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Immunomodulatory drugs in multiple myeloma: mechanisms of action and clinical experience

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Abstract

Over the last two decades, the outcomes for patients with multiple myeloma, a plasma cell malignancy, have dramatically improved. The development of the immunomodulatory drugs (IMiDs) which include thalidomide, lenalidomide, and pomalidomide, has contributed significantly to these improved outcomes. While thalidomide is now less commonly prescribed, lenalidomide is widely used in the treatment of newly diagnosed transplant-eligible and transplant-ineligible patients, in the maintenance setting post-transplant and in the relapsed/refractory setting, while pomalidomide is currently utilized in the relapsed/refractory setting. The IMiDs have been reported to have a multitude of activities, including anti-angiogenic, cytotoxic, and immunomodulatory, however, the more recent discoveries that the IMiDs bind to cereblon and thus regulate the ubiquitination of key transcription factors including IKZF1 and IKZF3, have provided greater insight into their mechanism of action. Here the clinical efficacy of these agents in myeloma is reviewed as well as discussion of structure-function relationship, the molecular mechanisms of action, and the association of IMiDs with second primary malignancies and thrombosis.

1. Multiple myeloma

Multiple myeloma is a plasma cell malignancy characterized by the production of monoclonal protein, anemia, and disordered bone remodeling with lytic bone disease. Until the 2000's, there were very limited treatment options for myeloma, primarily consisting of corticosteroids, melphalan, the VAD regimen (vincristine, doxorubicin, dexamethasone), and autologous stem cell transplant. Median survival during that era was 2–3 years. With the advent of the immunomodulatory drugs (IMiDs) and the proteasome inhibitors (PIs) in the

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2000's the outcomes of patients are now significantly improving, with many patients living with their disease for more than 10 years. IMiDs are now widely used as induction therapy for both transplant eligible and ineligible patients, in the post-transplant maintenance setting, and for relapsed/refractory disease. Presently, the novel agents in the myeloma armamentarium consist of not only multiple IMiDs and PI's, but also a histone deacetylase inhibitor (HDAC) as well as two monoclonal antibodies.

2. Thalidomide

The first-in-class IMiD, thalidomide, has had a complicated history. It was initially synthesized in the 1950's and was noted to be "virtually non-toxic" to mice, and as a consequence, thought to be nontoxic to humans as well. Its first therapeutic use was in Europe and Canada where it could be obtained without a prescription and where it was primarily used as a sleep aid and as an anti-emetic during pregnancy (Figure 1). Its use was not approved in the United States due to concerns by the FDA over the safety of the drug. In 1961, a marked increase in occurrence of infants born with phocomelia ("seal extremities") was noted in Germany and Australia [1, 2]. Other malformations were also noted including other limb and bone abnormalities such as amelia, syndactyly, and underdeveloped long bones as well as atresia of the esophagus, duodenum, and anus, cardiac abnormalities, and aplasia of the gallbladder and appendix [1–4]. Subsequent investigations revealed that the mothers of these newborns had used thalidomide. The most critical period for exposure was found to be 20–34 days post-fertilization [5]. Unfortunately, around 10,000 infants were born with malformations by the time thalidomide was withdrawn from the market and it was estimated that up to 40% of affected infants died within one year. Subsequent testing in other species has demonstrated marked differences in interspecies sensitivity with respect to the teratogenic effects, with rabbits and primates being very sensitive [6].

The next stage in the evolution of thalidomide occurred following the observation that thalidomide had activity in patients with reactive lepromatous leprosy [7]. In 1975 the FDA allowed thalidomide to be used in the treatment of leprosy through a compassionate use program. The FDA approved the use of thalidomide for the treatment of leprosy in 1998. Beneficial effects with thalidomide have also been observed in other inflammatory dermatoses including, but not limited to, cutaneous lupus erythematosus, recurrent erythema multiform, recurrent aphthous ulcers in HIV patients, Behçet disease, cutaneous sarcoidosis, and pyoderma granulosum [8] as well as chronic graft vs host disease [9].

In the 1990's five myeloma patients with end-stage disease were given thalidomide through a compassionate-use protocol [10]. One patient experienced a significant response despite being refractory to prior therapies. This observation prompted a phase II study in 84 patients with refractory disease [10]. The starting dose was 200 mg nightly and was escalated to 800 mg. Twenty-nine percent of patients achieved at least a 50% reduction in their paraprotein, including 2 patients who achieved a complete response (CR). The most common adverse events included constipation, weakness/fatigue, somnolence, numbness/tingling, dizziness, rash, mood changes/depression, incoordination, tremors, and edema. Subsequent studies focused on the combination of thalidomide with dexamethasone in both relapsed/refractory [11, 12] and newly diagnosed patients [13–15] and this quickly became the standard of care

for newly diagnosed patients with FDA approval for this indication in 2006. Eight randomized studies investigated the use of thalidomide following ASCT (for review, see [16]). These studies varied with respect to thalidomide dosing and inclusion of corticosteroids. While all demonstrated a progression-free survival (PFS) benefit there was not a consistent overall survival (OS) benefit. Prolonged use of thalidomide in the post-transplant setting was generally limited to one year due to toxicities, particularly peripheral neuropathy.

