Role of Immunomodulatory Drugs and Proteasome Inhibitors in the Treatment of Myeloma Bone Disease: Literature of Review

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Abstract

Multiple myeloma (MM) is a clonal plasma cell malignancy, characterized by the proliferation of neoplastic plasma · cells. Currently, with an improved understanding of the genetic as well as biological abnormalities that are a hallmark of multiple myeloma, cytogenetics, and other risk stratification methods are increasingly being proposed to guide the treatment of myeloma. Among others, recent advances have been useful in defining high-risk groups with poor outcome after standard and high-dose chemotherapies. The use of novel agents have improved prognosis for a subset of patients with high-risk disease.

Keywords: *Myeloma, Agents, Immunomodulatory*

INTRODUCTION

Presently, High-dose chemotherapy (HDCT) with autologous stem cell transplantation (ASCT) is still routinely incorporated as treatment strategy either early in the disease course of myeloma or at the time of relapse in eligible patients. However, with the availability of novel chemotherapeutic agents like thalidomide, Bortezomib, and Lenalidomide; therapeutic options have expanded and current trials are focusing on incorporating these agents in the transplant paradigm. Despite recent advances in conventional treatments, till now multiple myeloma remains an incurable disease. A vast majority of myeloma patients usually relapse regardless of treatment regimen or initial response to treatment.[1] Recent advances in the understanding of the patho-biology of multiple myeloma have highlighted the role of molecular mechanisms by which myeloma cell host bone marrow interactions and regulate tumor-cell growth, survival, and drug resistance in the bone marrow milieu. Therefore, recent therapeutic interest has shifted to the development of therapeutic agents and regimens targeting both the malignant cell and the microenvironment that is crucial to tumor growth and progression. Such novel therapies are now increasingly moving from preclinical evaluation to clinical application of multiple myeloma.[2]

Biology of Myeloma Bone Disease

Bone disease is a hallmark of multiple myeloma, presenting as lytic lesions associated with bone pain, pathological fractures requiring surgery and/ or radiation to bone, spinal cord compression and hypercalcemia.[3] Increased osteoclastic activity unaccompanied by a compensatory increase in osteoblast function, leading to enhanced bone resorption results in bone disease. The interaction of plasma cells with the bone marrow microenvironment has been shown to play a vital role. Also, interactions of myeloma cells with osteoclasts enhance myeloma growth and survival, and thereby create a vicious cycle leading to extensive bone destruction and myeloma cell expansion.[4]

Novel Agents: Immunomodulatory Drugs

The recent discovery of the activity of this class of drugs represents a major step forward in the treatment of multiple myeloma. Immunomodulatory drugs (IMiDs) represents a group of compounds that are analogues of thalidomide, a glutamic acid derivative with Immunomodulatory and anti-angiogenic properties and with potent anti-inflammatory effects.[5,6]

Thalidomide

Thalidomide [α-N-(phthalimido) glutarimide] is a synthetic derivative of glutamic acid, with a property and history of causing birth defects when used as an antiemetic during pregnancy in the late 1950s and early 1960s. Despite its withdrawal from most markets, its therapeutic uses however persisted in the treatment of several diseases like erythema nodosum leprosum, a cutaneous inflammatory complication of leprosy characterized by high levels of serum tumor necrosis factor-alpha

(TNF-α).[5] In the late 1990s, thalidomide was also shown to be effective for the treatment of multiple myeloma.[7]

1. Mechanism of Action

Although, the exact mechanism of action of thalidomide is still unclear, its anti-tumor activity of has been attributed to pleiotropic effects (a) direct anti-proliferative/ pro-apoptotic effects against myeloma cells, probably mediated by one or more in vivo metabolites of thalidomide, and include inhibition of the transcriptional activity of NF-ƙB and its anti-apoptotic target genes e.g. (the caspase inhibitors FLIP, cIAP-2, or the anti-apoptotic Bcl-2 family member A1/Bfl; (b) indirect targeting of myeloma cells by inhibiting tumor cell protection conferred by cell adhesion molecules or cytokine mediated (eg., IL-6) interactions with bone marrow stromal cells (BMSC); (c) anti-angiogenic effects; and (d) different Immunomodulatory effects, including enhanced natural killer (NK) cell-mediated cytotoxicity against tumor cells.(Figure-1)[2,8]

