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Journal of Drug Delivery and Therapeutics
Open access to Pharmaceutical and Medical research

MINI REVIEW

LENALIDOMIDE: RECENT ARMAMENTARIUM IN MANAGEMENT OF MULTIPLE MYELOMA

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ABSTRACT

Lenalidomide is an analogue of thalidomide. It is an oral immunomodulatory compound with potent activity and different toxicity profile than thalidomide. Lenalidomide is one of the novel drug agents used to treat multiple myeloma. Multiple myeloma (MM) is a B cell malignancy characterized by excess monotypic plasma cells in the bone marrow. Lenalidomide in combination with dexamethasone is one of the most promising MM novel treatment options. It induces at least additive direct cytotoxicity in multiple myeloma cells.The lenalidomide has possibility of being used as an adjuvant in support of more specific immunotherapeutic interventions including cancer chemotherapy, anticancer vaccines and adoptively transferred cells which warrants further investigation.
Key words: Dexamethasone, Immunomodulation, Lenalidomide, Multiple myeloma

INTRODUCTION

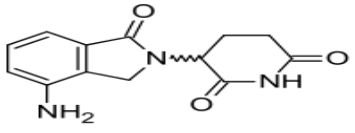
Lenalidomide is a novel oral immunomodulatory derivative of thalidomide with potent activity and with a much improved toxicity profile to the parent compound. Thalidomide has a potential to treat inflammatory and neoplastic condition like multiple myeloma but was withdrawn from the market after its teratogenic effects were established.[1]Lenalidomide, a potent analogue of thalidomide was developed with improvement in safety and efficacy than the parent drug, thalidomide.It was created using thalidomide as a template by adding an amino group to the 4th carbon of the phthaloyl ring and removal of a carbonyl group.

Lenalidomide possesses immunomodulatory, anti-angiogenic, antineoplastic and anti-inflammatory activities. Lenalidomide has been extensively studied and approved for refractory / relapsing multiple myeloma (MM), mantle cell lymphoma (MCL) and myelodysplastic syndromes (MDS).[2]

Multiple myeloma is a B cell malignancy characterized by accumulation of plasma cell clone in the bone marrow, monoclonal protein in serum and/or urine, reduced immunoglobulin levels and lytic bone disease.[3]Alkylating agents, anthracyclines and corticosteroids were commonly used drugs in multiple myeloma which extended patient's survival to median 3-4 yearsas compared to median survival of 4-5 years with high dose of these drugs followed by autologous transplantation.[4] Due to the development of tumor cell resistance to all therapies, multiple myeloma still remains incurable, requiring further study on novel treatment strategies.[5] The survival in MM patients has improved significantly in the past decade due to the introduction of novel agents including immunomodulatory drugs (thalidomide, lenalidomide and pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, marizomib and ixazomib citrate), monoclonal antibodies (elotuzumab, siltuximab, daratumumab and BT-062), and drugs affecting an interaction with the tumor microenvironment (anti-VLA4 monoclonal antibody, chemokine CXCR4 inhibitor AMD-3100 and selectin inhibitor GMI-1070).[6-8]

Lenalidomide has been found to be more potent in the stimulation of T-cell proliferation and INF gamma and IL-2 production than thalidomide, whereas both thalidomide and pomalidomide, another thalidomide analogue, have been found to be more potent at inhibiting sprout formation than lenalidomide when antiangiogenic properties were assessed in a human umbilical explant model. Thalidomide was associated with dose-limiting toxicities including somnolence, constipation, neuropathy, and increased incidence of venothromboembolism (VTE), especially when combined with dexamethasone[9].No clinical trials directly comparing these agents have been performed, lenalidomide appears to have a lower incidence of constipation, peripheral neuropathy, and somnolence than thalidomide.[2]