Thalidomide has been studied in combination with multiple different agents, in both the upfront and relapsed/refractory setting, including with low dose melphalan [17], oral cyclophosphamide [18–21], liposomal doxorubicin-containing regimens [22–25], bortezomib [26–29], carfilzomib [30, 31], elotuzumab [32], as well as more intensive chemotherapy regimens such as D-PACE (dexamethasone, cisplatin, doxorubicin, cyclophosphamide, etoposide) [33] and hyperfractionated cyclophosphamide [34]. Notable phase III trials which demonstrated improved outcomes with thalidomide-containing triplets include thalidomide with oral melphalan and prednisone (versus melphalan + prednisone) [35, 36] and thalidomide with bortezomib and dexamethasone (versus thalidomide + dexamethasone) [37].

3. Lenalidomide

In 2006 lenalidomide, the second member of the IMiD class, was approved for use in combination with dexamethasone for the treatment of relapsed/refractory myeloma. In 2015, this combination was approved for the treatment of newly diagnosed multiple myeloma. The initial phase I study determined the maximal tolerated dose to be 25 mg, demonstrated a lack of typical thalidomide side effects such as somnolence, constipation, or neuropathy, and showed activity in patients who had received prior thalidomide [38]. Subsequent studies revealed overall response rates of 48–61% and 46–57% response rates in patients previously treated with thalidomide [39–41]. The most common toxicities were hematological in nature, including neutropenia (grade 3/4 25–40%), anemia (grade 3/4 9–26%), thrombocytopenia (grade 3/4 11–15%). In the newly diagnosed setting, lenalidomide with dexamethasone was found to have an overall response rates of 68–91% [42, 43] and this regimen supplanted thalidomide/dexamethasone as one of the most commonly used induction regimens in the United States. A study comparing “high-dose” dexamethasone (40 mg days 1–4, 9–12, 17–20 of a 28-day cycle) to “low-dose” dexamethasone (40 mg days 1, 8, 15, 22 of a 28-day cycle) in combination with lenalidomide revealed a better one-year overall survival rate with an improved side effect profile for the low-dose weekly dexamethasone [43]. This weekly dosing of dexamethasone is now routinely used in many lenalidomide-based regimens. More recently, the triplet combination of lenalidomide, bortezomib, and dexamethasone [44] has become a standard of care of newly diagnosed patients. In the post-transplant maintenance setting, lenalidomide is widely used. Several randomized phase III studies have been performed, all of which have demonstrated significant PFS benefit with lenalidomide [45–47]. One of the studies, CALGB 100104, revealed a significant OS benefit [45] and a recent meta-analysis of the three studies confirmed an OS benefit [48].

As with thalidomide, lenalidomide has been studied in combination with multiple different agents including alkylating agents (low-dose cyclophosphamide [49–51], bendamustine [52, 53], melphalan [54]), liposomal doxorubicin [55, 56], proteasome inhibitors (bortezomib [57, 58], carfilzomib [59–61], ixazomib [62]), HDAC inhibitors (panobinostat [63], ricolinostat [64]), and monoclonal antibodies (elotuzumab [65], daratumumab [66], pembrolizumab [67]). Several recent phase III studies have been reported in which lenalidomide/dexamethasone was compared with triplet regimens in the relapsed/refractory setting [68–71]. The results of these studies are summarized in table 2. Of note, these studies consisted of lenalidomide-sensitive patients, with the majority being lenalidomide-naïve.

4. Pomalidomide

The third member of the IMiD class, pomalidomide, was approved for the treatment of relapsed/refractory myeloma in 2013 for patients who had received at least two prior regimens including lenalidomide and bortezomib. Thus far pomalidomide has not been studied in the upfront setting or in the post-transplant setting for myeloma. The primary toxicities with pomalidomide are hematologic in nature (50–60% grade 3–4 myelosuppression, 25–33% anemia, and 24–32% thrombocytopenia) while the most common grade 3–4 non-hematological adverse events are pneumonia (~11%) and fatigue (~6%) [72–74]. The rates of grade 3–4 peripheral neuropathy have been quite low (0–3%) [73–75]. In one phase II study, the combination of pomalidomide and dexamethasone (pomalidomide dosed 2 mg daily) had a 63% overall response rate including 40% ORR in lenalidomide-refractory patients and 37% ORR in thalidomide-refractory patients [74]. In another study which included only lenalidomide-refractory patients, the overall response rate was 47% [76]. An alternative dosing strategy of 4 mg daily for 21 out of 28 days was also explored and the ORR was 35–42% [72, 77]. The latter dosing schedule was approved by the FDA.

Pomalidomide has been used in combination with the other typical classes of myeloma drugs including proteasome inhibitor (bortezomib [78, 79], carfilzomib [80], ixazomib [81, 82]), alkylating agents (cyclophosphamide [83, 84]), and monoclonal antibodies (daratumumab [85], pembrolizumab [86]).

