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Review

Preclinical and clinical results with pomalidomide in the treatment of relapsed/refractory multiple myeloma

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ABSTRACT

Despite the evolution of effective frontline treatment strategies, many patients with myeloma inevitably relapse. Treatment can be complicated by the interplay of disease-, treatment-, and patient-related factors. Unfortunately, many patients eventually develop disease that is refractory to lenalidomide and bortezomib and have few treatment options. Pomalidomide is a distinct IMiD® agent recently approved in the US and Europe. We review the pomalidomide mechanism of action, summarizing its direct antimyeloma, immunomodulatory, and stromal-support inhibitory activities. We also detail its clinical development, including establishment of the approved dose/schedule, phase 2 and 3 trials in relapsed and refractory patients, and novel pomalidomide-based combinations.

Contents

1. Introduction

Multiple myeloma (MM) is a panoply of clinically, molecularly, and biologically distinct B-cell neoplasms that primarily affect the elderly [1,2]. The introduction of novel therapeutic agents and autologous stem cell transplantation during the past decades has improved the overall survival (OS) of young and medically fit patients with MM [3,4]. Continuous therapy, consolidation strategies, as well as the use of novel combinations have extended first-line response durations to 4–5 years [5–8]. However, despite these advances, the majority of patients with MM will eventually relapse [3,4]. Additionally, with each successive therapy, response durations become shorter and relapses occur more quickly [9].

Bortezomib, lenalidomide, and thalidomide have become the backbones of most therapeutic regimens for the treatment of MM. However, patients who are intolerant of or refractory to these agents have an extremely poor prognosis and limited treatment options [9]. Specifically, the median OS is only 9 months and the median event-free survival is 5 months for those who are no longer eligible for treatment with lenalidomide or thalidomide and bortezomib [9]. Thus, there is an unmet need for additional therapies that are both active and tolerable.

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Table 1
Summary of pomalidomide mechanism of action.

Effect	Mechanism
Direct antimyeloma	
Gene regulation	– Downregulation of IRF4 [21–23]
Apoptosis	– Activation of caspase 8 [24]
Cell-cycle arrest	– Induction of $p21^{WAF-1}$ and subsequent inhibition of CDK2 and phosphorylation of Rb [23]
Immunomodulatory	
Increased immune cell proliferation	– Increased proliferation of T and NK cells [31–34]
Enhanced immune cell function	– Increased Th1 cytokine production by T and NK cells [31,34,35] – Increased cytokine and chemokine production by DCs [32] – Enhanced NK-cell mediated cytotoxicity [33,34]
Immune synapse repair	– T cell immune synapse repair via Rho GTPase activation [36]
Decreased immunosuppression	– Inhibition of Treg proliferation and function [37]
Stromal cell support inhibition	
Osteoclast inhibition	– Decreased production of growth factors including TNF-α and IL-6 [31,38] – Inhibition of transcription factor PU.1 and RANKL production [10,39]
Anti-angiogenesis	– Reduced expression of adhesion molecules that mediate production of growth factors and angiogenic molecules including VEGF [39]

Abbreviations: CDK, cyclin-dependent kinase; DC, dendritic cell; IRF, interferon regulatory factor; NK, natural killer; RANKL, receptor activator for nuclear factor κB ligand; Rb, retinoblastoma; Th, helper T cell; TNF, tumor necrosis factor; Treg, regulatory T cell; VEGF, vascular endothelial growth factor.

Patients with relapsed and refractory MM have likely received multiple lines of therapy and may present with complicated clinical and tumor characteristics. Patient outcomes, as well as quality of life and ultimately treatment choice, are directly affected by the interplay of these factors. Disease-related features include advanced skeletal disease, immune dysfunction, accumulation of additional deleterious cytogenetic features, and response duration to prior therapy [1,10–15]. Previous treatments can affect patients by contributing to immune suppression, and to the development of peripheral neuropathy, osteoporosis, and muscle loss [13,16,17]. Patients may also be affected by diabetes and its related comorbidities, renal insufficiency, an inability to tolerate full-dose therapy, and burdens associated with travel to the center [18]. These issues need to be considered when managing patients with relapsed and refractory MM.

This review will discuss the mechanism of action and clinical profile of pomalidomide—a member of a group of drugs called IMiD® immunomodulatory agents (which includes lenalidomide; Celgene Corporation) which was recently approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of relapsed/refractory MM.

