Journal of Blood Transfusions and Diseases
JBTD, 3(1): 136-143
www.scitcentral.com

ISSN: 2641-4023

Review Article: Open Access

Immunomodulatory Drugs and Plasmacytoid Dendritic Cells: Cooperation in Multiple Myeloma Treatment

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Received April 13, 2020; Accepted April 17, 2020; Published April 27, 2020

ABSTRACT

Multiple myeloma (MM) is characterized by immune dysfunctions including defective dendritic cell (DC) and T cell functions, which are associated with poor clinical outcomes. Therefore, drugs that improve the immune status are considered as effective therapeutic strategies for MM. Lenalidomide (LEN), as an immunomodulatory drug (IMiD), is an important backbone drug for MM treatment to quantitatively and qualitatively enhance several immune cell types. Plasmacytoid DCs (pDCs) represent a major source of type-I interferons (IFNs) that not only directly induce cell arrest, but also activate immune effectors to induce clearance of pathological cells in protective anti-tumor and anti-viral immunities. Some functions of IFNs overlap with those of IMiDs. Thus, pDCs are an important cellular component for recovery of the immune status by MM therapy using IMiDs. This review focuses on the immunological link between IMiDs and pDCs in the immune dysfunctions of MM. pDCs are localized frequently in bone marrow (BM) of MM patients and BM-infiltrating pDCs display unfavorable functions to prolong survival of MM cells by their reduced ability to promote T-cell proliferation in the BM milieu. However, CpG-oligodeoxynucleotide (ODN) stimulation, while triggering the IFN response, restores T-cell responses of pDCs and represses MM cell growth. Proteasome inhibitor bortezomib suppresses type-I IFN production by pDCs. Moreover, non-uniformity of LEN functions against pDCs in recent reports might be attributed to different experimental settings. However, LEN at the clinical concentration range might not, at least, inhibit strongly, but sustain the ability of pDCs to produce type-I IFNs in MM treatment. These effects may explain the low incidence of herpes zoster viral infection observed during LEN treatment compared with bortezomib treatment. IMiDs orchestrate the activities of wide varieties of immune cell types, including sustaining pDC functions, thereby leading to amplification of a positive-immune axis to eliminate MM cells.

Keywords: lenalidomide, Pomalidomide, IMiDs, Plasmacytoid DCs, Type-I IFNs, Multiple myeloma

Abbreviations: MM: Multiple myeloma; DCs: Dendritic cells; IMiDs: Immunomodulatory-drugs; LEN: Lenalidomide; POM: Pomalidomide (POM); pDC: Plasmacytoid dendritic cells (pDCs); CTL: Cytotoxic T lymphocytes, NK: Natural killer; IFN: Interferons; BM: Bone marrow; Tregs: Regulatory T cells; IL: Interleukin (IL); PBMC: Peripheral blood mononuclear cells; TLR: Toll-like receptor; PFS: Progression-free survival (PFS); OS: Overall survival

INTRODUCTION

Multiple myeloma (MM) is a multistep malignancy of plasma cells in bone marrow (BM), leading to bone destruction, renal dysfunction and disruption of normal BM functions reflected by anemia. MM is generally regarded as incurable. However, treatment of MM has been evolving with the introduction of new drugs such as immunomodulatory drugs (IMiDs), including lenalidomide (LEN) and pomalidomide (POM), proteasome inhibitors and antibody drugs. Thus, the 5-year survival rate has increased gradually because of new drug development over the last decade.

MM is characterized by immune dysfunctions, including defective dendritic cell (DC) and T cell functions, which are associated with poor clinical outcomes.

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Citation: Ito T. (2020) Immunomodulatory Drugs and Plasmacytoid Dendritic Cells: Cooperation in Multiple Myeloma Treatment. J Blood Transfusions Dis 3(1): 136-143.

IMiDs enhance a wide variety of immune cell types quantitatively and qualitatively and are important backbone drugs for MM treatment. Plasmacytoid DCs (pDCs) represent the major source of type-I interferons (IFNs) that not only directly induce cell cycle arrest, but also activate immune effectors to eliminate pathological cells in protective anti-tumor and anti-viral immunities. Because some functions of type-I IFNs overlap with those of IMiDs, pDCs are an important cellular component as an additional cellular target of IMiDs for recovery of the immune status by MM therapy. This review focuses on pDC functions in the immune dysfunctions of MM and immunological cooperation of IMiDs and pDCs in MM treatment.