5. Structure-function relationship

From a chemical perspective, the IMiDs are small molecules which share common phthalimide and glutarimide moieties with differences found only in the glutarimide portion (Table 1). Although the chemical structures are quite similar, the clinically used IMiDs (thalidomide, lenalidomide, pomalidomide) differ with respect to several pharmacological properties, including half-life, metabolism, clearance, and side-effect profile (Table 1). Thalidomide is not a substrate for the hepatic CYP 450 system but has been shown to undergo non-enzymatic hydrolytic cleavage at physiological pH, resulting in the generation of up to 50 different metabolites [87]. Interestingly, the (R)- and (S)-enantiomers have different clearances, resulting in higher blood concentrations of the (R)-enantiomer, although interconversion between the enantiomers *in vivo* has been noted [88, 89]. Lenalidomide undergoes minimal metabolism and is primarily excreted in the urine

unchanged, while pomalidomide is a substrate for CYP1A2 (major), CYP2C19 (minor), CYP2D6 (minor), CYP3A4 (major) and is thus at risk for drug-drug interactions [90, 91].

Prior to beginning to understand the molecular mechanisms of the IMiDs, it was appreciated that this drug class displayed a wide range of biological activities, many of which appeared to be relevant from an anti-myeloma perspective. In 1994, thalidomide was found to have anti-angiogenic properties associated with the inhibition of basic fibroblast growth factor [92]. While thalidomide displays little activity in cytotoxicity assays, both lenalidomide and pomalidomide have been shown to induce MM cell death [93]. These cytotoxic effects have been attributed to a variety of mechanisms, including inhibition of NFkB, decrease in IRF-4 production as a consequence of downregulation of C/EBPβ, activation of caspases, increased expression of pro-apoptotic factors and decreased expression of anti-apoptotic factors, and disruption of the PI3K/Akt pathway [93–96]. The ability of IMiDs to disrupt the myeloma cell-bone marrow stromal cell interaction was attributed to a decrease in expression of cell surface adhesion molecules and decreased IL-6 production [97]. There is a very complex relationship between myeloma cells, osteoclasts, osteoblasts, stromal cells and other members of the bone marrow microenvironment. Lenalidomide has been shown to downregulate osteoclastogenic hyperactivity and to inhibit secretion of osteoclastogenic factors such as MIP-1a, BAFF, APRIL, and RANK-L [98, 99].

Even more complex, were the myriad observations reported involving the immunomodulatory effects. Lenalidomide was noted to be significantly more potent than thalidomide in decreasing TNF-α, IL-1β, IL-6, and IL-12 production and in increasing IL-2 and IFN-γ synthesis [100]. Le Blanc et al. reported that IMiDs co-stimulate T cells via the B7-CD28 pathway [101]. IMiDs were also noted to increase T cell priming and to enhance tumor antigen uptake by dendritic cells with increased efficacy of antigen presentation [102]. IMiDs have been shown to increase and enhance the activity of both NK and NK T cells [103, 104] as well as inhibit the proliferation and function of T regulatory cells [105]. IMiDs decrease IL-2, IFNγ, and SOCS1 expression in CD4 T cells, CD8 T cells, NK T cells, and NK cells in the peripheral blood and bone marrow of myeloma patients [106]. A central mechanism of action underlying these effects was not readily apparent.

6. Cereblon-binding agents

In 2010, Ito et al., identified cereblon (CRBN) as the primary target of thalidomide teratogenicity [107], proving to be a major breakthrough for this field. CRBN is ubiquitously expressed and forms a complex with three other proteins (*CUL4, DDB1, and Roc1)* to produce the cullin-4 RING E3 ligase (CRL4) complex which has E3 ubiquitin ligase activity [107–109]. The importance of CRBN in mediating the anti-myeloma effects of IMiDs was demonstrated by studies in which knockdown of CRBN decreased myeloma cell viability and conferred resistance to lenalidomide and pomalidomide [110]. IMiDs have also been shown to stabilize CRBN and inhibit its own ubiquitination, thus leading to an increase in CRL4-mediated degradation of target proteins [111]. CRBN has also recently been shown to have a ubiquitin-independent function related to chaperone-like activity which facilitates the formation and activation of the CD147-MCT1 transmembrane complex [112]. IMiDs compete with CD147 and MCT1 for CRBN binding, leading to destabilization of the

CD147-MCT1 complex, which in turn contributes to the anti-tumor and teratogenic effects [112].

In 2014, several groups identified Ikaros (IKZF1) and Aiolos (IKZF3) as key CRBN-interacting proteins [113–115]. IKZF1 and IKZF3 were known to be zinc finger transcription factors involved in B and T cell development [116]. In addition, IKZF3 is important for the development of long-lived plasma cells [117]. Following binding of an IMiD to CRBN, there is enhanced affinity of CRBN for IKZF1 and IKZF3, with subsequent ubiquitination and degradation of these transcription factors [113–115]. This in turn leads to changes in gene transcription including decreased expression of IRF4 and increased expression of IL-2.

With the identification of CRBN as an IMiD-binding protein, studies were performed to determine whether either CRBN mRNA or protein levels could be used as a predictive biomarker. Gene expression profiling studies failed to show differences in CRBN expression levels between normal or malignant plasma cells [118] and real time PCR studies of bone marrow mononuclear cells did not show differences in CRBN expression [119]. However, these studies did suggest a correlation between CRBN expression and response to IMiD/dexamethasone therapy [118, 119]. It should be noted that the interpretation of CRBN expression studies is complicated by multiple factors: 1) the presence of alternative splice variants of CRBN mRNA, 2) CRBN gene expression and CRBN protein levels do not appear to correlate with each other, and 3) the CRBN gene is located on chromosome 3, and chromosome 3 trisomy is a common feature of hyperdiploidy [120]. Thus currently there is insufficient evidence to support the use CRBN expression as predictive biomarker. While very low IKZF1 expression has been reported to be associated with lack of responsiveness to IMiD therapy in refractory patients treated with pomalidomide and dexamethasone [113], further validation of IKZF1 expression as a biomarker is also needed.