2. Efficacy

In a study, evaluating the antitumor activity of thalidomide in patients with refractory multiple myeloma, single agent thalidomide resulted in a response rate of 32%.[9] Reductions in the paraprotein levels were shown to be apparent within two months of therapy in 78% of the patients with a response and were associated with decreased number of plasma cells in bone marrow and increased haemoglobin levels. Thereafter, after 12 months of follow-up, the mean (+_SE) rates of event-free survival and overall survival for all patients were 22+_15% and 58+_15%, respectively. Moreover, regimens combining thalidomide with dexamethasone, melphalan, doxorubicin and/ or cyclophosphamide have been extensively studied in relapsed/ refractory myeloma disease and resulted in considerably higher response rates providing effective options for the management of such patients.[10]

3. Dosage

In the past, thalidomide at a higher dose of 800 mg/d were used. Currently, more modest doses of 50-200 mg are employed. The dosing of thalidomide should be adjusted mainly based on patient tolerance. In a randomized prospective French trial, it has showed no significant difference in survival rates between doses of 100 and 400 mg.[11] Additionally, reducing the daily dose of thalidomide from 400 to 100 mg, significantly reduced the drug's potentially severe side effects. Dosage adjustment recommendations of thalidomide for patients with renal dysfunction or undergoing haemodialysis are not clearly available, as well as data is lacking.[8]

4. Side Effects

The frequency and severity of side effects of thalidomide are shown to be dose related and time dependent, and commonly include constipation, anorexia, fatigue, somnolence, and peripheral neuropathy. It has been shown that, immediate thalidomide dose reduction or discontinuation, when paresthesia is complicated by pain or sensory as well as motor deficit, will usually decrease the severity of neuropathy.[8,12] Moreover, the dispensing and use of thalidomide is strictly regulated due to its teratogenicity effect.[10] Studies have shown that, in the era before the use of thromboprophylaxis, thalidomide and high-dose dexamethasone resulted in thromboembolic events in approximately 15% of individuals with rates increasing to about 25-30%, when thalidomide is combined with an anthracyclines.[13] Although, thromboprophylaxis is not recommended in patients receiving single-agent thalidomide (if no other risk factors for DVT are simultaneously present), yet it is strongly recommended in those who receive thalidomide in combination with high-dose dexamethasone or doxorubicin. Moreover, the presence of individual risk factors (e.g., age, obesity, comorbidities, and surgical procedures) as well as myeloma-related risk factors (e. g. diagnosis and high-tumor mass) further determine the risk of deep vein thrombosis (DVT). Till now, the superiority of any one anticoagulant over the other has not been clearly determined. Evidence suggests that aspirin suffices for thromboprophylaxis in patients with low risk of DVT. Low molecular weight heparin or full-dose warfarin should be used in high-risk myeloma patients. Presently, with the introduction of anticoagulant prophylaxis, the rate of thromboembolism has been shown to be reduced to less than 10%.[10]

Lenalidomide

Shortly after the therapeutic potential of thalidomide was recognized, lenalidomide (an oral thalidomide analogue) was synthesized with the aim to increase efficacy and minimize nonhematologic toxicity associated with thalidomide .[14]

1. Mechanism of Action

Like thalidomide, Lenalidomide is an anti-angiogenic agent which shown to inhibits the adhesion of myeloma cells to bone marrow stromal cells. Additionally , Lenalidomide also decreases the secretion of growth and survival factors, induces proapoptotic factors for myeloma cells, down-regulates the activity of nuclear factor-kappa-B (NF-ƙB) and, promotes the cytotoxic activity of NK and T cells against myeloma cells by stimulating their proliferation and the secretion of interleulkin-2 (IL-2) and interferon gamma.[8]

2. Efficacy

With impressive response rates in relapsed multiple myeloma (even following failure of thalidomide)[12,15] Lenalidomide is currently approved by the Food and Drug Administration (FDA) for the treatment of multiple myeloma in combination with dexamethasone in patients who have failed at least one prior therapy.[15] Two randomized trials in patients with relapsed multiple myeloma comparing Lenalidomide plus dexamethasone with dexamethasone plus placebo demonstrated superior response rates and improved median progression-free survival and overall survival in the Lenalidomide group.[16,17]