Structure



(*RS*)-3-(4-Amino-1-oxo 1,3-dihydro-2*H*-isoindol- 2-yl)piperidine-2,6-dione

Mechanism of action

Lenalidomide haspotent immunomodulatory, antiangiogenic and antineoplastic properties.[10,11] Novel biological agents target not only the MM cell, but also MM cell–host interactions, cytokines, and their sequelae in the bone marrowmilieu. Lenalidomide is several thousand fold more potent than thalidomide at inhibiting TNFα/il-1β secretion from mononuclear cells stimulated with lipopolysaccharide. The combination of lenalidomide and corticosteroid synergizes the inhibition of cell proliferation and the induction of apoptosis. Lenalidomide may inhibit MM cell growth by several different mechanisms.[5,12-14] Itdirectly induces tumor cell apoptosis and/or growth arrest (A); enhances NK and/or NK cell activity via activation of cd28/nf-at2 pathway (B); inhibits MM cell adhesion to host microenvironment (C); inhibits angiogenesis (D); inhibits osteoclastogenesis (E); inhibits cytokine secretion (F).

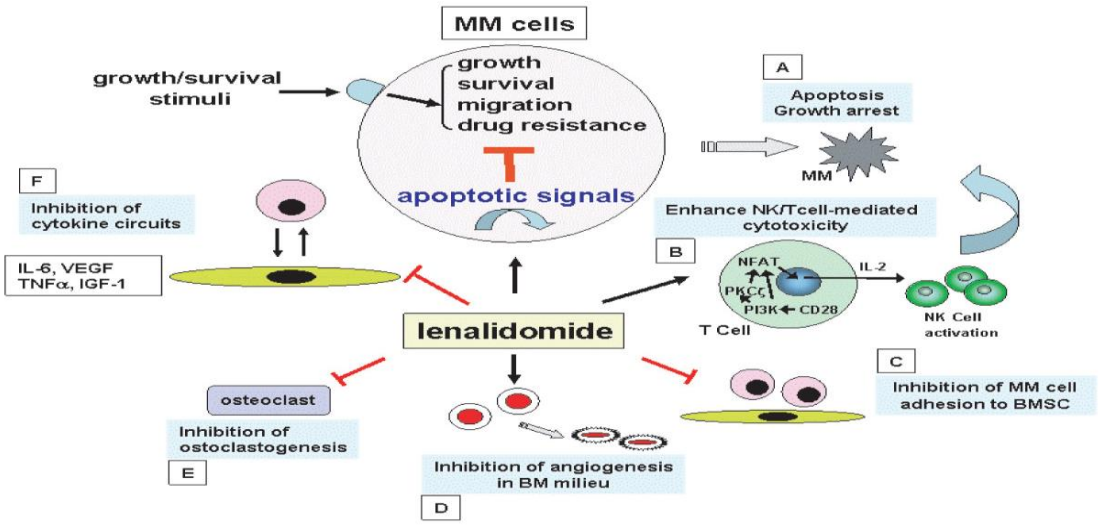


Figure 1: Potential mechanisms of action of anti-MM activity of lenalidomide.[2]

Pharmacokinetics

Lenalidomide is rapidly absorbed following oral administration and food has no change in AUC but Cmax may be reduced to 36%. Plasma protein binding is approximately 30%. Lenalidomide -undergoes limited metabolism with two identified metabolites hydroxy-lenalidomide and n-acetyl-lenalidomide; each constitutes less than 5% of parent drug levels in circulation. Unchanged lenalidomide, about 67%, is the predominant circulating component primarily excreted by renal route. The mean half-life of lenalidomide is 3 hours in healthy subjects and 3 to 5 hours in patients with MM, MDS or MCL.[15]

Clinical efficacy

A multicenter, open-label, phase 2 study of lenalidomide plus low-dose dexamethasone in Chinese patients with relapsed/refractory multiple myeloma (RRMM) conducted to assess the efficacy, safety, and pharmacokinetics of lenalidomide plus low-dose dexamethasone showed high response rate and acceptable safety profile in heavily pretreated Chinese patients with RRMM, including those with renal impairment and IgD subtype.[15,16]

Two phase III randomized studies validated the role of lenalidomide in combination with dexamethasone for the treatment of relapsed/refractory MM patients showed overall response rate of 83%, including 29% of complete response as seen by negative immunofixation on the serum and urine.[17] The toxicity profile of the treatment was in line with that reported in previous studies and led to dose reductions and treatment interruption in 44% and 17% of patients, respectively.[18] These results led the US Food and Drug Administration (FDA) on June 29, 2006 to grant approval to lenalidomide in combination with dexamethasone in patients with MM who have received one prior therapy.