X-ray crystallography studies have provided additional insight into how IMiDs interact with CRBN. A crystal structure of human CRBN in complex with DDB1 and lenalidomide revealed that the IMiD-binding site consists of a shallow hydrophobic pocket on the surface of CRBN in which there are three tryptophan residues which interact with the glutarimide ring [121]. Interestingly, in studies involving a resistant cell line, re-expression of wildtype human CRBN restored drug sensitivity, however, expression of either human CRBN with mutations in the key tryptophans or wildtype mouse CRBN could not restore sensitivity [121]. The latter is noteworthy considering prior data which demonstrated that mice are resistant to IMiD-induced teratogenicity. Additional x-ray crystallography studies revealed that thalidomide, lenalidomide, and pomalidomide have almost identical binding modes and affinities for CRBN [122]. Despite this, lenalidomide and pomalidomide more efficiently target IKZF1 and IKZF3 for degradation [114, 115, 120]. This difference is thought to be due to the solvent-exposed C4 aniline functionality shared by lenalidomide and pomalidomide, as adding small functional groups to C4 of thalidomide improved IKZF1 degradation [122]. Consistent with prior *in vitro* experiments [123], the crystallography studies also revealed that the IMiD-binding pocket favors the (*S*)-enantiomer over the (*R*)-enantiomer [122]. Finally, these studies also confirmed the inherent complexity of the effects of IMiDs by demonstrating that IMiDs can block endogenous substrates such as MEIS2

from binding the CUL4-RBX1-DDB1-CRBN complex while IKZF1 or IKZF3 are being recruited, thus revealing that IMiDs can both upregulate and downregulate ubiquitination [122].

While it is clear that IKZF1 and IKZF3 are important players in mediating the effects of IMiDs, it should also be noted that in work by Zhu et al., 46 different CRBN-binding proteins were identified as being decreased following lenalidomide treatment [113]. Notably, gene expression profiling studies have revealed that lenalidomide treatment induced at least a two-fold change in expression of 1200 genes (600 upregulated and 600 downregulated) in a myeloma cell line [110]. In contrast, lenalidomide treatment of cells made resistance to the drug by knocking down CRBN expression results in the upregulation of 150 genes and downregulation of 30 genes, suggesting the existence of non-CRBN-mediated pathways [118].

There remain a number of unanswered questions regarding the current understanding of the IMiD-CRBN-IKZF1/3 axis and its relationship to clinical observations, including the synergy of IMiDs and PIs, the different side effect profiles and resistance patterns of the IMiDs. *In vitro* studies have demonstrated that pre-treatment with the PI MG132 prevents lenalidomide-induced downregulation of IKZF1/3 [115, 120], consistent with the dependence of IMiDs on proteasomal activity. However, clinically it is established that the combination of an IMiD and a PI (along with a corticosteroid) induce better responses than doublet therapy and can at least partially overcome the adverse outcomes associated with high-risk cytogenetic features [30, 59, 68, 70, 80]. It remains to be determined whether this seeming paradox can be explained by selective activity of the clinically used PIs or whether there are other factors at play. With respect IMiD cross-resistance, patients who have previously been exposed to thalidomide have a lower overall response rate to lenalidomide/dexamethasone than thalidomide-naïve patients [124] and approximately 30–47% of patients who are refractory to lenalidomide respond to pomalidomide/dexamethasone [76, 125]. There are some data which suggest that resistance to lenalidomide can be overcome by concurrent administration of thalidomide and lenalidomide [126]. In aggregate these findings would suggest that these drugs interact with CRBN in different ways leading to differential downstream effects and/or that there are other relevant targets.

7. IMiDs and monoclonal antibodies

The immune-modulating properties of the IMiDs include the potentiation of monoclonal antibody therapy. This was first noted in a mouse model of lymphoma where synergistic activity was observed between the anti-CD20 antibody rituximab and lenalidomide or pomalidomide [127]. *In vivo* depletion of NK cells abrogated this effect [127]. One report showed that lenalidomide enhances NK cell and monocyte-mediated antibody-dependent cellular cytotoxicity (ADCC) of rituximab-treated CD20-positive lymphoma cell line cells [128]. Lenalidomide in combination with SGN-40, an anti-CD40 antibody, enhanced direct apoptosis and ADCC against primary CLL cells, presumably as a consequence of lenalidomide-induced upregulation of CD40 expression on CLL cells and activation of NK cells [129]. Subsequently, the clinical efficacy of lenalidomide and rituximab has been

demonstrated in both indolent and aggressive B-cell lymphomas as well as CLL [130–136]. In some cases, lenalidomide appears to overcome rituximab resistance [137, 138].