In the first phase III, placebo-controlled trial, a response was observed in 60% of patients receiving Lenalidomide plus dexamethasone as compared to 24% in the group who received dexamethasone plus placebo ($p < 0.001$) with a complete response rate of 15.9% as compared to 3.4% in the placebo group ($p < 0.001$).[16] The time to progression was demonstrated significantly longer in the Lenalidomide group than placebo group (median, 11.3 months vs. 4.7 months; $p < 0.001$). The median overall survival (OS) was not reached in the Lenalidomide group and was 20.6 months in the placebo group ($p = 0.03$). Overall survival (OS) was also significantly improved in the Lenalidomide group among patients who had pre- viously received thalidomide ($p = 0.04$). In a similar study conducted in North America, complete, near-complete, or partial responses occurred in 61.0% of patients in the Lenalidomide group and in 19.9% of patients in the placebo group ($p < 0.001$); complete responses occurred in 14.1% and 0.6%, respectively ($p < 0.001$).[17] The median time to progression (11 vs. 4.7 months; $p < 0.001$) and median overall survival (29.6 vs. 20.2 months; $p < 0.001$) were also significantly higher in the Lenalidomide group. Moreover, in both the trials, grade 3/4 adverse events, including neutropenia and venous thromboembolism were higher in the Lenalidomide group.

3. Dosage

In the pivotal trials, Lenalidomide was administered at a dose of 25 mg once daily on days 1-21 along with dexamethasone 40 mg orally on days 1-4, 9-12, and 17-20 of each 28 days cycle for the first four therapy cycles. Starting with cycle five, Lenalidomide dose remained 25 mg once daily, but the dexamethasone dose is decreased to 40 mg daily on days 1-4 of each 28-day cycle. Lenalidomide is extensively eliminated unchanged by the kidneys. Recently, dose adjustment recommendations have been proposed in patients with a creatinine clearance rate of less than 50 ml/min.[8]

4. Side effects

As compared to thalidomide, Lenalidomide has a better safety profile and does not cause significant adverse affects like somnolence, constipation, or peripheral neuropathy, although myelosuppression is of concern, especially thrombocytopenia and neutropenia. Dose interruption or adjustment is recommended for patients with a platelet count less than 30,000/ ml^3 and/ or neutrophil count less than 1,000/ml.[3] Like with thalidomide, there is an increased incidence of thromboembolic events with Lenalidomide and hence similar thromboprophylactic strategies are recommended. Effective contraception is also required considering its known teratogenic potential.[8,12]

The Ubiquitin-Proteasome System and Proteasome Inhibitors in Multiple Myeloma

The Ubiquitin-Proteasome pathway is an intracellular proteolytic system which is shown to be involved in the degradation of a broad spectrum of intracellular proteins. The 26S Proteasome complex is a multisubunit complex, which processes ubiquitinated proteins for degradation. It has two 19S units flanking a barrel-shaped 20S Proteasome core. The 19S subunits control entry of ubiquitinated proteins into the core where they are degraded by enzymatic subunit with chymotrypsin, trypsin, and caspase-like activities into small peptides.[2,18]

Protein ubiquitination and degradation via Ubiquitin-Proteasome pathways regulates cell cycle progression, tumor suppression, transcription, deoxyribonucleic acid (DNA) replication, inflammation, and apoptosis. Therefore, inhibition of Ubiquitin-Proteasome pathway by Proteasome inhibitor affects a broader spectrum of proteins with diverse functions.[19] Proteasome inhibitors by blocking protein degradation are thought to cause accumulation of misfolded/ damaged proteins, which in turn triggers heat shock response and cell death.[19,20] Nuclear factor- kappa-B is thought to be a major target of therapy with Proteasome inhibitors.[21] NF-ƙB is linked to proliferation and drug resistance in cancer cells, including multiple myeloma. Proteasome inhibitors suppress NF-ƙB activity by stabilizing the inhibitory molecule IƙB, which binds NF-ƙB and prevents its nuclear translocation; thereby down-regulating levels of its targets and producing a potent antimyeloma effect.