MM involves immune dysfunctions

MM is characterized by immune dysfunctions [1-3]. Aberrant production and release of monoclonal proteins from MM cells into the bloodstream and urine causes reduced normal immunoglobulin secretion and increased susceptibility to infection. In terms of other cellular functions, reduced T-cell immunity has been reported during MM disease progression [4,5], such as an increased number of regulatory T cells (Tregs) associated with poor clinical outcomes [6,7]. PD-L1 and PD-1 expression are increased in MM cells and immune effector cells [i.e., cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells], respectively, in MM patients [1,8]. In addition, DCs are pivotal in orchestrating both innate and acquired immunities as a commander of the immune regulatory system and a series of analyses have clarified the functional plasticity of DCs to induce Th1 or Th2 response. Recent studies have demonstrated several defective immunological properties in DCs of MM patients with a lack of CD80 and CD86 molecules, functional inability of antigen presentation, and accumulation of both immature and inactivated DCs in BM [2,3]. Other mechanisms lead to tumor escape and immune tolerance, which are apparently dependent on high release of transforming growth factor-β, interleukin (IL)-10, IL-6, vascular endothelial growth factor, and FAS/FASL in the myeloma BM environment, resulting in DC dysfunction in T-cell activation and proliferation [9]. These findings explain, at least in part, the defective immune functions in MM patients, which are associated with a poor prognosis.

Functions of plasmacytoid DCs in MM patients

In humans, DCs consist of two major subsets: $CD11c^+$ myeloid DCs and pDCs. They play distinct roles in innate and acquired immunities by their expression of specialized cytokines and molecules.

Although the essential function of DCs is to prime naïve and memory T cells to differentiate into inflammatory Th1, Th2, or Th17 cells in acquired immunity, pDCs paradoxically have an intrinsic capacity to prime naive T cells to differentiate into IL-10-producing Tregs at a mature stage [10]. pDCs suppress inflammatory responses against pathogens [11] and allergens [12] and promote oral tolerance [13] and engraftment of hematopoietic stem cells [14] as well as vascularized grafts [15]. Immunosuppressive effects of tumor-infiltrating pDCs have been demonstrated in solid tumors [16,17] and pDC infiltration correlates with poor clinical disease outcomes of breast cancer [18]. Furthermore, among hematopoietic malignancies, chronic myeloid leukemia patients with high $CD86^+$ pDC counts have a higher risk of relapse after treatment discontinuation [19]. Additionally, in MM patients, pDCs induce growth and prolong survival of MM cells in the milieu of pathological BM [20]. Thus, pDCs have been implicated in contribution, at least in part, to immune dysfunctions due to the reduced ability of pDCs to induce T cell proliferation in BM [20] and peripheral blood [21] of MM patients.

In addition to the antigen-presenting function in acquired immunity, pDCs have a unique aspect as a type-I IFN-producer in innate immunity. Although they comprise only a small fraction of peripheral blood mononuclear cells (PBMCs), pDCs represent a major source of type-I IFNs in the blood and lymphoid tissues of both humans and mice [22,23]. Human pDCs respond to viral infection through their selective expression of toll-like receptor (TLR)7 and TLR9 [24], which sense viral RNA and DNA, respectively, and dedicate a large proportion of their transcriptional machinery to producing type-I IFNs [25]. Accumulating evidence suggests that type-I IFNs enhance immune effector cells [26-28], leading to enhancement of the entire immune system including CTLs, NK cells, neutrophils, and monocytes. Thus, pDCs exert protective anti-viral inflammatory effects through secretion of vast amounts of type-I IFNs that not only directly inhibit viral replication, but also activate an immune network of cytotoxic effector cells to induce clearance of infected cells. These pDC/type-I IFN-mediated immune processes may contribute to both tumor cell cycle arrest and activation of immune effectors to eliminate several types of malignancies. Indeed, type-I IFNs trigger direct anti-tumor cytotoxicity in B-cell malignancies by inducing apoptosis [29] and inhibit cell proliferation [30,31]. Furthermore, recombinant IFN-α has shown activity against B-cell hematologic neoplasms by immune activation of cytotoxic effector cells [32]. The efficacy of recombinant IFN-α in patients with MM was reported before drug development of IMiDs and proteasome inhibitors [32,33]. Type-I IFN-based maintenance regimens, despite some conflicting results, have also shown some clinical benefits [34]. TLR stimulation by CpG-ODNs to induce large amounts of type-I IFNs restores the *in vitro* T-cell response of pDCs from MM patients and blocks MM cell line growth [20]. In this context, pDCs may be a target of immunotherapy to substitute for recombinant IFN treatment.