Lenalidomide appears to augment NK cell activity via a variety of mechanisms. Lagrue et al. reported that lenalidomide lowers the threshold for NK cell activation and increases the amount of IFNγ production in stimulated cells [139]. Examination of immune synapses revealed that lenalidomide increases the area of the actin mesh which can be penetrable to vesicles containing IFNγ [139]. Of note, pomalidomide had previously been demonstrated to reorganize the actin cytoskeleton via modulation of Rho GTPase activity [140]. Fionda et al., reported that IMiDs enhance the expression of NK cell activating receptor ligands MICA and PVR/CD155 in malignant plasma cells, thereby enhancing the recognition of the plasma cells by the NK cells [141]. This mechanism is dependent on IMiD-induced degradation of IKZF-1/IKZF-3 and IRF4 [141]. Interestingly, the ability of lenalidomide to stimulate NK cell activity has been reported to be diminished by concurrent dexamethasone treatment [142]. Due to its ability to stimulate cytokine production and enhance ADCC activity, lenalidomide has been studied in combination with cetuximab for colorectal and head and neck cancer [143, 144].

In myeloma, lenalidomide has been combined with a number of monoclonal antibodies, including elotuzumab, daratumumab, isatuximab, pembrolizumab, and an anti-KIR antibody [145]. Elotuzumab is a monoclonal antibody targeting SLAMF-7 (CS1), a cell surface glycoprotein which is expressed on plasma cells and to a lesser extent NK cells and CD8+ T cells. Preclinical studies demonstrated that elotuzumab enhances NK cell ADCC against myeloma cells [146, 147]. Although elotuzumab was subsequently determined to lack activity as a single agent in relapsed/refractory myeloma [148], it did show efficacy in combination with lenalidomide and was recently FDA-approved for relapsed/refractory disease [65, 69]. Daratumumab is an anti-CD38 monoclonal antibody which induces myeloma cell death via a variety of mechanisms including ADCC, antibody-dependent cellular phagocytosis, apoptosis, and inhibition of CD38 enzymatic activity [149, 150]. While daratumumab has impressive single agent activity in heavily treated relapsed/refractory patients (overall response rates of 29–36%) [151, 152], recent studies have demonstrated even better activity when combined with either lenalidomide [66, 153] or pomalidomide [85]. Of note, daratumumab has recently been demonstrated to have its own immune modulatory effects related to depletion of CD38-positive regulatory T cells and an increase in T-helper cells, cytotoxic T cells, and T-cell receptor clonality [154] and further studies are needed to understand how these effects are modulated by co-treatment with an IMiD. Isatuximab is another anti-CD38 monoclonal antibody [155, 156] with single agent activity (ORR ~30%) and also has activity when used in combination with lenalidomide (overall response rate of 50%) [157]. There has also been interest in combining IMiDs with checkpoint inhibitor therapy, including pembrolizumab, an anti-PD-1 antibody. While single agent activity in myeloma has not been reported, studies have been performed combining this agent with either lenalidomide [67] or pomalidomide [86] and have shown impressive activity in patients with heavily treated disease.

8. IMiDs and thrombosis

Although patients with myeloma have an increased risk for both venous and arterial thrombotic events [158, 159], this risk is further increased by the IMiD therapy. While the incidence of venous thromboembolic events (VTE) was generally less than 5% in studies using thalidomide as monotherapy, the addition of dexamethasone significantly increased the risk (8–26%) (reviewed in [160]). This risk was even greater when thalidomide was added to traditional chemotherapy agents, particularly anthracyclines (6–58%) (reviewed in [160]). In initial studies involving lenalidomide with dexamethasone without the use of thromboprophylaxis, the rates of VTE were 8–75% ((reviewed in [160]). Subsequently, studies began to routinely incorporate thromboprophylaxis, including aspirin [54, 161–165]. In a phase III study involving previously untreated patients receiving thalidomide-containing regimens, patients were randomized to receive aspirin (100 mg/day), low-dose warfarin (1.25 mg/day), or enoxaparin (40 mg/day) [166]. Serious thromboembolic events, acute cardiovascular events or sudden death in the first six months were observed in 6.5% of patients, with no statistically significant differences between the treatment groups. Another phase III study compared low-dose aspirin to low-molecular weight heparin (LMWH) in newly diagnosed patients receiving lenalidomide/dexamethasone induction and melphalan/prednisone/lenalidomide consolidation [163]. The incidence of VTE was 2.27% with aspirin and 1.20% with LMWH. There is limited data for VTE risk associated with pomalidomide as almost all studies have included thromboprophylaxis, however a phase I study of pomalidomide in patients with relapsed/refractory disease, 4/24 patients (17%) developed VTE [167]. Aspirin has now become the standard of care for patients receiving IMiD therapy without other risk factors for VTE, while for those patients at higher risk, LMWH or full-dose warfarin therapy is recommended [168].

Proposed mechanisms underlying the IMiDs pro-thrombotic effects include changes in thrombomodulin levels, transient elevations in factor VIII and von Willebrand factor, and protective effects on endothelial cell PAR-1 expression following exposure to cytotoxic agents [169–171]. Interestingly, there are data which suggest that the addition of bortezomib to IMiD therapy lowers the risk of thrombosis [172]. The mechanisms underlying these observations are as yet fully identified, however, bortezomib has been shown to have an inhibitory effect on platelet aggregation [173].

