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Review Article

Review on special emphasis of bortezomib on relapsed/refractory myeloma

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ABSTRACT

Refractory or relapsed Multiple Myeloma (MM) is a plasma cell neoplasia characterized by paraproteins in the urine or serum and a bone marrow plasmacytosis of over 10%. Multiple/refractory myeloma is a neoplasm of plasma cells and exact cause of multiple myeloma is remain unidentified, it is characterized by accumulation of malignant plasma cells in the bone marrow, leading to bone marrow failure, anemia, skeletal destruction, renal failure, increased susceptibility to infection and hypercalcemia. The survival time for the patients with refractory or multiple myeloma can be prolonged with treatment of newer and more target specific approach. The proteasome inhibitors are an important class of anti-myeloma drugs that have efficacy to disrupt the proteolytic structure of tumor cells and enhancing their susceptibility to apoptosis. Bortezomib has a significant clinical efficacy against refractory multiple myeloma. Bortezomib is the most commonly used and clinically tested proteasome inhibitor and which is effective in prolonging the overall survival in several trials. Bortezomib combinations with other drugs such as dexamethasone and cyclophosphamide are the choice of treatment for standard risk patients following the mSMART guidelines. The success with lower dosage of bortezomib in elderly patient's proven efficacious subcutaneous usage and its useful proteasome inhibitor to enhance patient's compliance and reduces toxicity and costs of therapy. This review discusses on special emphasis of bortezomib on relapsed/refractory multiple myeloma as front-line treatment.

Keywords: Bortezomib, Neoplasia, Proteasome inhibitors, Relapsed/refractory multiple myeloma

INTRODUCTION

Myeloma arises from an asymptomatic premalignant proliferation of monoclonal plasma cells that are derived from post-germinal-center B cell. Multistep genetic and micro-environmental changes take place for transformation of these cells into a malignant neoplasm. Myeloma is thought to progress most commonly from a monoclonal gammopathy of undetermined clinical significance that progress to smoldering myeloma and, finally, to symptomatic myeloma. Several genetic abnormalities occur in plasma cell of tumor and play major role in the pathogenesis of myeloma.[1]

Multiple/refractory myeloma is a neoplasm of plasma cells and exact cause of multiple myeloma is remain unidentified, it is characterized by accumulation of malignant plasma cells in the bone marrow, leading to bone marrow failure, anemia, skeletal destruction, renal failure, increased susceptibility to infection and hypercalcemia. Bone pain, recurrent infections and fatigue, typically related to anemia, are common symptoms at first presentation. A number of biological parameters, including serum b2-microglobulin, C-reactive protein, lactate dehydrogenase, and albumin, are important prognostic factors, as are cytogenetic abnormalities, which are detected by Fluorescent *In Situ*

Hybridization (FISH) or conventional karyotyping. Indeed, FISH-defined cytogenetic alterations have been identified in 90% of patients with newly diagnosed multiple myeloma.[2]

Notably, the chromosomal alterations del (13), t (4; 14), and del (17p) have been observed in 48, 14 and 11% of patients, respectively, and are associated with poor overall survival (OS).[2]

Relapsed and refractory Multiple Myeloma (MM) constitutes a specific and unmet medical need. The response to therapies is identically short and median survival time is six to nine months. [3]

Patients with relapsed/refractory myeloma are defined as those who have achieved minor response to treatment, relapse and then progress while on appropriate therapy, or occurrence of progression within 60 days of their last treatment. [3]

Although several prognostic factors are responsible for newly diagnosed myeloma, factors that are retain to identify the prognostic concern of relapsed/refractory myeloma to be comprehensively defined. Several prognostic factors and progression of disease is shown in Figure 1 & 2.[3]

THERAPY FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA

According to the NCCN 2010 treatment guidelines for multiple/refractory myeloma, second-line therapies with the highest level of supportive evidence include bortezomib with pegylated liposomal doxorubicin (in patients who have received at least one prior non-bortezomib therapy), or lenalidomide-dexamethasone. Recommendations with a lower level of evidence include bortezomib-dexamethasone, or single-agent dexamethasone or lenalidomide. Thalidomide-dexamethasone and-or chemotherapy are also an option. Alternatively, patients can be treated with high-dose cyclophosphamide, cyclophosphamide-VAD (vincristine, doxorubicin, and dexamethasone) or cyclophosphamide-dexamethasone chemotherapy or retreated with primary induction therapy if relapse occurs after more than 6 months after its completion.[4]