2. Pomalidomide mechanism of action

Pomalidomide is a distinct IMiD immunomodulatory agent with a tumoricidal mechanism of action consisting of direct antimyeloma, immunomodulatory, and stromal-support inhibitory effects (Fig. 1) [19,20]. These activities are summarized in Table 1. The antimyeloma activity of pomalidomide occurs through several mechanisms: gene regulation, apoptosis, and cell-cycle arrest. Pomalidomide upregulates expression of the tumor suppressor protein $p21^{WAF-1}$ and downregulates expression of a critical oncogenic protein, interferon regulatory factor 4, in MM cells [21–23]. Induction of $p21^{WAF-1}$ inhibits cyclin-dependent kinase 2 activity, which leads to phosphorylation of the retinoblastoma protein, and then results in cell-cycle arrest at the G1 phase [23]. Interferon regulatory factor 4 is a critical survival factor for MM cells, and its downregulation by pomalidomide may increase the sensitivity of MM cells to treatment [22]. Additionally, pomalidomide induces MM cell apoptosis via the activation of caspase 8 [24]. Relapsed MM patients often have disease that is resistant, or refractory, to previously used antimyeloma therapies. Importantly, pomalidomide retains antiproliferative activity in MM cell lines resistant to the chemotherapeutics melphalan and doxorubicin as well as dexamethasone and lenalidomide [25–27]. The combination of dexamethasone and pomalidomide has been shown to be synergistic in vitro and to significantly enhance the activity of pomalidomide in lenalidomide-refractory MM cells [28]. These in vitro data provided the rationale for clinical trials investigating pomalidomide for the treatment of patients with MM who have received multiple lines of therapy.

As mentioned previously, immune suppression is an important aspect of MM pathophysiology. Therapies that enhance the antitumor effects mediated by T and natural killer (NK) cells, in addition to restricting tumor growth, may prolong remissions [29,30]. Complementary to its antiproliferative activity against MM cells, pomalidomide enhances the function and proliferation of immune cells, including T cells, NK cells, and dendritic cells [31–34]. The most thoroughly investigated area of this immune-enhancing function has been the effects of pomalidomide on T cells. Pomalidomide enhances the production of T helper 1 cytokines, which are critical for effective antitumor immune responses [31,35]. Pomalidomide induces Rho GTPase activation and improves the formation of T-cell immune synapses, which are the structural and signaling bonds between 2 immune cells that are critical for effective immune cell activation [36]. Pomalidomide has also been shown to decrease the proliferation of and inhibitory function of regulatory T cells, which normally suppress the function of immune cells [37]. These data suggest that the enhancing effects of pomalidomide on T and NK cells may directly contribute to antitumor immune responses.

Stromal cell support of MM cells through both soluble factors and direct cell–cell interactions with the bone marrow stroma is implicated in MM progression and the development of drug resistance [25]. Additionally, osteoclasts in the bone marrow microenvironment mediate osteolytic bone disease. Pomalidomide treatment has been shown to decrease production of soluble growth factors, including tumor necrosis factor α and interleukin 6, through direct effects on cells such as monocytes and stromal cells [31,38]. Additionally, pomalidomide reduces the expression of adhesion molecules that mediate the production of growth factors and angiogenic molecules, including vascular endothelial growth factor [39]. Pomalidomide has been demonstrated to inhibit angiogenesis in a variety of models [32,40,41]. In vitro data suggest that pomalidomide may affect osteolytic bone disease in patients with MM because it inhibits osteoclast formation through inhibition of the transcription factor PU.1 and RANKL production [10,39]. These data demonstrate that pomalidomide affects multiple aspects of MM stromal support.

Cereblon (CRBN), a recently identified E3 ubiquitin ligase component, has been identified as a direct protein target of pomalidomide, lenalidomide, and thalidomide. Initially identified as the mediator of thalidomide teratogenicity in a zebrafish model, CRBN has been shown to form an E3 ubiquitin ligase complex with CUL4, DDB1, and Roc1 [42]. Subsequent studies have shown that CRBN mediates many of the antimyeloma and immunomodulatory effects of pomalidomide [27,43]. In a zebrafish model, expression of a mutant CRBN protein that is unable to bind thalidomide attenuates the teratogenic effects of thalidomide on embryo development. CRBN directly binds to thalidomide as well as to lenalidomide and