9. IMiDs and second primary malignancies

In 2010, two large randomized studies investigating lenalidomide as maintenance therapy post-ASCT reported an increased rate of second primary malignancies (SPMs) in patients receiving lenalidomide compared with placebo. Attal et al. [174] reported a SPM incidence of 2.6% in the lenalidomide group vs. 0.04% in the placebo group while McCarthy et al. [175] reported incidences of 2.6% vs. 1.7%, respectively. In addition, a non-transplant trial conducted by Palumbo et al. [176] reported an incidence of 8% in the arm which contained lenalidomide in both induction and maintenance as compared with 6% in the arm which contained lenalidomide in the induction phase only and 3% in the arm which did not contain lenalidomide. With longer follow-up, the CALGB 100104 study reported that the cumulative incidence risk of SPM was greater in the lenalidomide arm than in the placebo arm

(p=0.005) with a total of 14 (6.1%) hematological malignancies and 11 (4.8%) solid tumors in the lenalidomide arm compared with 3 (1.3%) and 5 (2.2%) in the placebo arm [177]. The most recent update of the Attal study reported a total of 20 (6.6%) hematological malignancies and 24 (7.8%) solid tumors in 35 patients in the lenalidomide arm and 6 (1.9%) hematological malignancies and 11 (4.8%) solid tumors in 20 patients in the placebo arm [178]. While the majority of the hematologic SPMs noted in the CALGB 100104 and IFM 2005–02 studies were MDS/AML, there have also been B-cell acute lymphoblastic leukemia (ALL) cases, including on 5 on CALGB 100104 and 3 on IFM 2005–02 [177, 178].

Determining the extent to which factors such as IMiD therapy, alkylator therapy, transplant, or the underlying myeloma contribute to the SPM risk is an area of active investigation. Multiple studies have observed an increased risk of hematological malignancies in patients with myeloma, pre-dating the era of novel agents. In a retrospective cohort study in Asian patients, the incidences of SPM in 3970 newly diagnosed myeloma patients and 15880 patients without myeloma were compared and although the overall incidence of SPM in myeloma patients was not statistically significantly different from that of the control group, the incidence of hematological malignancies was 11-fold greater [179]. A SEER database analysis of myeloma cases between 1973–2008 showed an overall lower risk of breast, prostate, and colon cancers but a higher risk of hematological malignancies (particularly AML) [180]. A Swedish cancer registry study demonstrated an 11-fold increase in the incidence of AML/MDS in myeloma patients [181]. Of note, an 8-fold increase in the incidence of AML/MDS was observed in MGUS patients who would not have received chemotherapy. These studies suggest that patients with plasma cell disorders have a predisposition to myeloid disorders, possibly due to an intrinsic defect in the hematopoietic system.

Several studies have demonstrated that ASCT is associated with an increased risk of SPM. A retrospective cohort study examined the risk of SPM after ASCT for myeloma and found an overall cumulative incidence of 5.3% at 5 years and 11.2% at 10 years (excluding non-melanoma skin cancers) [182]. In an analysis of 4161 myeloma patients in the Center for International Blood and Marrow Transplant Research database who underwent ASCT between 1990–2010 (prior to the routine use of lenalidomide maintenance), an increased incidence of AML and melanoma were observed (observed/expected ratios of 5.19 (p=0.0004) and 3.58 (p<0.0001), respectively) [183].

An association between prolonged use of melphalan for the treatment of myeloma and the development of acute myeloid leukemia (AML) was first noted in the 1970's [184–186]. More recently conducted studies involving IMiDs and melphalan have been reported the incidence of SPMs. The ECOG E1A06 study randomized newly diagnosed transplant ineligible patients to MPT (melphalan, prednisone, thalidomide) vs MPR (melphalan, prednisone, lenalidomide). The incidence rate (per 100 person-years) was 3.46 in the MPT arm and 2.01 in the MPR arm with 10 hematologic SPMs in the MPT arm and 4 in the MPR arm [164]. The higher hematologic SPM rate in the thalidomide arm was attributed to the MPT regimen having a higher melphalan dose (9 mg/m^2) than the MPR regimen (5 mg/m^2).

HOVON87/NMSG18 also compared MPT to MPR in newly diagnosed transplant ineligible patients [187]. The numbers of patients with SPMs were not significantly different between the two groups (28 in the MPT arm and 39 in the MPR arm (p=0.37)), and when non-melanoma skin cancers were excluded, the incidence rates were 2.9 (MPT) and 2.1 (MPR) per 100 patient-years (p=0.34). In the FIRST trial, MPT was compared with lenalidomide/dexamethasone (continuous vs 18 cycles) in newly diagnosed transplant-ineligible patients. The incidence of SPMs was 3% in patients on continuous lenalidomide/dexamethasone, 6% in the 18 cycle group, and 5% in the MPT group [188]. There were more hematologic cancers in the MPT arm (12 cases, 2%) than in the lenalidomide/dexamethasone arms (2 cases (<1%) in each arm).