Clinical recommendations by the European Society for Medical Oncology (ESMO) for the treatment of relapsed or refractory multiple myeloma include thalidomide (dexamethasone and/or chemotherapy); bortezomib (dexamethasone or chemotherapy); or lenalidomide/dexamethasone. VAD is not considered to be a standard salvage treatment option by the ESMO.[5]

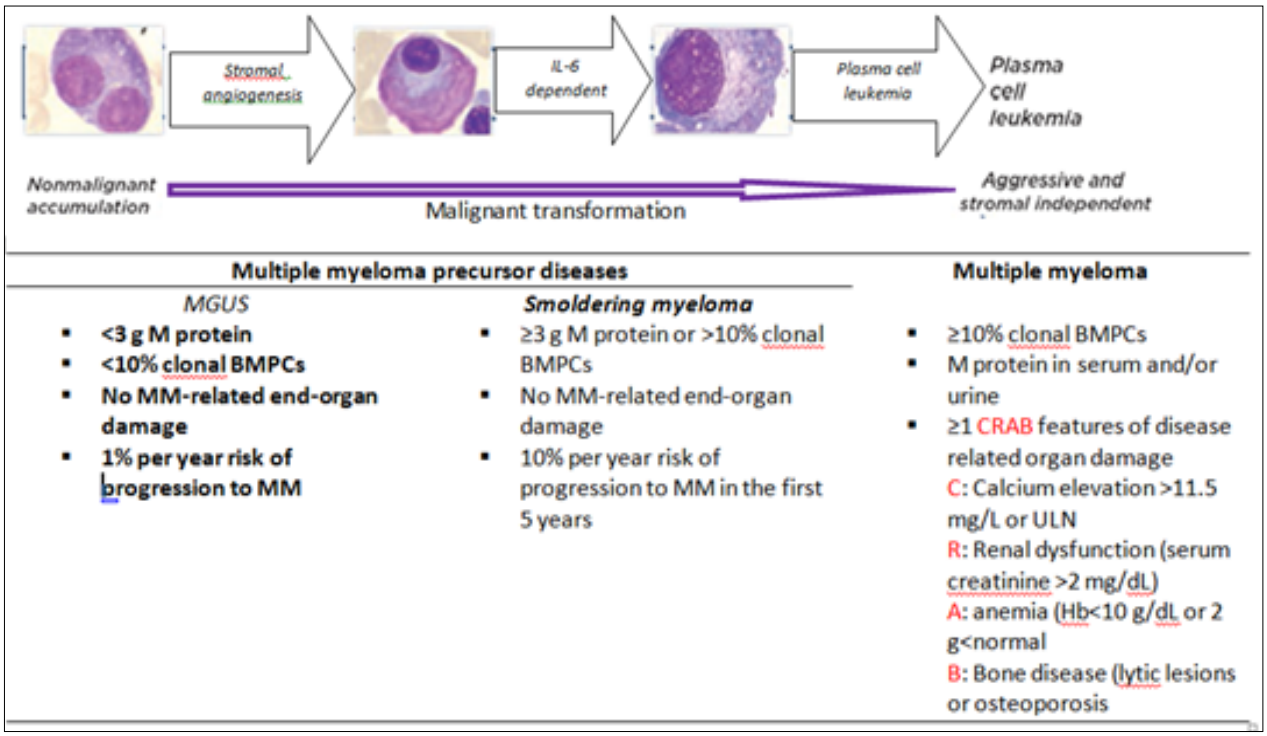

Figure 1: Multiple myeloma disease continuum and disease characteristic.[6]

IL-6 (Interleukin-6); MGUS (monocolon gammopathy of unknown significance); M protein (myeloma protein); BMPCs (bone moarrow plasma cell); MM (multiple myeloma); ULN (upper limit of normal); Hb (hemoglobin)

