grade 3 or greater non-hematologic adverse events were reported in 47% of patients and included fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%), and rash (6%). Myelosuppression was minimal, most likely reflecting the preserved bone marrow reserve in this group of previously untreated patients. All patients were placed on low dose aspirin prophylaxis, based on the efficacy of low dose aspirin in preventing VTE among patients treated on the thalidomide plus dexamethasone regimen (47), and only one patient developed a VTE. In addition, Len+Dex combination therapy appeared to be a useful pre-transplant conditioning regimen, as there was no adverse effect on stem cell mobilization among these patients. With successful responses and better tolerability obtained from early trials, lenalidomide is rapidly being incorporated into front-line regimens. The Southwest Oncology Group (SWOG) and Eastern Cooperative Oncology Group (ECOG) have ongoing randomized, phase III trials assessing Len+Dex as primary therapy in the front-line setting. The SWOG trial compared Len+Dex to dexamethasone alone in patients with newly diagnosed MM (38). In this study, 198 patients were randomized, 100 received lenalidomide 25 mg/day (28 of 35 days for 3 induction cycles, then 21 of 28 days as maintenance thereafter) plus dexamethasone 40 mg/day (days 1-4, 9-12, and 17-20 as induction, then days 1-4, and 15-18 as maintenance) and 98 received dexamethasone plus placebo. In the 133 patients who were assessable for response, the ORR was significantly higher (85,3% vs. 51,3%; p=0,001) and 1-year PFS was significantly longer (77% vs. 55%, p=0,002) with Len+Dex. The 1-year OS was high and there was no difference between arms (93% vs. 91%). Grade 3/4 neutropenia (13,5% vs. 2,4%, p=0,010) and infections (all grades: 38% vs. 24%; grade 3 or higher: 14% vs. 8%, p=0,003) were more common with Len+Dex. VTE was reported in 25% of patients treated with Len+Dex vs. 7% of patients treated with dexamethasone alone; most patients (81%) who experienced VTE received aspirin as thromboprophylaxis, however it is to be noted that those patients received the full dose of aspirin at 325 mg daily which his known to be thrombogenic as it inhibits the prostacyclin activ-