Bortezomib

Although numerous Proteasome inhibitors were developed, the initial compounds lacked specificity and were not suitable for clinical use. Later Adams et al. designed and developed several boronic acid derived compounds that inhibit the Proteasome pathway in a highly specific manner. Bortezomib, a boronic acid dipeptide that reversibly inhibits the chymotrypsin-like activity of the 20S

Proteasome, was then selected for preclinical and clinical testing.[21,22]

1. Mechanism of Action

Bortezomib has shown to have rapid antimyeloma activity, with apoptosis of myeloma cells occur- ring within several hours after exposure. Bortezomib directly inhibits proliferation and induces apoptosis of human myeloma cell lines and freshly isolated patient-derived myeloma cells, even in myeloma cells resistant to conventional therapies. NF-ƙB is an important and specific target of Bortezomib within the myeloma cells. It has shown that, Bortezomib decreases the adherence of myeloma cells to the bone marrow stromal cells, thereby inhibiting paracrine (IL-6)-mediated growth of myeloma cells and enhancing susceptibility to therapeutic agents. Apoptosis is induced as a result of activation of caspase-8/ 9 and caspase-3. Additionally, Bortezomib also induces pro-apoptotic regulators, such as the TNF-α related apoptosis-inducing ligand (TRAIL) receptor, and suppresses antiapoptotic proteins such as survivin and Bcl-2.[2,19,20] Moreover, Bortezomib also has important effects on the development and progression of myeloma-associated bone disease. This results from decreased levels of receptor activator for nuclear factor KB ligand (RANKL) and dickhopf-1 (DKK-I) and increases levels of alkaline phosphatase and osteocalcin, two markers of bone formation with Bortezomib. Further, Bortezomib appears to inhibit osteoclast differentiation and augment osteoblast proliferation by inducing the differentiation of mesenchymal stem cells into osteoblasts.(Figure-2)[18,23,24]

2. Efficacy

Initial studies with Bortezomib in relapsed/refractory multiple myeloma showed high response rates. In the phase II Study of Uncontrolled Multiple Myeloma Management with Proteasome Inhibition Therapy (SUMMIT), relapsed/refractory myeloma patients were treated with Bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11 every 3 weeks. Dexamethasone was allowed in patients with suboptimal responses to Bortezomib alone.[25] The overall response rate was 35%, including 10% complete or near complete responses with a median overall survival of 16 months. The Clinical Response and Efficacy Study of Bortezomib in the Treatment of refractory myeloma (CREST) trial, comparing two dosages of Bortezomib (1.3 vs. 1.0 mg/m^2) showed that a reduced dose was able to produce responses in up to one-third of the patients with a trend towards a lower toxicity.[26] The Assessment of Proteasome Inhibition for Extending Remissions (APEX) has subsequently shown that Bortezomib was more effective than high-dose dexamethasone in relapsed myeloma, as demonstrated by a significant improvement in response rate (38% vs. 18%; $p < 0.001$), and median time to progression (6.2 vs. 3.4 months; $p < 0.001$).[27] An analysis after median follow-up of 22 months of APEX trial showed that median survival was 29.8 months for Bortezomib vs. 23.7 months for dexamethasone ($p = 0.0272$), a six-months benefit, despite substantial crossover from dexamethasone to Bortezomib.[28]

A phase III, randomized, multicenter, international trial compared the combination of Bortezomib with liposomal doxorubicin vs. Bortezomib alone in myeloma patients who had not previously received Bortezomib, and had received at least one prior therapy.[29] Although the response rates were not statistically significant between the two groups, the time to progression was significantly prolonged in the combination arm compared with Bortezomib Monotherapy (9.3 months vs 6.5 months; $p < 0.0001$). Among the responding patients, the median duration of response was longer with the combination arm (10.2 months) compared to the Monotherapy arm (7.0 months). Review of the above data led to the approval of use of liposomal doxorubicin in combination with Bortezomib in patients with multiple myeloma who have not previously received Bortezomib, and have received at least one prior therapy.

