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Review Of Synergistic Effects Of Immunomodulatory Drugs And Corticosteroids In Multiple Myeloma: Therapeutic Insights And Clinical Implications"

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Abstract:
Immunomodulation poses significant challenges within the medical field. However, advancements in drug design have led to the development of more selective immunomodulators, which help mitigate the side effects associated with novel pharmacological treatments.
A promising class of immunomodulators are immunomodulatory drugs (IMiDs), which are structurally and functionally similar to thalidomide. IMiDs offer potential treatment options for various inflammatory, autoimmune, and neoplastic diseases.
Importantly, the development of IMiDs examples include lenalidomide, thalidomide and pomalidomide improve patient recovery. These drugs are also known as 'Cereblon modulators' as they target the protein Cereblon (CRBN). Their mechanisms involve modulation of key proteins like TNF, IL-6, VEGF, and NF-kB, among others. This review explores the combination of IMiDs and corticosteroids (CSs) in treating multiple myeloma (MM).

Keywords: *Immunomodulatory drugs, Corticosteroids, Pomalidomide, Combination therapy, Multiple Myeloma (MM).*

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I. Introduction

Immunomodulatory Drugs (IMiDs) -

This category of drugs modifies the immune system's response and plays a crucial role in treating immunological disorders. They can either strengthen or suppress the immune system, depending on the condition being treated.[1] IMiDs, like thalidomide, lenalidomide and pomalidomide, have revolutionized the treatment landscape for hematological malignancies, particularly MM. Understanding their mechanisms of action is crucial for optimizing therapeutic outcomes.[3]

Immunostimulants and immunosuppressants are the two categories into which immunomodulators fall.[1] Immunostimulants are drugs that enhance the body's innate immune response, particularly important for patients with weakened immune systems, thereby bolstering the body's ability to fend off infections.[2]

Conversely, immunosuppressive medications are employed to reduce immune activity, alleviate hypersensitivity reactions, and mitigate autoimmune responses where the immune system targets healthy cells of the body.[2]

One special family of oral antineoplastic drugs called immunomodulatory drugs (IMiDs) has great impact in the treatment of hematological malignancies patient, especially multiple myeloma (MM). [4]

These IMiDs can generally be classified into four broad categories: adjuvants, agonists, cytokines, and checkpoint inhibitors.[5]

Immunomodulatory medications, or IMiDs, as potent immune system modulators, are structurally and functionally similar to thalidomide. Among the most prominent IMiDs are lenalidomide and pomalidomide, which are currently available in the market alongside thalidomide.[6]

IMiDs are a class of drugs consisting that are made up of two parts: phthalimide and glutarimide, of which is only one part of phthalimide replaced.[6]

This encouraged greater study into creating analogues that are both less toxic and more potent analogs. The second IMiD, lenalidomide, was created by substituting a single oxo group (the phthaloyl ring) with an amino group at position four in order to boost the immunomodulatory potential and, thus, the antitumour action of the thalidomide analogues.[4]

As with thalidomide, lenalidomide also produced remarkable clinical improvements in patients with cancerous diseases. Significant clinical benefits have also been seen in a variety of other hematologic MM malignancies, like myelodysplastic syndromes, chronic lymphocytic leukaemia and non-Hodgkin lymphoma, but the initial effects of IMiDs were seen among patients with MM.[4]

IMiD working mechanism

Detailed overview of how IMiDs (Immunomodulatory drugs) function through the modulation of the CRL4CRBN E3 ubiquitin ligase complex- IMiDs have been identified as CRBN E3 ligase modulators (CELMoDs), as they modulate the activity of the CRL4CRBN complex to induce targeted protein degradation. Proteomics studies have identified additional proteins targeted by IMiDs, expanding their potential therapeutic applications. CRBN (Cereblon) serves as the substrate receptor within the CRL4 (Cullin-RING Ligase 4) complex. The CRL4CRBN complex includes DNA damage-binding protein 1 (DDB1), a small RING protein (RBX), and Cullin 4A/4B. [7]