In a phase I clinical dose-escalation (5 mg/day, 10 mg/day, 25 mg/day, and 50 mg/day) study of lenalidomideat Dana-Farber cancer institute, no dose-limiting toxicity (DLT) was observed in patients treated at any dose level within the first 28 days; however, grade 3 myelosuppression developed after day 28 in all 13 patients treated with 50 mg/day lenalidomide. Dose reduction to 25 mg/day was well tolerated in 12 patients and therefore considered to be the maximal tolerated dose (MTD). Most importantly, no significant somnolence, constipation, or neuropathy, the most common toxicities of thalidomide, has been seen in any cohort.[19]

A multicentric, open-label, randomized phase II study evaluated 2 dose regimens of lenalidomide for relapsed, refractory MM with either 30 mg once-daily or 15 mg twice-daily oral lenalidomide for 21 days of every 28-day cycle. Responses were evaluated according to European group for blood and marrow transplantation (EBMT) criteria and overall response rate to lenalidomide alone was 25%; 24% for 30 mg once-daily and 29% for 15 mg twice-daily cohort. This study indicates that lenalidomide is active and well tolerated in relapsed, refractory myeloma, with the 30-mg once-daily regimen providing the basis for future studies as monotherapy and with dexamethasone.[5,19]

Two double blind, multicentric phase III clinical trials showed significant improvement with lenalidomide plus

dexamethasone compared to dexamethasone in overall response. In this study patients with relapsed or refractory MM not resistant to dexamethasonewere treated with dexamethasone40 mg daily on days 1–4, 9–12, and 17–20 every 28 days and were randomized to receive either lenalidomide 25 mg daily orally on days 1–21 every 28 days or placebo. Results show significant improvement with lenalidomide plus dexamethasone compared to dexamethasone alone in overall response.[5]

Available in four dosage strengths - 5mg, 10mg, 15mg and 25mg hard capsules. For multiple myeloma, initially, 25 mg orally daily with water (as a single 25 mg capsule) on days 1 to 21 of a 28-day cycle; co-administer dexamethasone 40 mg/day orally on days 1 to 4, 9 to 12, and 17 to 20 of each 28-day cycle for the first 4 cycles, then 40 mg/day orally on days 1 to 4 every 28 days; continue therapy, with dose adjustments for toxicities, until disease progression. The dose of lenalidomide may vary from patient to patient for several reasons depending on the nature and stage of the person's myeloma, any side effect a person may have and how the myeloma is responding to treatment.[20-22]

Drug interactions

Periodic monitoring of digoxin plasma levels is recommended due to increased Cmax and AUC with concomitant lenalidomidetherapy. Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of venous thromboembolism (VTE).Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.[9,17,21,22]

Adverse effects

Serious[17]

Cardiovascular: Deep venous thrombosis (7.8%)

Hematologic: Anemia (24.3 %), Febrile neutropenia (5.4%), Neutropenia (35.4%), Thrombocytopenia (16% to 61.5%)

Respiratory: Dyspnea (20.2%), Pneumonia (11.5%), Pulmonary embolism (3.2%)

Common [2,7]

Cardiovascular: Peripheral edema (21.1%)

Dermatologic: Pruritus (41.9%), Rash (35.8%)

Endocrine metabolic: Hyperglycemia (15%), Hypokalemia (11.3%)

Gastrointestinal: Abdominal pain (12.2%), Constipation (38.7%), Diarrhea (48.6%), Indigestion (13.9%), Loss of appetite (13.6%), Nausea (23.6%), Vomiting (10.1%), Weight decreased (18.2%)

Hematologic: Leukopenia (8.1%)

Musculoskeletal: Arthralgia (21.6%), Backache (20.9%), Cramp (30.1%), Muscle weakness (15%)

Neurologic: Dizziness (20.8%), Headache (19.6%), Insomnia (32.1%), Peripheral neuropathy (8.1%), Tremor (19.7%)

Ophthalmic: Blurred vision (14.7%)

Psychiatric: Asthenia (23.4%), Fatigue (31.1%)

Renal: Dysuria (6.8%)

Respiratory: Upper respiratory infection (14.9%)

Others: Fatigue (38.4%), Fever (23.1%)

Contraindications

Thalidomide is a known human teratogen that causes life-threatening human birth defects or embryo-fetal death. Lenalidomideby being a thalidomide analogue, is contraindicated for use during pregnancy(Pregnancy category X).Women of childbearing potential are also to be cautioned for its use unless adequate precautions are taken to prevent pregnancy since it runs high risk of potential for birth defects.Hypersensitivity to this drug is absolute contraindication.

