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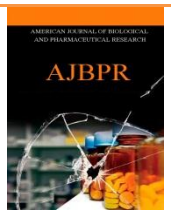

POMALIDOMIDE – A NOVEL IMMUNOMODULATOR (IMiD)

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ABSTRACT

In this review, the recently approved drug pomalidomide is discussed. Thorough literature search was made regarding the status of drug in various diseases using pubmed, google scholar etc. Pomalidomide is a derivative of thalidomide and is a racemic mixture of the S-enantiomer (CC-5083) and the R-enantiomer (CC-6016) which interconvert in plasma. Pomalidomide is an immunomodulatory agent with antineoplastic activity. In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. The U. S. Food and Drug Administration granted accelerated approval to pomalidomide for the treatment of patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy. The recommended dose and schedule for pomalidomide is 4 mg taken orally on days 1-21 of repeated 28-day cycles. Cycles are repeated until disease progression. It is available in US as capsules: 1 mg, 2 mg, 3 mg and 4 mg. Pomalidomide is also being tried for number of diseases. The following review provides the pharmacology and current status of pomalidomide.

INTRODUCTION

IMiDs are structural and functional analogues of thalidomide that represent a promising new class of Immunomodulators for treatment of a variety of inflammatory, autoimmune, and neoplastic diseases [1]. Thalidomide was initially discovered and used as sedative and anti-nausea drug in late 1950s. Around this time, Australian obstetrician Dr. William McBride discovered that the drug also alleviated morning sickness and several thousands of pregnant women were prescribed by this drug [2]. In the early 1960s, the teratogenic effects of thalidomide became widely known and approximately 5,000-7,000 malformed infants were born to women who ingested thalidomide during pregnancy [3]. This tragedy led to the downfall of thalidomide and later being banned by various regulatory agencies. After being removed from the pharmaceutical market, thalidomide has been the subject of significant clinical research. As researchers look at novel properties of drugs and new indications in the oncologic setting, thalidomide has made a comeback [4]. It re-entered clinical practice, initially because of its clinical efficacy in erythema nodo sumleprosum, for which it received approval in 1998. Further research revealed its anti-angiogenic and immunomodulatory effects, and these findings triggered experimental trials in cancer, most notably against multiple myeloma (MM) and gained FDA approval for its use in combination with dexamethasone in 2006 [5,6].Thalidomide, though effective, was associated with dose-limiting toxicities including somnolence, constipation, peripheral neuropathy and increased incidence of veno thromboembolism (VTE), especially when combined with dexamethasone. Hence, a new class of thalidomide derivatives called IMiDs was developed that, albeit structurally related, had their unique set of anti-inflammatory, immunomodulatory, antiproliferative, antiangiogenic and toxicity profiles [7].

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Pomalidomide [CC-4047; (RS)-4-amino-2-(2, 6-dioxopiperidin- 3-yl)-isoindoline-1, 3-Dione] is a derivative of thalidomide. Pomalidomide is a racemic mixture of the S-enantiomer (CC-5083) and the R-enantiomer (CC-6016) which interconvert in plasma via both enzymatic and non-enzymatic pathways [8].

MECHANISM OF ACTION

The precise cellular targets and molecular mechanisms of IMiDs have only recently become clear. Pomalidomide is an immunomodulatory agent with antineoplastic activity. In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in the in vitro umbilical cord model [9].

A landmark study recently identified cereblon (CRBN) as a primary target of thalidomide teratogenicity. Subsequently it was demonstrated that CRBN is also required for the anti-myeloma activity of thalidomide and related drugs, the so-called immune-modulatory drugs (IMiDs). Low CRBN expression was found to correlate with drug resistance in MM cell lines and primary MM cells [10].

Stimulates the immune system (NK cell production & functionality) to attack the myeloma cells. Inhibits proliferation and induced apoptosis of hematopoietic tumor cells. Pomalidomide also blocks the growth of new blood vessels that supply the myeloma cells with oxygen and nutrition (anti-angiogenesis). Inhibits production of survival & proliferation factors (e.g., TNF-α and IL-6) by monocytes.

PHARMACOKINETICS

The pharmacokinetics of pomalidomide in patients with relapsed or refractory MM following single or multiple (4 weeks) oral daily doses of 1, 2, 5 or 10 (single dose only) mg as capsules showed non-dose dependent absorption with a median Tmax between 1.5 and 2.75 h following a single dose and between 2.9 and 4.0 h following multiple doses. Pomalidomide had a half-life of 6.5–8.0 h and showed little accumulation after once-daily administrations.