IMiDs (such as thalidomide and lenalidomide) bind to CRBN and hijack the CRL4CRBN E3 ligase complex. This complex is then utilized to ubiquitinate and degrades specific proteins. For instance: IKZF3 (Aiolos) and IKZF1 (Ikaros), which are essential lymphoid transcription factors. CK1α, involved in del(5q) myelodysplastic syndrome (MDS). Degradation of these proteins leads to downstream effects such as the downregulation of MYC and IRF4, contributing to the cytotoxic effects on multiple myeloma (MM) cells. [7]

Thalidomide-induced malformations have been linked to the degradation of proteins like PLZF, P63, and SALL4. IMiDs represent the first class of drugs that function by inducing the degradation of cellular proteins, (Fig. 1) which is a novel therapeutic approach. This mechanism opens avenues for the development of new therapeutic compounds that target specific proteins for degradation, potentially treating a range of diseases. In essence, IMiDs exert their therapeutic effects by leveraging the CRL4CRBN E3 ligase complex to degrade specific proteins crucial for disease pathogenesis, underscoring their importance in modern pharmacology and drug development. [7]

IMiDs show therapeutic effects by various mechanisms containing modulation of cytokine production.

In particular, they inhibit the synthesis of proinflammatory cytokines such as interleukin-12 (IL-12), tumor necrosis factor- α (TNF-α), IL-16, monocyte chemoattractant protein-1 (MCP-1) , macrophage inflammatory protein-1 α (MIP-1α), and IL-1β. Conversely, when peripheral blood mononuclear cells (PBMCs) are stimulated with lipopolysaccharide (LPS), IMiDs enhance the production of anti-inflammatory cytokines such as IL-2, interferon-gamma (IFN-γ), IL-10 and regulated upon activation, normal T-cell expressed, and secreted (RANTES). [7]

This dual action on cytokine production contributes to the immunomodulatory effects of IMiDs, which play a crucial role in their therapeutic efficacy in various conditions, including hematological malignancies like multiple myeloma and myelodysplastic syndrome.[7]

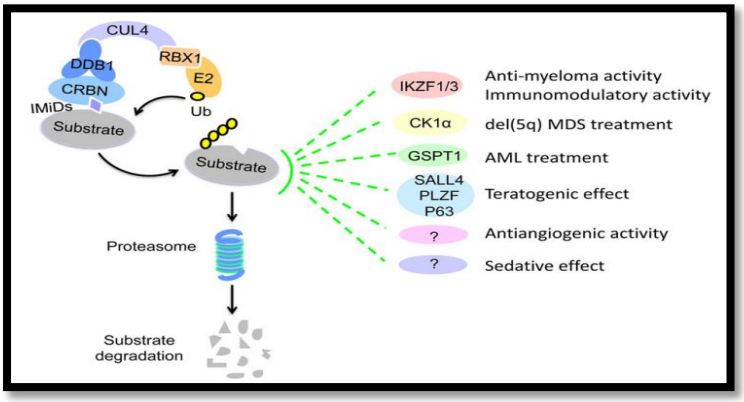
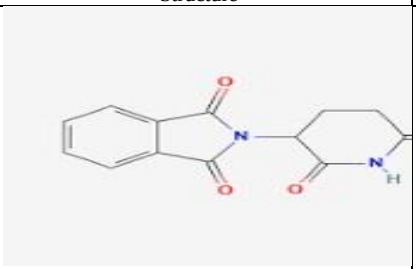
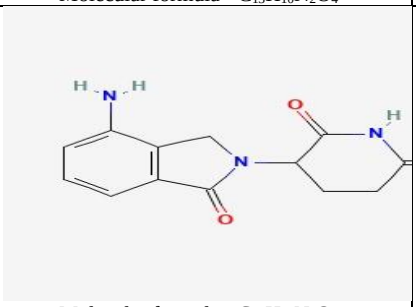
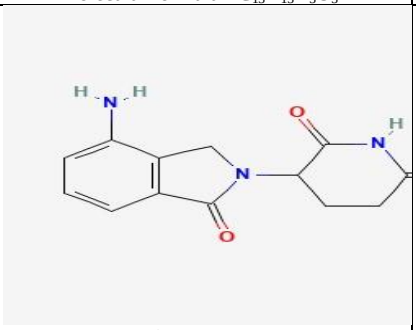


Figure1: Molecular mechanism of IMiD activity.