ity this negating its anti-platelet role (48, 49). Patients in the dexamethasone arm who progressed were allowed to cross over to the Len+Dex arm. Of 40 patients who crossed over, the ORR in 23 who were assessable for response was 70,4%. These data confirm the superior efficacy with Len+Dex in newly diagnosed patients. The ECOG trial compared lenalidomide plus standard-dose dexamethasone (RD) to lenalidomide plus low-dose dexamethasone (Rd), in an attempt to further diminish adverse events while maintaining the response rate. In this study, patients in the RD arm were treated with lenalidomide 25 mg/day on days 1-21 of each 28-day cycle and dexamethasone 40 mg/day on days 1-4, 9-12, and 17–20 of each 28-day cycle, and patients in the Rd arm received dexamethasone 40 mg on days 1, 8, 15, and 22 of each 28-day cycle (50). A total of 445 patients were randomized, 223 to RD and 222 to Rd. Grade 3 or higher adverse events were more common in the RD arm (49% vs. 32%; p<0,001), including neutropenia (10% vs. 19%; p=0,01), VTE (25% vs. 9%; p<0,001), and infections (16% vs. 6%; p<0,001). Although response rates during the first 4 cycles were higher with RD (ORR: 82% vs. 70%; p=0,007; CR + VGPR: 52% vs. 42%; p=0,06), OS was significantly higher in the Rd arm, p=0,006, (1-year OS: 96% vs. 88%; 2-year OS: 87% vs. 75%). The 2-year OS rate for the 102 patients who underwent stem cell transplant (94%) was comparable to the 2-year OS for patients in the Rd arm who continued primary therapy beyond 4 cycles (91%). These data demonstrated superior outcome with lenalidomide plus low-dose dexamethasone in patients with newly diagnosed MM compared to lenalidomide plus high-dose dexamethasone. The dose and schedule of dexamethasone will need to be evaluated further in light of the differences between the results of the SWOG and ECOG studies. There is probably a group of patients that could benefit from high dose dexamethasone administered according to the SWOG schedule and for others a lower dose may achieve similar disease outcome with less toxicity and mortality. Baz et al. combined pegylated liposomal doxorubicin, vincristine, and dexamethasone (DVd) regimen with lenalidomide (DVd-R) in a phase I/II study among patients with relapsed or refractory MM (51). The study objectives were to determine the MTD and evaluate the safety and efficacy of DVd-R. Lenalidomide was administered orally at doses of 5, 10, and 15 mg/day for 21 days of each 28-day cycle in cohorts of 3-6 patients. Patients were treated for at least 4 cycles, and a maximum of 2 cycles after best response. Maintenance therapy included continuation of lenalidomide with the addition of prednisone 50 mg every other day until disease progression. Low-dose aspirin (81 mg) was administered as VTE prophylaxis. Sixty-two patients were enrolled in the study (40 refractory to prior therapy). The MTD of lenalidomide with DVd chemotherapy was 10 mg. The ORR was 75% with CR or near CR in 29%. After a median follow-up of 7.5 months, the median PFS was 12 months and the median OS had not been reached. Grade 3/4 adverse events included neutropenia (32%), febrile neutropenia (7%), peripheral neuropathy (5%), and VTE (9%). This novel combination appears to be well tolerated, and resulted in a high response rate in a group of patients with MM, most of whome were refractory to prior therapy. In addition to the ability of lenalidomide to exert an effective anti-tumor activity through direct anti-malignant plasma cell effects, it also exerts immune modulatory effects. Lenalidomide stimulates the immune cellular system leading to a beneficial impact on infectious complications, especially those that rely on the cellular immune system. One of the major viral infections in patients with multiple myeloma is herpes zoster that occurs in 15% of multiple myeloma patients over the course of the disease. Herpes zoster has high morbidity especially in this age group where post herpetic neuralgia could be crippling to the patients. With lenalidomide based therapy the incidence of herpes zoster is less than 5% as compared to other regimens that include proteasome inhibitors, where the incidence ranges from 15-60%. (52, 53) The clinical activity of pomalidomide was first demonstrated in a phase I study in which 24 patients with relapsed or refractory MM were treated with pomalidomide as a single agent (42). The MTD was established at 2 mg/day. The ORR was 54%, including CR in 17%. Four patients (17%) experienced VTE. Pomalidomide therapy was associated with significantly elevated serum IL-2 receptor and IL-12 levels, which is consistent with activation of T cells, monocytes and macrophages. Based on these results, a recent phase II study has evaluated the safety and efficacy of pomalidomide (2 mg/day) combined with low-dose dexamethasone (40 mg/day on days 1, 8, 15, and 22 of each 28-day cycle) in 37 patients with relapsed or refractory MM (24). Most patients had received prior ASCT (76%) and prior IMiD® therapy (62%). The ORR was 62%, including VGPR in 24%. Objective responses were also reported 4 of 13 patients (29%) who were refractory to lenalidomide. Grade 3 hematologic adverse events included neutropenia (31%), thrombocytopenia (3%), and anemia (3%). There was no grade 3 neuropathy, but grade 1-2 neuropathy was reported in 16% of patients. Due to the incidence of VTE in the phase I study, all

patients received aspirin as thromboprophylaxis and there were no cases of VTE. Pomalidomide appears to be another promising agent with a role for further studies as an immunostimulatory modality of treatment among patients with relapsed or refractory MM.

Conclusion

The treatment paradigm for MM has evolved rapidly in recent years, with significant advances in the translation of novel biologically derived therapies from research to clinical application. Studies of lenalidomide and pomalidomide have demonstrated significant clinical benefits in patients with MM, along with an improved safety profile compared to thalidomide. Both IMiDs® are significant additions to the therapeutic armamentarium for MM therapy due to their more potent immunomodulatory properties, as well as their improved tolerability. Further studies of these orally bioavailable IMiDs® in MM patients are warranted, not only in combination with other biologics and chemotherapeutic agents, but with thalidomide as well.

G. Srkalovic has no potential conflict of interest relevant to this article. M.A. Hussein is employee of Celgene Corporation, manufacturer of IMiDs®

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