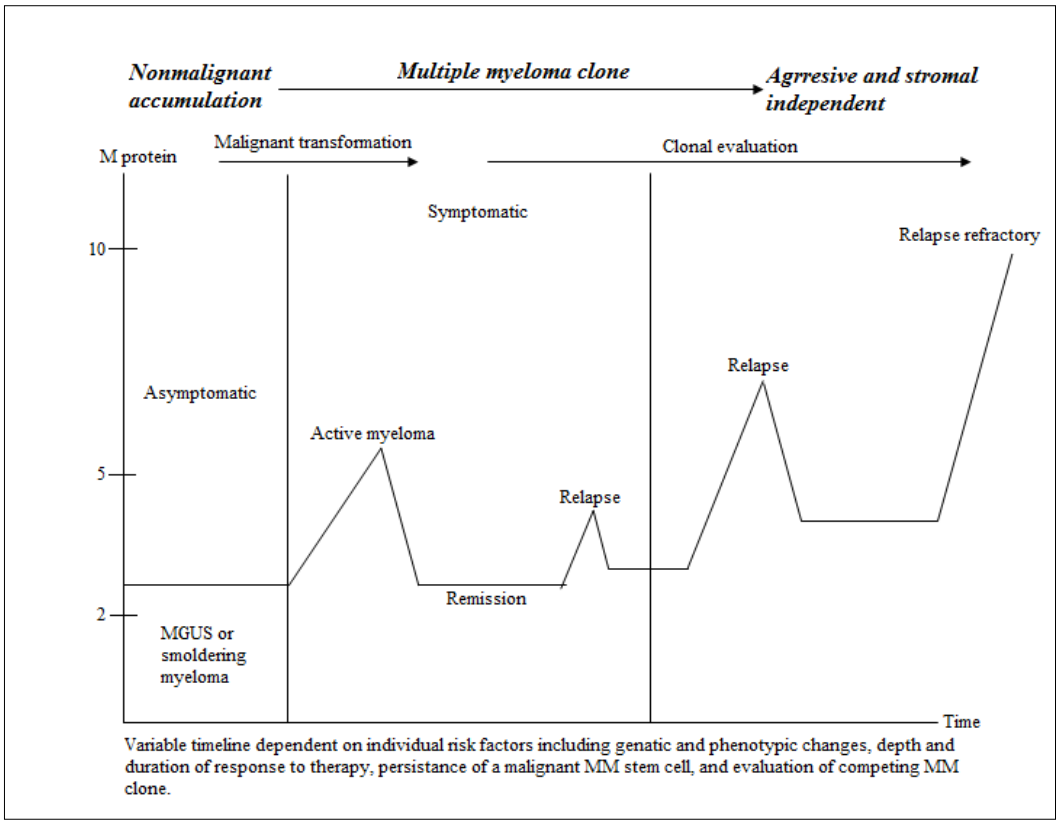

Figure 2: Multiple myeloma diseases trajectory characterized by malignant transformation; serial cycles of response, remission, and relapse in the presence of treatment; and clonal evaluation with diminished depth and duration of response over time.[6]

BORTEZOMIB

Bortezomib is the first new class of antineoplastic agents called proteasome inhibitors. Proteasome are multi-enzyme complexes of every cells and their inhibition prevents cell cycle leading to cell death. Cancerous cells are more sensitive to bortezomib compared normal cells. Bortezomib is approved drug under exceptional circumstances, for their use in patients who have already received at least two prior therapies for Multiple Myeloma (MM), and have reported with disease-progression on the last therapy.[7]

Bortezomib is the first Food and Drug Administration (FDA)-approved proteasome inhibitor for multiple myeloma. In 2003, the FDA granted accelerated approval for the marketing of bortezomib (Velcade, PS-341) as a single agent for the treatment of MM. Approval was based on phase II clinical study reports where of the 188 patients enrolled with MM, 27.7% experienced either a Complete Remission (CR) or Partial Response (PR) with treatment of bortezomib. The employed dosage was 1.3 mg/m^2 and which was approved for usage in multiple myeloma patients who experienced disease progression with last treatment. Later in 2005 the FDA granted permission for use of bortezomib in patients with only one prior treatment with disease progression.[8]

CLINICAL EVIDENCES ON BORTEZOMIB

The open label phase II clinical trial by Jagannath et al. have enrolled newly diagnosed subjects with multiple or refractory myeloma with no prior exposure to steroids.[9] In this study the bortezomib was administered at a dose of 1.3 mg/m^2 and responses were evaluated with reference of EBMT criteria. Around 40% of study population was responded by 2nd cycle which resulting in one Complete Response (CR), 11% was noted as near Complete Response (nCR) and 28% of study participants were noted with Partial Response (PR). Combine treatments of bortezomib with dexamethasone in 22 subjects were shown additional response in 68% of study population. A 40% RR was noted with the treatment of bortezomib alone and the RR was improved up to 88% with combine treatment. An estimated survival rate was 87% after 12 months of treatment. A 31% of study population experienced with grade 2 or 3 neuropathy while 25 % subjects were reported with painful neuropathy. Neuropathic pain was disappeared in three months of stopping bortezomib. Other side effects such as constipation, myalgia and fatigue were note of varying

severity. Overall response was found 90% on their extended follow-up with combine treatment. Furthermore the estimated survival rate was found 67%.[10,13]