Precautions

- Increased mortality: serious and fatal cardiac adverse reactions were observed in patients with Chronic Lymphocytic leukemia.
- Second primary malignancies (SPM): higher incidences of SPM were observed in controlled trials of patients with multiple myeloma.
- Hepatic failure including fatalities; monitor liver function.
- Serious tumor flare reactions have occurred during investigational use for chronic lymphocytic leukemia and lymphoma
- Patients with renal insufficiency: adjust the starting dose of with moderate or severe renal impairment and on dialysis

Indications

Lenalidomide is a second-generation immunomodulatory drug (iMID) currently approved by the US Food and Drug Administration (FDA) for the management of various hematologic malignancies as below:

1. Multiple myeloma: On June 29, 2006, FDA granted approval to lenalidomide for use in combination with dexamethasone in patients with multiple myeloma who have received one prior therapy [9]. The dose of lenalidomide is 25 mg/day orally and dexamethasone at a dose of 40 mg/day. On 23 April 2009, The National Institute for Health and Clinical Excellence (NICE) issued a Final Appraisal Determination (FAD) approving lenalidomide, in combination with dexamethasone, as an option to treat patients of multiple myeloma who have received two or more prior therapies in England and Wales.[20,21]
2. Myelodysplastic syndromes: On December 27, 2005, the U.S. Food and Drug Administration granted Subpart H approval (restricted distribution) to lenalidomide oral capsules for use in patients with transfusion-dependent anemia due to low or intermediate-1risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. It was approved on June 17, 2013 by the European Medicines Agency for use

in low- or intermediate-1-risk myelodysplastic syndromes (MDS) patients who have the deletion 5q cytogenetic abnormality and no other cytogenetic abnormalities, are dependent on red blood cell transfusions, and for whom other treatment options have been found to be insufficient or inadequate.[22,23]

3. Mantle cell lymphoma: In June 2013, the U.S. Food and Drug Administration approved lenalidomide capsules for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.The recommended dose is 25 mg orally once daily on days 1-21 of repeated 28 days cycle. FDA approved lenalidomide for this indication on June 2013.[7]

Other indications

Lenalidomide is an active first-line treatment option for CLL that is well-tolerated if a conservative approach with low doses and slow dose-escalation is used.[24] Many studies have been done on assessing the safety and therapeutic profile of lenalidomide in patients with cancers like acute myeloid leukemia, prostate carcinoma, renal cell carcinoma, B-cell lymphoma, astrocytoma, glioma, hepatocellular carcinoma, pancreatic cancer, etc. The lenalidomide has possibility of being used as an adjuvant in support of more specific immunotherapeutic interventions including anticancer vaccines and adoptively transferred cells which warrants further investigation.[25] Lenalidomide is undergoing clinical trial for Hodgkin's lymphoma and non-Hodgkin's lymphoma, chronic lymphocytic leukemia (CLL) and solid tumor cancersof the pancreas.[26,27] One Phase 3 clinical trial being conducted by Celgene in elderly patients with B-cell chronic lymphocytic leukemia was halted in July 2013 when a disproportionate number of cancer deaths were observed during treatment with lenalidomide versus patients treated with chlorambucil.[28]

CONCLUSION

Lenalidomide is an important addition to the treatment armamentarium for relapsed or refractory MM, MDS and MCL. Lenalidomide is administered in combination with low-dose glucocorticoids (most often dexamethasone or prednisone), which are well known for their immunosuppressive potential. Lenalidomide is more potent, more active and less toxic than its parent drug thalidomide.

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 ISSN: 2250-1177 CODEN (USA): JDDTAO