In a pooled analysis of 2459 newly diagnosed patients from 9 European Myeloma network trials, the cumulative incidence of SPM at 3 years was 2.0% for patients who had received lenalidomide and alkylator therapy and 1.1% for those who had not received lenalidomide [189]. Overall, however, the incidence of SPMs was lower than expected and the cumulative incidence of death from myeloma was lower in the group which received lenalidomide (13.8% vs. 26.1%). Another pooled analysis of 11 clinical trials involving lenalidomide and relapsed/refractory myeloma showed an overall incidence rate of SPM of 3.62, but when non-invasive skin cancers were excluded this rate dropped to 2.08 and was comparable to the expected rate of older adults using SEER data [190]. An analysis of 703 patients from the MM-009 and MM-010 phase III trials revealed an SPM incidence rate of 3.98 in the lenalidomide-dexamethasone arms vs. 1.88 in the placebo/dexamethasone arms [190]. However, when non-melanoma skin cancers were excluded, there was not a significant difference in rates between the treatment arms or compared to the expected age-specific incidence rates [190]. An analysis of the Arkansas TT2 (+/− thalidomide) and TT3A/B (TT3A included thalidomide as part of the maintenance regimen, TT3B included lenalidomide as part of the maintenance regimen) trials found no difference in the development of SPMs between the two TT3 trials. In the TT2 arms a trend towards an increased risk of solid tumor SPMs was noted in the thalidomide arm (p=0.31) as well as a trend towards a decreased risk of hematologic malignancies[191].

A meta-analysis of more than 3000 patients from seven trials investigating lenalidomide in newly diagnosed patients showed a cumulative 5-year incidence of 6.9% in patients who received lenalidomide vs. 4.8% in patients who had not (p=0.037) [192]. The increased risk associated with lenalidomide was due to hematological malignancies (3.1% vs. 1.4%, p=0.029) and not solid tumors. Exposure to lenalidomide and oral melphalan was associated with an increased risk of hematological SPMs while exposure to lenalidomide and intravenous melphalan, cyclophosphamide, or dexamethasone were not. This study also noted that the cumulative incidences of death due to myeloma or treatment-related events were higher than those due to SPM. An analysis of patients who had had long-term lenalidomide exposure in the context of the BiRD (clarithromycin, lenalidomide, dexamethasone) regimen showed that SPM development was not associated with age, ASCT history, or length of lenalidomide therapy [193]. Furthermore, the incidence of SPM was not significantly different than what was expected based on SEER data (2.85 vs 2.1 per 100 person-years). In a retrospective cohort study of myelodysplastic syndrome (MDS) patients, lenalidomide was not associated with an increased risk of SPM or transformation to AML

[194]. Finally, a recent report of lenalidomide with rituximab and bendamustine as first line therapy for elderly mantle cell lymphoma patients showed a higher number of SPMs than expected, with 9 SPMs in 8 patients (16%) including 2 hematologic and 5 solid tumors [195].

In aggregate these studies demonstrate an increased risk of SPM with lenalidomide, primarily in the post-transplant maintenance setting in a patient population which has an inherent risk of SPM due to the underlying myeloma as well as the transplant and melphalan exposure. This increased risk with lenalidomide is small and generally appears to be out-weighed by the benefit of lenalidomide on overall survival. There is significantly less evidence for an association between thalidomide and SPMs and data are lacking for pomalidomide. Further research is required in order to determine the molecular mechanisms underlying the association between lenalidomide and SPMs. It is interesting to note that loss of IKZF1 has been linked to high-risk B-ALL [196, 197], and whether IMiD-induced changes in IKZF1 might contribute to development of B-ALL remains to be determined.

10. Summary

The IMiDs have made a profound difference in the treatment of multiple myeloma and contributed significantly to the understanding of the pathophysiology of the disease. IMiDs remain the backbone of therapy for both newly diagnosed and relapsed disease and are continuing to be incorporated with new therapeutic strategies, many of which themselves have immune modulating activity. Clinical experience with the IMiDs in myeloma over the past several decades has led to a refinement in steroid dosing, the incorporation of thrombotic prophylaxis, a deeper awareness of the risk of SPMs in this patient population and an appreciation for the synergy between this class of drugs and other key therapies, including PIs and monoclonal antibodies. There is clearly further work to be done in order to fully understand the mechanisms by which IMiDs act in myeloma, to better guide treatment decisions, to understand resistance patterns, and to allow for further drug development targeting these pathways.

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Key Points

- The immunomodulatory drugs (IMiDs), including thalidomide, lenalidomide, and pomalidomide, have contributed to the marked improvement in outcomes for patients with multiple myeloma.
- IMiDs have pleiotropic effects on myeloma cells and other immune cells.

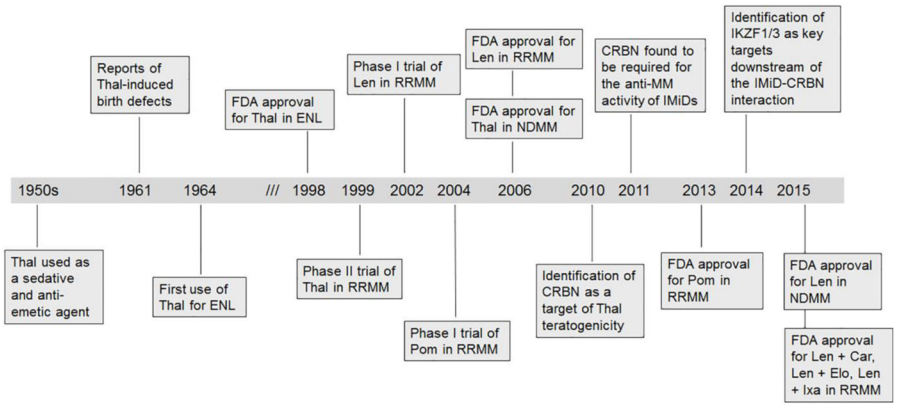


Figure 1.