First prospective, randomized open labelled clinical study was conducted by San *et al* in 2008 which is known as VISTA trial. Study was conducted to evaluate efficacy of Bortezomib-Melphalan-Prednisone (VMP) as a front line therapy in earlier untreated MM patients. Study included 682 participants in which 340 received VMP and 337 received MP (Melphalan-Prednisone). The median of time to progression was noted 24 months in VMP arm and 16.6 months in the MP arm. CR rate were observed significantly (P <0.001) higher in VMP arm (30%) when compared to MP arm (4%). Interestingly the results of VMP arm was not affected with age and renal impairment as the achieved CR rate and median time for progression were found identical.[14]

The phase III study by Michele et al. have evaluated efficacy of VTD vs. TD as followed by tandem SCT and consolidation with the same regimens respectively. Induction of VTD therapy before double autologous stem-cell transplantation significantly improves rate of complete or near complete response, and represents a new standard of care for treatment of multiple myeloma.[15]

Wang et al have evaluated safety and efficacy of subcutaneous administration of bortezomib in 26 (multiple/refractory myeloma) MM subjects. In this study, 12 patients received bortezomib via subcutaneous administration while 14 patients received bortezomib via conventional intravenous administration. In this study the overall response (OR) rates in subcutaneous and intravenous treatment group were 75.00% and 71.43% respectively, in which Complete Remission (CR) plus Very Good Complete Remission (VGPR) rates were 50.00% and 47.14%, while CR rates were 16.67% and 28.57%, respectively. Time required to achieved effectiveness in two group was found similar with statistical significant P <0.05. Moreover the rate of peripheral neuropathy was found significantly lower in subcutaneous group when compared to intravenous group. Subcutaneous administration of bortezomib enhances the safety and efficacy compared to intravenous administration in MM subjects.[16]

Ghosh et al. have assessed beneficial effect of bortezomib with thalidomide on multiple/refractory myeloma. Steroid free phase II clinical study achieved high RR ($PR = 81.5%) with 25.6% $ nCR and a 3 year OS of 74% (CI: 54%-89%) without SCT. A 22% subjects were reported with grade III Painful Neuropathy (PN) and 80% subject have noted with resolved symptom of PN with discontinuation. Prominently, no hyperglycemic complications or thrombotic events were noted, a phenomenon which has previously been reported.[17] Other trial was shown comparable results of treatment with bortezomib, pegylated doxorubicin and thalidomide combination with 78% ORR, of which 35% achieved CR + nCR. The overall toxicity was manageable without treatment associated death.[18] The promising results of phase II study of steroid-free regimens indicates further phase III verification for the safety and efficacy.

CONCLUSION

Bortezomib is first new class anticancer medical agent which act through inhibiting proteasome. Inhibition of proteasome is responsible to disrupt the cell cycle leading to cell death. Cancerous cells are highly sensitive to bortezomib than normal cells. Bortezomib is been approved and can be used for the patients who received at least two prior treatment and have experienced with progression of MM.

Phase III clinical study on the comparison of treatment with other anticancer drug suggests superiority of bortezomib. And subcutaneous administration of bortezomib is more safe and efficacious compared to conventional intravenous administration in MM patients. Most common adverse effects reported with clinical studies of bortezomib were pyrexia, asthenic condition, thrombocytopenia, neuropathic pain, gastrointestinal disturbance and anemia.

Proteasome Inhibitors have provided a major new therapeutic strategy for the treatment of multiple Myeloma. Bortezomib, is a first-in-class of proteasome inhibitors and has come after long time of its clinical development as a most safe and efficacious drug for multiple/refractory myeloma. Many research concluded that the bortezomib combine regimens increases the therapeutic spectrum from first-line induction to follow-up treatment for MM. Bortezomib is effective at every stage of MM. bortezomib have shown specific role with certain clinical condition of disease. Many clinical trials revealed that the bortezomib can be part of high-risk population and needs to be given for an extended time period for follow-up. Insufficient renal excretion of drugs decreases the importance of drug for the patients with renal sufficiency. In the multiple or refractory myeloma a bortezomib can be repetitive with combine treatment with other drugs. As a final point, subcutaneous administration of bortezomib at once in a week has significantly reduces neurological toxicity which is allowing for its prolong use in MM patients.

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