Numbers of plasmacytoid DCs in MM patients

The number of immune cells in MM patients has been reported to be small. However, no conclusion has been

reached regarding blood DC numbers in MM patients. One report showed a decreased number of blood pDCs in MM patients compared with healthy donors [21] and pDC depletion with downregulation of the IKZF1 protein level by LEN treatment [35], whereas three other studies found that blood pDC numbers in MM patients were nearly identical to those in normal donors [2,20,36]. Studies have shown that the MM genome is complex, and that MM patients are extremely diverse with genomic heterogeneity [37]. Accordingly, the controversy about the blood pDC numbers in MM patients might be attributed to the fact that all of these studies were conducted with a small number of cases with heterogeneity of the disease status or progression phase.

One of these studies has also evaluated the distribution of pDCs in MM patients [20]. Although there is no significant difference in pDC numbers between BM and peripheral blood in healthy donors, increased pDCs are observed in BM compared with peripheral blood in MM patients. The other possibility for the non-uniformity of the pDC number is migration from blood to BM due to different MM progression phase. Considering the defective function of pDCs in BM of MM patients in regards to the ability for T cell proliferation, frequent localization of pDCs in BM may cause the immune dysfunctions in MM.

IMiDs enhance immune functions

LEN and POM have both direct tumoricidal and indirect immunomodulatory effects. Both drugs are important backbone drugs for MM and continuous treatment with LEN until disease progression confers a survival benefit for MM patients [38]. The immune dysfunctions are associated with a poor prognosis of MM patients and clinical outcomes can be improved by recovery of the immune status [6,7]. Therefore, immunotherapies or drugs that improve the immune status are considered to be effective therapeutic strategies, making IMiDs backbone drugs for MM because of their immunopotentiating activity as described below. LEN has been shown to improve humoral immunity with non-neoplastic globulin recovery in MM patients, especially patients exhibiting with long-term therapeutic benefits [39]. Furthermore, patients with humoral responses improved by LEN have better outcomes of both PFS and OS [39,40]. Considering that myeloma is a malignancy of plasma cells and based on the pathology of humoral immune dysfunction, restoring humoral immunity by IMiDs treatment may improve clinical outcomes.

Studies have revealed a wide array of immune cell types targeted by IMiDs. LEN and POM promote the proliferation of some immune effector cell types *in vivo*. The total percentage of proliferating S-phase $CD4^+$ T cells, $CD8^+$ T cells, and NK cells increases after administration of LEN in MM patients [41]. In addition to this quantitative enhancement, several studies have shown that LEN induces qualitative activation of several immune cell types. For example, LEN augments NK cell cytotoxicity and CTL activity [42-47], and inhibits the proliferation and functions of Treg cells [48,49]. In addition, POM increases cytotoxic effector cells (CTLs/NK cells) quantitatively and qualitatively *in vivo* [50].

Moreover, LEN downregulates PD-L1 on primary MM cells and PD-1 on NK cells and CTLs of MM patients, leading to enhanced immune responses induced by immune checkpoint blockade [1,8]. Thus, the function of IMiDs, which facilitates the attack of MM cells by activated immune effectors, is supported by the elaborate immunostimulatory effect, which is relevant to the treatment of MM patients with immune dysfunctions. Some of these functions in the immune system appear to overlap with IFN functions. Therefore, validating the effect of IMiDs to target the pDC-IFN pathway might be useful and may provide a rationale for the clinical use of IMiDs in MM patients.

IMiDs for plasmacytoid DC functions

There is evidence of immunomodulatory activities of LEN and POM in mouse conventional DCs [47,51] and a synergistic effect of DC vaccination in murine models of MM [52-54] and colon cancer [55]. In this context, DCs would be important cellular components for recovery of the immune status by MM treatment, especially therapy using IMiDs. Several recent studies have elucidated the functions of IMiDs in human DC subsets [35,36,56,57], especially pDCs [20,35,36]. These findings provide new insights into a possible mechanism through which IMiDs operates as a pleiotropic immunomodulator in MM patients.