Pomalidomide has a mean apparent volume of distribution (Vd/F) between 62 and 138 L at steady state. Human plasma protein binding ranges from 12% to 44% and is not concentration dependent. Pomalidomide is primarily metabolized in the liver by CYP1A2 and CYP3A4. Pomalidomide is eliminated with a median plasma half-life of approximately 9.5 hours in healthy subjects and approximately 7.5 hours in patients with multiple myeloma.

ADVERSE EFFECTS

The most common side effects reported in the clinical trial include fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper respiratory tract infections, back pain, and pyrexia. Pomalidomide is approved with a Boxed Warning alerting patients and healthcare professionals that the drug can cause embryo-fetal toxicity and venous thromboembolism.

Because of this embryo-fetal risk, pomalidomide is available in United States only through a restricted distribution program called the POMALYST Risk Evaluation and Mitigation Strategy (REMS) Program. Prescribers must be certified with the POMALYSTREMS Program by enrolling and complying with the REMS requirements. Patients must sign a Patient-Physician Agreement Form and comply with the REMS requirements. Female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements. Males must comply with contraception requirements [11].

CURRENT STATUS & FUTURE POTENTIAL

The U. S. Food and Drug Administration granted accelerated approval to pomalidomide for the treatment of patients with multiple myeloma who have received at least two prior therapies, including lenalidomide and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy. The recommended dose and schedule for pomalidomide is 4 mg taken orally on days 1-21 of repeated 28-day cycles. Cycles are repeated until disease progression. It is available in US as capsules: 1 mg, 2 mg, 3 mg and 4 mg. Pomalidomide is also being tried for number of diseases. The following are the few of the disease conditions and clinical trials where pomalidomide is being evaluated.

In a phase II randomized, multicenter, double-blind, adaptive design study, Pomalidomide has shown the efficacy in the treatment of in Anemia of Myelofibrosis. Pomalidomide therapy was given at a dose of 0.5 or 2 mg/d with or without an abbreviated course of prednisone [12].

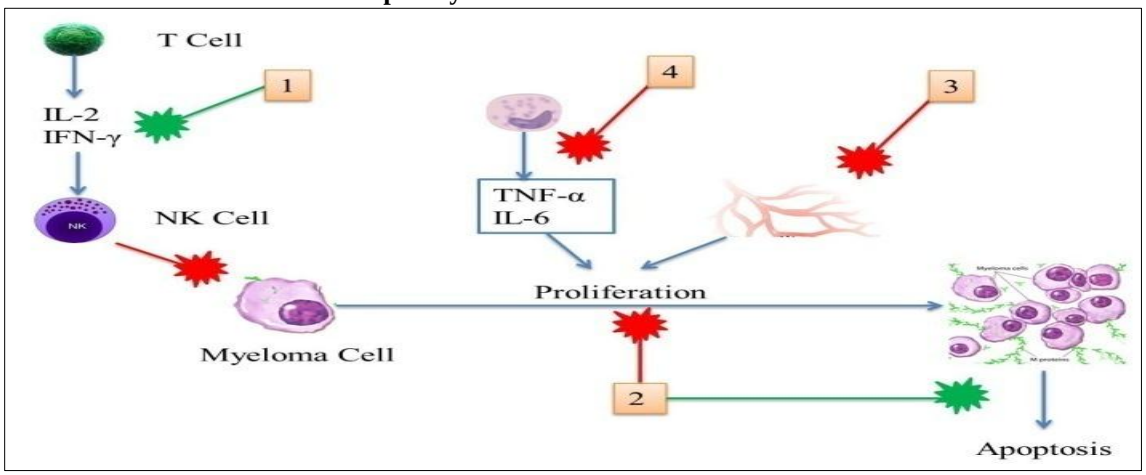
One more study has to say that pomalidomide induced apoptosis signaling and growth arrest in childhood acute lymphoblastic leukemia cells both in vitro and in vivo. So, further clinical trials in large scale are required to establish the efficacy of pomalidomide in childhood ALL [13].

The results of the prospective phase II trial indicate that Pomalidomide in combination with weekly dexamethasone (Pom/dex) is active in relapsed immunoglobulin light chain amyloidosis, with an overall hematologic response rate of 48% [14]. Pomalidomide is effective for prevention and treatment of experimental skin fibrosis.

ADVANTAGES OVER EXISTING DRUGS

Pomalidomide is thought to have advantages over both thalidomide and lenalidomide. So far, pomalidomide has been found to be much more potent than either thalidomide or lenalidomide and therefore can be given at much lower doses. It has also been shown to have considerable anti-myeloma activity when given alone, so may not need to be combined with other treatments to produce a similar response. Studies have also shown that pomalidomide may be particularly effective for heavily pre-treated patients who have become resistant (refractory) to some of the current drugs, including thalidomide and lenalidomide.

Fig1. Mechanism of Pomalidomide in Multiple Myeloma



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