Pomalidomide

Pomalidomide (CC-4047 or Actimid) represents the latest and most potent member of the Immunomodulator class. Its clinical development is expected to revolutionize the treatment landscape for multiple myeloma (MM) patients. Pomalidomide is distinguished from its predecessor thalidomide by the addition of two oxo groups and at the fourth position an amino group of the phthalide ring. [4]

Table 1: Immunomodulatory Drugs Chemical structure [15].

	Structure	Maximum daily dose	Half life (in year)
Thalidomide	 Molecular formula - $C_{13}H_{10}N_2O_4$	50mg- 200mg	5.5–7.3
Lenalidomide	 Molecular formula - $C_{13}H_{13}N_3O_3$	2.5mg-25mg	3–5
Pomalidomide	 Molecular formula - $C_{13}H_{11}N_3O_4$	1mg-4mg	7.5–9.5

While the precise biological pathways influencing pomalidomide's ability to hinder cancer growth remain ambiguous, IMiDs as a class appear to impact multiple aspects of the cellular environment where tumors form and expand.

In particular, IMiDs may alter the levels of various cytokine signals secreted by the immune system in the tumor microenvironment, thereby affecting the division and survival of cancer cells.[4]

Pomalidomide, the latest IMiD compound, exhibits stronger inhibitory effects on cytokines compared to its sister drug, demonstrating increased potency based on preclinical data. Results of clinical trials in MM patients with drug-resistant patients to lenalidomide or bortezomib (or both), demonstrate the utility of this observation in the therapeutic environment. Responses to pomalidomide were more pronounced when given with dexamethasone, consistent with previous experience with other IMiDs.

Although the responses to pomalidomide treatment in relapsed or relapsed/refractory populations of patients are encouraging, it should be noted that the frequency of clinical response has decreased due to increased early treatment and/or increased patient enrollment in the studies described above. No clinical research proving CR among patients has been conducted. This will be a significant obstacle to the pomalidomide treatment, as many of the state-of-the-art treatment regimens may provide greater rates of it provides higher complete response (CR) rates even in relapsed or refractory patients, underscoring the clinical significance of its anti-myeloma efficacy.[4]

Future research examining pomalidomide's usefulness in the upfront context of treatment-naive patients is necessary, as all of the trials undertaken so far have involved patients with advanced-stage myeloma. In the absence of such data, it is difficult to design an appropriate method for sequencing IMiD compounds for biological response along with therapeutic efficacy. Novel medicines have dramatically improved the overall survival of patients with MM. The increased anti-myeloma action of these innovative drugs has led to a significant improvement in overall survival for MM patients. This has raised questions about the continued use fulness of IMiDs, especially considering the risks associated with their use.[4]

Dexamethasone-

Dexamethasone is indeed an effective treatment for multiple myeloma (MM), a type of blood cancer. It has been shown to induce apoptosis (programmed cell death) in MM cells in vitro, which is thought to be correlated with its clinical effect on patients. The mechanism by which dexamethasone induces apoptosis in MM cells involve the binding of dexamethasone to its cognate receptor, the glucocorticoid receptor (GR). These binding causes the GR to translocate to the nucleus, where it interacts with specific DNA sequences called glucocorticoid response elements (GREs).[9]

Dexamethasone is a synthetic corticosteroid that is used as a direct chemotherapeutic agent in certain hematological malignancies, including multiple myeloma (MM). It's often used alone or in combination with other chemotherapeutic agents to treat MM. Dexamethasone is 25 times more potent than hydrocortisone. Its high potency makes it an effective treatment option for MM, where it can induce apoptosis in cancer cells and inhibit their proliferation.[16]

In fact, GR-induced proceecing called transactivation has been implicated in a many models of GC-induced apoptosis in malignant and non- malignant lymphocytes, most likely through the production of pro-apoptotic genes. However, reduction of NFκb transcription factor is also a consequence of ligand binding to GR. Additionally; GC-induced MM cell death has been explained theoretically by this so-called transrepression. It is most likely due to inhibition of NFκB target anti-apoptotic genes. The study by Chauhan et al. sheds light on a new mechanism of action of dexamethasone in inducing apoptosis in multiple myeloma (MM) cells. They found that dexamethasone can activate the RAFTK kinase (also known as Pyk2), which is a tyrosine kinase that plays a crucial role in the regulation of cell signaling pathways. The GR is a transcription factor that is activated by dexamethasone, and its activation leads to the induction of pro-apoptotic proteins. In this study, the researchers found that overexpression of a kinase-inactive RAFTK mutant induced apoptosis in MM cells treated with dexamethasone. This suggests that the activation of RAFTK is essential for the pro-apoptotic effects of dexamethasone in MM cells. [9]