Cytlak. et al. demonstrated that ikaros family zinc finger 1 (IKZF1) deficiency induces pDC depletion using PBMCs from individuals carrying an IKZF1 mutation [35]. They also reported that the absolute pDC count showed a significant positive correlation with the IKZF1 protein level in MM patients treated with LEN, which induces proteasomal degradation of IKZF1, and that IKZF1 deficiency or LEN treatment induced less secretion of IFN-α by pDCs. They concluded that LEN has a negative effect on pDC functions and differentiation. In contrast, we have recently demonstrated that LEN significantly enhances IFN-α production by pDCs stimulated with low concentrations of CpG-ODN, but not an optimal high concentration [36]. Clinical pharmacokinetics show that clinical peak plasma LEN concentrations of MM patients administered 10 or 25 mg oral LEN are around 1.2 μM (311 ng/mL) and 2.7 μM (714 ng/mL), respectively [58]. The former study showed that IFN-α-producing cell numbers were decreased modestly among pDCs treated with increasing concentrations (0.1, 1 or 10 μM) of LEN. Meanwhile, the latter study showed that 0.1–3 μM LEN (covering the clinical in vivo plasma concentration range of oral LEN administration) did not affect pDC survival, although pDCs were susceptible to the

cytotoxic effects of proteasome inhibitor bortezomib. Moreover, IFN-α production by pDCs in response to CpG-ODN 2216 was not decreased significantly after exposure to a clinical concentration range of LEN (0.01-3 μM).

In the former experimental setting, a TLR agonist cocktail consisting of CpG-ODN, poly (I: C), CL075, and LPS was added to total PBMCs, and then the number of cytokine-producing cells was analyzed by intracellular staining of each cell type [35]. This was a condition under which pDCs were affected by cytokines produced by other cell types, such as IL-10 and TNF. Furthermore, CpG-ODN 2216 was added at a very high concentration of 7.5 uM. In the latter experimental setting, pDCs purified from PBMCs were applied to an IFN-α production assay. In addition, to address the possibility that LEN could not further enhance IFN-α production by pDCs because of exhaustion following maximal CpG-ODN 2216 stimulation, a low and suboptimal concentration of CpG-ODN 2216 (0.1 μM) was examined to stimulate pDCs [36]. Although pDCs rapidly produce vast amounts of type-I IFNs following stimulation by viruses or CpG-ODN [22], pDCs are incapable of mounting a secondary type-I IFN response for further stimulation [25]. In this context, pDCs do not retain a sufficient capacity to further produce type-I IFNs by the maximal response to optimal stimulation. The latter experiments showed that LEN promotes the residual capacity of pDCs to produce IFN-α by suboptimal stimulation. Thus, LEN at a clinical concentration range might, at least, not inhibit strongly, but could possibly sustain the ability of pDCs to produce type-I IFNs in MM treatment.