3. Dosage

The recommended starting dose for Bortezomib is 1.3 mg/m^2 administered as a 3-5 seconds bolus intravenous injection on days 1, 4, 8, and 11 of an every 21-day cycle. Dose interruption and modification are recommended for patients experiencing adverse events. The pharmacokinetics of Bortezomib does not appear to be influenced by the degree of renal impairment. However, dialysis may reduce Bortezomib concentrations; so it should be administered following dialysis.[8] Recently, in a phase 3 prospective randomized international study (MMY-3021), subcutaneous Bortezomib demonstrated comparable efficacy to intravenous Bortezomib (overall response rate after 8 cycles: 52% vs. 52%).[30] Pharmacokinetic and pharmacodynamic evaluation revealed that Bortezomib exposure following subcutaneous injection was equivalent to that following intravenous injection. More importantly, the use of subcutaneous Bortezomib was associated with reduced rate of peripheral neuropathy (PN) when compared to intravenous route (Grade < 3 PN: 38% vs. 53%; $p = 0.04436$ and Grade ≥3 PN: 6% vs. 16%; $p = 0.02636$, respectively).

4. Side Effects

The major adverse effects of Bortezomib include fatigue, gastrointestinal upset, painful peripheral neuropathy, anaemia, thrombocytopenia, and neutropenia. There is also an increased incidence of herpes simplex and herpes zoster infections.[12]

CONCLUSION

The introduction of thalidomide represented a major milestone in the treatment of multiple myeloma and the subsequent availability of its analogue Lenalidomide, and the Proteasome inhibitor Bortezomib have expanded the therapeutic armamentarium for myeloma.[31] In a population-based analysis of long-term survival of patients with multiple myeloma, it has observed that the overall, 5-year relative survival rates have increased from 28.8% to 34.7% ($p < 0.001$), and 10-year relative survival increased from 11.1% to 17.4% ($p < 0.001$) between 1990-1992 and 2002-2004.[32] Moe significantly higher increases were observed in the age group younger than 50 years, leading to 5- and 10-year relative survival of 56.7% and 41.3% in 2002-2004, and in the age group 50-59 years, leading to 5 and 10 year relative survival of 48.2% and 28.6% in 2000-2004. Only moderate improvement was observed in the age group 60-69 years, and no improvement was achieved among older patients. In a second single institution analysis, a clear improvement in overall survival (OS) from the time of relapse was seen, with those relapsing after 2000 having a median overall survival of 23.9 vs. 11.8 months ($p < 0.001$) for those who relapsed prior to this date.[29] This improvement was independent of other prognostic factors. Patients treated with one or more of the novel drugs (thalidomide, Lenalidomide, and Bortezomib) had longer survival from relapse (30.9 vs. 14.8 months; $p < 0.001$).

The above figures certainly raise the hope that the advent of novel therapies has made multiple myeloma a chronic disease. The challenge now is to determine whether these drugs should be given concurrently or in sequence with other drugs. Additionally, it is also important to determine which subgroups of patients would benefit most from these drugs.