Key events in the development of the IMiDs for the treatment of myeloma. Abbreviations: Car, carfilzomib; Elo, elotuzumab; ENL, erythema nodosum leprosum; Ixa, ixazomib; Len, lenalidomide; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; Pom, pomalidomide; RRMM, relapsed/refractory multiple myeloma; Thal, thalidomide.

Table 1

Pharmacological properties of the IMiDs.

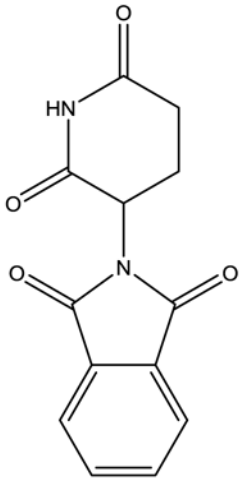
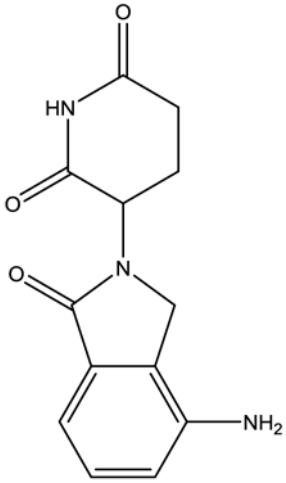
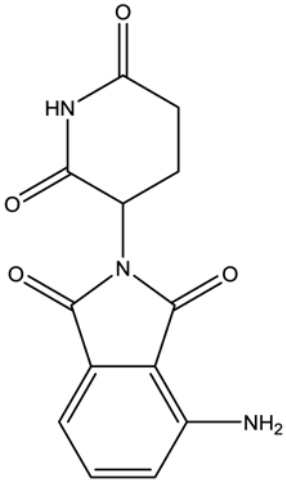
	Thalidomide	**Lenalidomide**	**Pomalidomide**
Structure			
Daily dosage (mg)	50–200	2.5–25	1–4
Half-life (hrs)	5.5–7.3	3–5 (3-fold increase with moderate/severe renal impairment)	7.5–9.5
Renal dosing	No adjustments needed	Adjustments recommended for CrCl <60 mL/min	Adjustments recommended for patients requiring dialysis (at least 25% reduction)
Liver metabolism	Minimal	Minimal	CYP1A2 (major), CYP2C19 (minor), CYP2D6 (minor), CYP3A4 (major)
Excretion	~90% in the urine (<4% as unchanged drug)	~80% in the urine as unchanged drug	~70% in the urine (2% as unchanged drug)
Side effects	Sedation, constipation, neuropathy, muscle weakness	Myelosuppression, fatigue, diarrhea/constipation, muscle cramps	Myelosuppression, fatigue, diarrhea/constipation
Non-myeloma FDA-labeled indications	Erythema nodosum leprosum	Del 5q myelodysplastic syndrome Mantle cell lymphoma	
Non-FDA-labeled indications	Behcet's syndrome Chronic graft vs host disease Lupus erythematosus Systemic mastocytosis Waldenstrom macroglobulinemia	Chronic lymphoid leukemia Light chain amyloidosis Myelofibrosis Waldenstrom macroglobulinemia Non-germinal center diffuse large B cell lymphoma	Light chain amyloidosis Myelofibrosis Kaposi sarcoma

Table 2

Summary of randomized phase III trials comparing lenalidomide/dexamethasone to lenalidomide/dexamethasone/novel agent in relapsed/refractory myeloma

Novel Agent	Patients with prior lenalidomide exposure (%)	Number of prior therapies	High-risk cytogenetics (%)	Response rates (%) (triplet vs doublet)	PFS (mos) (triplet vs doublet)	OS (triplet vs doublet)
Carfilzomib [68]	20	1–3	12–13	87 vs 67 (p<0.001)	26.3 vs 17.6 (p=0.0001); hazard ratio 0.69 (p=0.0001)	24 mos: 73% vs 65% (p=0.04)
Daratumumab [71]	18	>1	15–17	93 vs 64 (p<0.001)	Not reached vs 18.4; hazard ratio 0.37 (p<0.001)	Median OS: not reached vs 20.3 mos (p=0.0534)
Elotuzumab [69]	6	1–3	41–42	79 vs 66 (p<0.001)	19.4 vs 14.9 (p=0.014); hazard ratio 0.7 (p<0.001)	Median OS: 43.7 vs 39.6 mos (p=0.026)
Ixazomib [70]	12	1–3	17–21	78 vs 72 (p=0.04)	20.6 vs 14.7 (p=0.012); hazard ratio 0.74 (p=0.01)	Median OS not reached in either arm