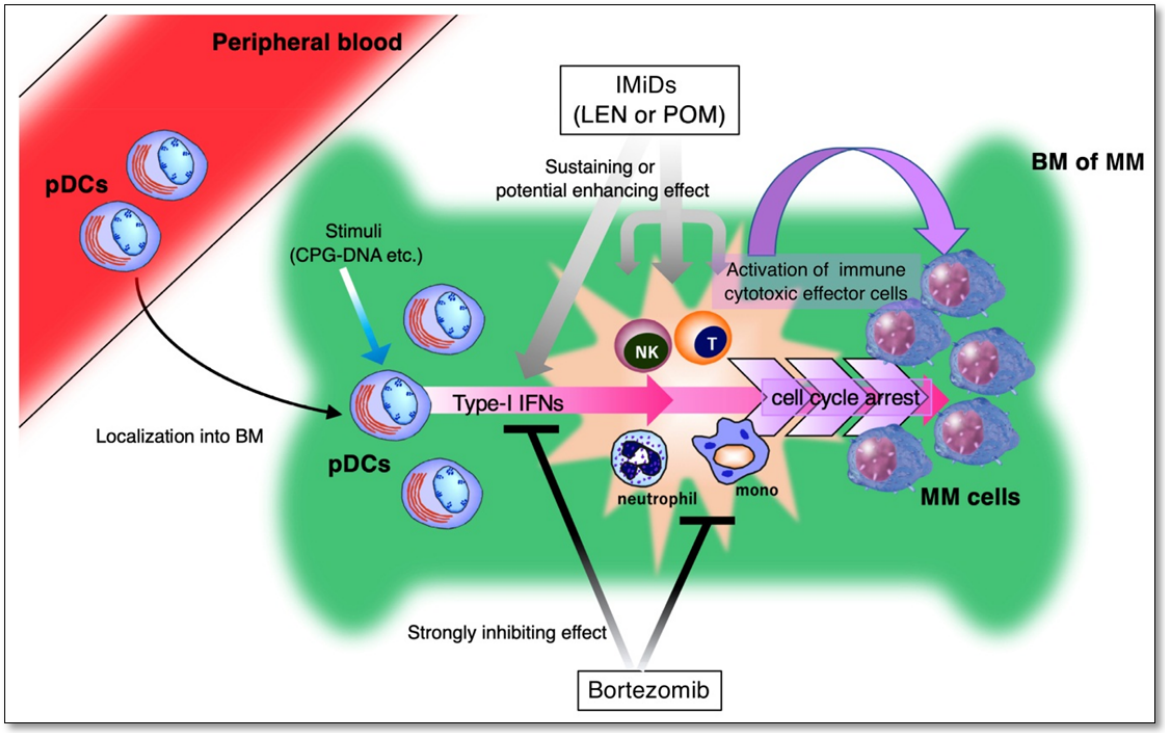

Figure 1. Immune cooperation of IMiDs and pDCs in MM treatment. IMiDs (lenalidomide and pomalidomide) have direct tumoricidal effects, but do not damage pDCs. In addition, IMiDs at a clinical concentration range might not, at least, inhibit strongly, but possibly retain or enhance the ability of pDCs to produce type-I IFNs that not only directly inhibit cell replication, but also activate an immune network of cytotoxic effector cells to eliminate MM cells. The immunomodulatory functions of IMiDs in MM cells might work synergistically with the effect of pDC-derived type-I IFNs to improve the immune status of MM immune dysfunctions. In contrast to IMiDs, proteasome inhibitor bortezomib suppresses immune responses and type-I IFN production by pDCs. Multiple myeloma (MM), dendritic cells (DCs), immunomodulatory drugs (IMiDs), Lenalidomide (LEN), pomalidomide (POM), Plasmacytoid DCs (pDCs), natural killer (NK), interferons (IFNs), bone marrow (BM).

Clinical relevance of IMiDs regarding pDC functions

pDCs as antigen-presenting cells with a tolerogenic function are considered to play a partial role in the immune dysfunctions of MM patients as mentioned above. However, pDCs trigger activation of the immune system as a part of their anti-viral and anti-tumor responses through type-I IFN production. Type-I IFNs and IMiDs appear to have some overlapping functions in the immune system. Thus, immunomodulatory functions of IMiDs in MM cells might

work synergistically to mediate the effect of type-I IFNs to enhance cellular and humoral immunities [42-49]. In this sense, considering the capability of IMiDs to activate immune effectors without strong inhibition of pDC functions or to potentially enhance the ability of pDCs to produce IFN-α by suboptimal stimulation, IMiDs may function as preservers of endogenous IFN and are therefore positive immunomodulators that activate surrounding immune cells in addition to their direct tumoricidal effects (**Figure 1**).

Thus, the immunological link between IMiDs and pDCs may participate in the immune processes in MM during treatment with IMiDs. In contrast to IMiDs, proteasome inhibitor bortezomib has been shown to suppress immune responses and type-I IFN production by pDCs [36, 59-61]. Consistent with the function of IMiDs to preserve endogenous type-I IFNs, there is relatively low incidence of herpes zoster viral infection during LEN treatment compared with bortezomib treatment [62-64]. Continuous treatment with low-dose LEN as a maintenance therapy after stem cell transplantation contributes to better survival of MM patients [65, 66]. The clinical pharmacokinetics of LEN shows a gentle curve from the peak plasma concentration. LEN at 10 mg administered orally to MM patients results in an approximate clinical peak plasma concentration of 1.2 μM [58]. Even at a low concentration (0.1–1.0 μM, equivalent to the clinical plasma concentration range resulting from oral administration of 10 mg LEN), LEN sustains IFN-α production by pDCs [36]. This finding suggests that low-dose LEN (i.e., 10 mg oral administration) functions as an immunostimulator during maintenance therapy and sustains the immune status. This could be one of the advantages of long-term continuous therapy with low-dose LEN.

CONCLUSION

IMiDs orchestrate the activities of a wide variety of both innate and acquired immune cell types, including pDC functions, leading to amplification of a positive immune axis able to eliminate MM cells **(Figure 1)**. Immunotherapies or drugs that improve the immune status are considered as effective therapeutic strategies, making IMiDs backbone drugs for MM.

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