Support: Nil

Conflict of Interest: None decelerated

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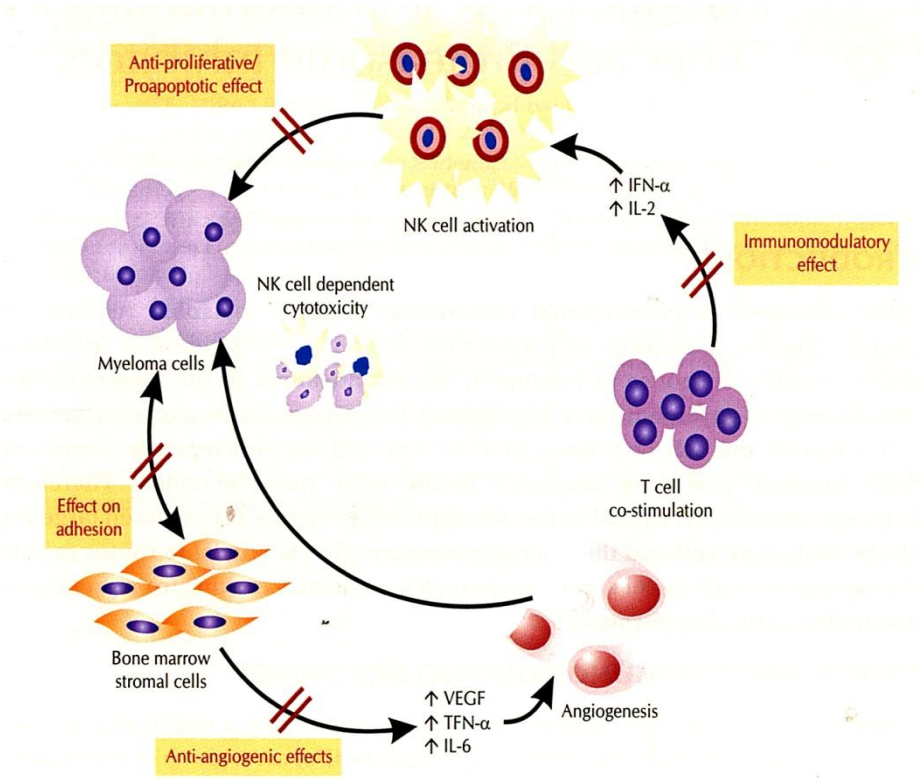

Figure-1: Mechanism of Action of Thalidomide. The Proposed Mechanism of Action of Thalidomide in Multiple Myeloma Include Direct Antiproliferative/Proapoptotic Effects Against Myeloma Cells, Indirect Targeting of Myeloma Cells By Inhibiting Tumor Cell Protection, Ant-Angiogenic Effects, And Immunomodulatory Effects.

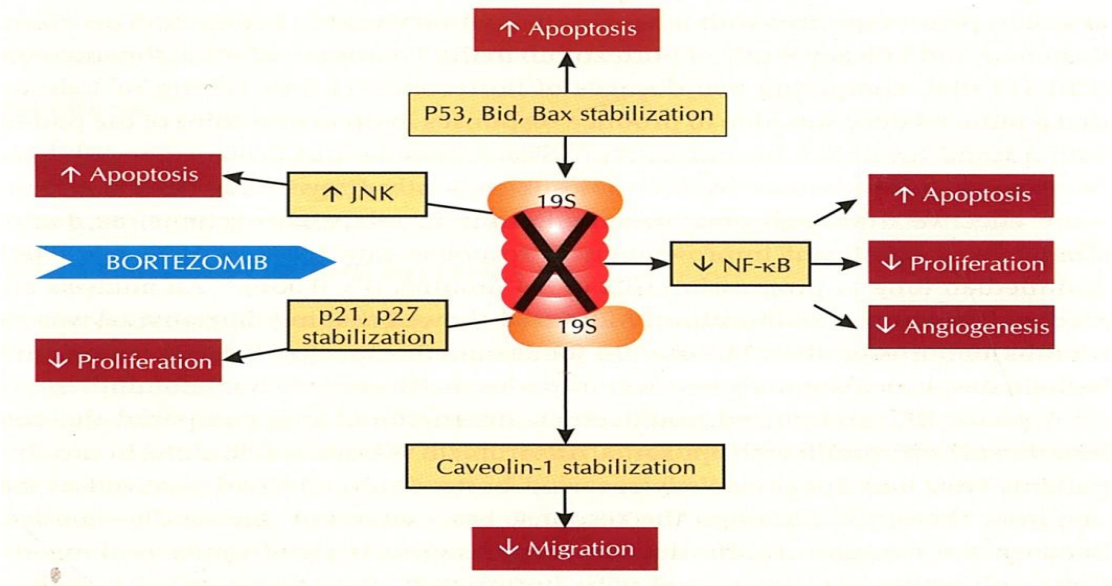

Figure-2: Bortezomib-Mechanism of Action. The Proteasome is a Multi-Subunit Enzyme Complex That Plays a Role in the Regulation of Cell-Cycle Progression and Apoptosis. Bortezomib is a Proteasome Inhibitor that Affects Various Growth and Sun/Ival Pathways in Multiple Myeloma Cells. Bortezomib Directly Inhibits Proliferation and Induces Apoptosis of Human Myeloma Cell Lines.