Combination Therapy: Pomalidomide with Dexamethasone

Thisincludespatientshaving relapsed and relapsed multiple myeloma andreceived at least two prior trea tments, including proteasome inhibitors and lenalidomide, and whose disease has worsened with or without trea tment within 60 days of the last treatment should be treated with dexamethasone receiving dexamethasone as a metastasis. [10]

AIDS-relatedKaposisarcoma(KS)inHIV-negative or HIV uninfected patients who resist or fail antiretroviral therapy (HAART). Pomalidomide capsule was approved based on response rate. The clinical benefit of pomalidomaide capsule for this usage is still being evaluated.[10]

It is not known whether pomalidomide capsules are effective and safe in children.[10]

Pomalidomide (POM), a new immunomodulator medication with strong antimyeloma effects. Pomalidomide has been shown to exhibit synergistic antiproliferative effects when combined with dexamethasone, particularly in lenalidomide-resistant multiple myeloma cells. This is an exciting development, as it provides a potential treatment option for patients who have relapsed or progressed after previous therapy with lenalidomide. The potency and individual modes of action of pomalidomide and lenalidomide may differ significantly, which could contribute to the activity of pomalidomide in cells that are resistant or refractory to lenalidomide. Pomalidomide has been shown to have a higher potency than lenalidomide in some preclinical models, which could contribute to its activity in resistant cells. The combination of pomalidomide and dexamethasone may lead to enhanced anti-tumor activity due to the synergistic effects on multiple pathways and cell populations. The combination of pomalidomide and dexamethasone is currently being investigated in clinical trials for the treatment of relapsed or refractory multiple myeloma, including patients who have progressed after prior therapy with lenalidomide.[11]

Corticosteroids (CSs)

A family of steroid hormones known as corticosteroids (CSs) are controlled by hypothalamic croticotropin-releasing hormone. Adrenal glands generate and release it in response to pituitary adrenocroticotropic hormone. Major endocrine system activities, such as controlling homeostasis and channelling stress, are managed by these hormones. Aldosterone (mineralocorticoids) and cortisol (glucocorticoids) are the two primary CSs generated by the adrenal cortex. While cortisol creates an alluring effect by preventing the production of swelling mediators, aldosterone affects the balance of salt and water.[8]

Dosage-

The recommended starting dose of pomalidomide is 4 mg per day, taken orally on days 1-21 of a 28-day cycle (every 28 days). This means that patients take pomalidomide daily for the first 21 days of each cycle, followed by a 7-day break.

Regarding dexamethasone, the recommended dose is 40 mg per day on specific days of each 28-day treatment cycle. The exact schedule is:

Dexamethasone 40 mg on days 1, 8, 15, and 22 of each 28-day cycle

This means that patients take dexamethasone on specific days within each cycle, with breaks in between.[13, 14]

Mechanism of action of POM along with dexamethasone

multi-faceted mechanisms of actions (MOA) of pomalidomide, a 3rd-generation immunomodulatory agent include immunomodulatory, antitumor activity, antimyeloma activity and anti-angiogenic properties (Figure2).

It exhibits a pleiotropicMOA, following the current approach to cancer therapy that focuses on the foll owing three actions: inducing tumor cell apoptosis, interfering with tumor- stroma interactions and ameliorating autoimmunity. [3]

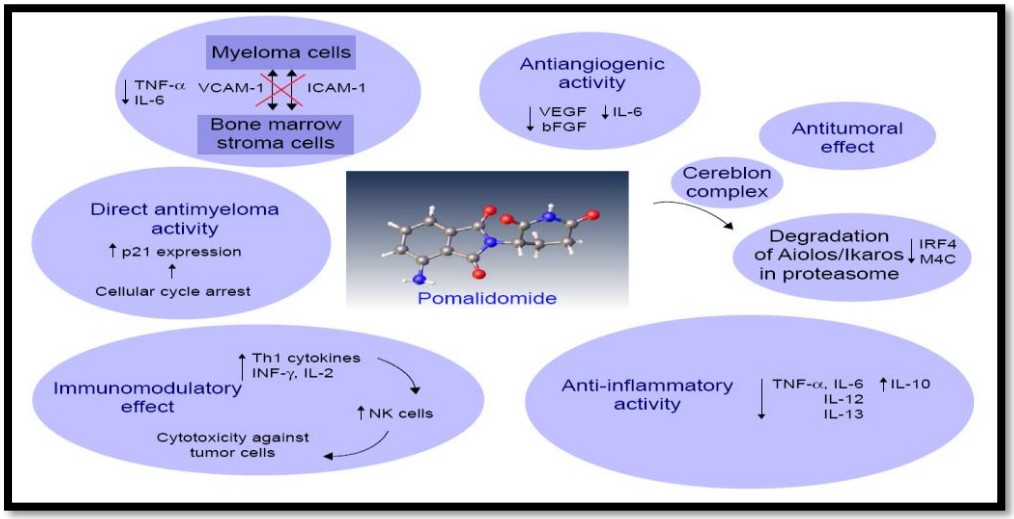


Figure 2: Schematic representation of the mechanism of action of POM

The clinical relevance of pomalidomide (POM), a 3rd-generation immunomodulator approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) in 2013, used in combination with dexamethasone to treat patients with multiple myeloma who have received two prior therapies containing both bortezomib and lenalidomide and failed to respond or relapsed means where the disease has progressed since the last treatment. Pomalidomide's clinical development has focused on this specific patient population, as it has shown significant activity in patients with relapsed/refractory multiple myeloma.[3]

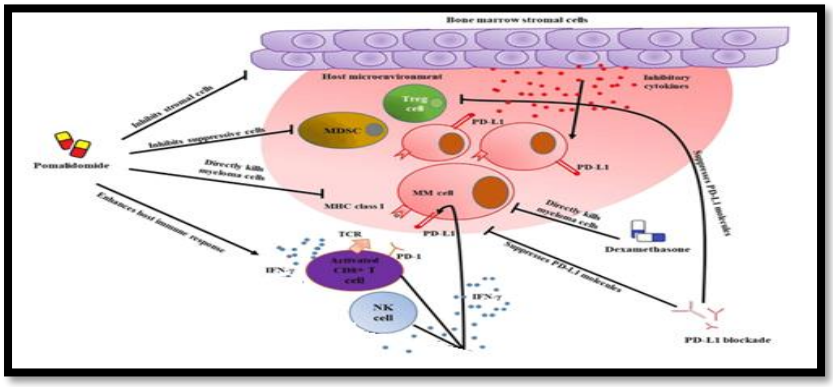


Figure 3: Pomalidomide along with dexamethasone mechanism of action

Pomalidomide along with dexamethasone have a direct antimyeloma effect on the immunosuppressive microenvironments. Pomalidomide inhibits PDL1 molecules expressed on antigen-presenting cells and myeloma cells which is more correlated to the infiltration of effector cells into the tumor bed, on the other hand, stimulates cytotoxic T lymphocytes (CTLs), suppresses Tregs, and modulates various cytokines; Programmed death ligand 1 (PD-L1)blockade.

Clinical Utility and Challenges: The combination of pomalidomide and dexamethasone has shown promising results in clinical trials. However, challenges remain, such as decreasing medical responses with increasing prior treatments and resistance to lenalidomide or bortezomib. Further research examining pomalidomide's usefulness in treatment-naive patients is necessary, as current trials mostly involve advanced-stage myeloma patients.

The efficacy and benefit of IMiDs such as pomalidomide may also be questioned due to the longterm o ccurrence of extramedullary myelomatosis (EMD) in patients living longer with MM.

II. Conclusion:

The combination of immunomodulators and corticosteroids represents synergistic therapeutic potential in managing multiple myelitis (MM) treatment, offering synergistic antitumor effects and improving therapeutic outcomes, particularly in refractory cases. Further research is warranted to explore their efficacy in different patient populations and treatment settings, ultimately advancing MM therapy paradigms.

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