ENORMITY OF THE DISEASE: THE ENDEMIC

Multiple myeloma (MM) is a violent and the second most hematological malignancy after non-Hodgkin’s lymphoma, characterized by proliferation of malignant plasma cells involving bone marrow, reason for roughly 15% of lymph hematopoietic cancers.\cite{1,2} It accounts for an estimated 14,000 new cases per year in the USA and accounts for 10% of all hematologic cancers with 10,790 deaths estimated in the U.S. in 2007 and 19,200 deaths in the European Union in 2004.\cite{2-6} The average years of life lost in patients with myeloma is higher than in many other cancers and amounts to >30 years in patients younger than 40 years old but decreases to <5 years in patients aged ≥80 years.\cite{7}

The horizon of treatment alternatives for patients with relapsed MM has radically changed over the past 10 years such that many patients can now enjoy long periods of remission following relapse.\cite{8} These retardations are due, in large part, to the development of new classes of agents, such as thalidomide, bortezomib and lenalidomide - all of which have substantial activity not achieved solely by aiming at classical targets of cytotoxic chemotherapeutics (e.g., DNA or cytoskeleton) but also by targeting of other molecular pathways implicated in regulation of the proliferation and survival of MM cells, including the molecular mechanisms underlying the protective effects of the bone marrow (BM) microenvironment on MM cells.\cite{8,9}

MULTIPLE MYELOMA

Biology of multiple myeloma: The entangled intricacy

Multiple myeloma is a neoplastic disease of either (i) transformed plasmablasts that has successfully completed somatic hypermutation and immunoglobulin H (IgH) switching in the germinal center before migrating to the BM or (ii) transformed terminally differentiated long-lived plasma cells in the BM.\cite{10} An increase in osteoclast function, along with an inhibition of osteoblast ability to produce new bone, results to the development of lytic lesions.\cite{11-14} Suppression of osteoblast precursor differentiation and induction of apoptosis in mature osteoblasts result in decreased bone formation. Increased production of molecules, such as dickkopf-1 and secreted frizzled-related protein 2, which act as Wingless-type signalling antagonists are, at least in part, responsible for the osteoblast dysfunction

**ABSTRACT**

The treatment of multiple myeloma (MM) has undergone significant developments in recent years. The availability of the novel agents includes thalidomide and its analogs, proteasome inhibitors, arsenic trioxide, farnesyltransferase inhibitors 2-methoxyestradiol and lenalidomide has extended treatment options and has improved the outcome and quality of life of patients with MM. This review presents the totality of evidence through a systematic review that assessed the efficacy, safety or toxicity of bortezomib in patients with relapsed/refractory myeloma with or without concomitant complications. This review has precisely covered the role of bortezomib in patients with relapsed/refractory myeloma and not the newly detected populace.

Key words: Bortezomib, multiple myeloma, relapsed/refractory myeloma
in MM [Figure 1].[15-17] Other molecules such as interleukin (IL)-7 and IL-3 have been shown to inhibit osteoblastic differentiation in vitro.[18,19] Furthermore, transforming growth factor β, whose release is increased by enhanced osteoclastic activity, inhibits osteoblast maturation and mineralization.[20,21]

Apoptosis of osteoblasts is mediated by increased expression of the Fas ligand and tumor necrosis factor (TNF)-related apoptosis-inducing ligand on myeloma cells, which activate the Fas receptor and the death receptor-4/5 on cells of the osteoblast lineage.[22] Osteoblast function is also impeded by the rapid growth of myeloma cells,[23] which attach to bone marrow stromal cells [BMSCs; Figure 1] stimulating the production of osteoclast-activating factors such as receptor activator of nuclear factor-kappa B ligand (RANKL), macrophage colony-stimulating factor, as well as an assortment of cytokines (IL-6, IL-1b, IL-11).[24,25] The secretion of TNFα and other cytokines into the myeloma bone microenvironment induces osteoblasts and BMSCs to produce additional RANKL and decrease the production of osteoprotegerin [Figure 1], the decoy receptor for RANKL.[26-28] Furthermore, macrophage inflammatory protein 1-alpha, hepatocyte growth factor, and vascular endothelial growth factor are increased in the bone microenvironment, further stimulating osteoclastogenesis and bone digestion.[26-30] Increased osteoclast activity can be detected by the production of type I collagen breakdown products, as well as by the release osteoclast-specific enzymes. Further changes in the cytokine milieu also contribute to bone loss.

**Relapsed and/or refractory myeloma**

Refractory myeloma is defined as disease that is non-responsive while on primary or salvage therapy, or progresses within 60 days of last therapy. Non-responsive disease is defined as either failure to achieve minimal response or development of progressive disease (PD) while on therapy. There are 2 categories of refractory myeloma: “relapsed-and-refractory myeloma” and “primary refractory myeloma.” Whereas relapsed myeloma is defined as previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either “primary refractory myeloma” or “relapsed-and-refractory myeloma” categories. Relapsed and refractory myeloma is defined as disease that is non-responsive while on salvage therapy, or progresses within 60 days of last therapy in patients who have achieved minimal response (MR) or better at some point previously before then progressing in their disease course.[31]

With perspective to relapsed and/or refractory, three groups of patients exist:[5,32]

- Patients whose first progression occurs in the absence of any therapy following successful initial therapy
- Patients having relapsed and refractory disease, who are defined as progression on a specific therapy, or within 60 days of completion of a given therapy (International Myeloma Working Group Consensus Panel, International Myeloma Workshop, February 2009)
- Patients who did not achieve a response following induction therapy

**MANAGEMENT APPROACHES TO RELAPSED/REFRACTORY MYELOMA**

The existing therapies for the treatment of relapsed/refractory myeloma have been outlined in Table 1.[8]

**A LIGHT ON THE PROTEASOME INHIBITOR - BORTEZOMIB**

Bortezomib is the first drug from the class of proteasome inhibitor with established efficacy in both newly diagnosed, as well as relapsed/refractory MM patients. The proteasome is a multiprotein complex comprised of a cylindrical 20S core particle associated with two 19S regulatory units. Bortezomib is a dipeptidyl boronic acid that potently and selectively inhibits the activity of the proteasome [Figure 2]. Bortezomib is the first proteasome inhibitor to be approved by the U.S. Food and Drug Administration (FDA) and the European Agency for the Evaluation of Medicinal Products (EMA) for the treatment of refractory or relapsed MM following the failure of at least two prior lines of therapy. Recently, it also received approval from the FDA for use as a second-line agent. Subcutaneous bortezomib is approved by the U.S. FDA for the treatment of multiple myeloma and relapsed mantle cell lymphoma in January 2012, and by Health Canada for the treatment of MM in March 2012. Committee for Medical Products for Human Use (CHMP) of the European Medicines Agency (EMA) has granted a positive opinion recommending...
approval of subcutaneous (under the skin) administration of bortezomib. Subcutaneous bortezomib has fewer side effects and offers greater convenience for patients, with similar efficacy compared to intravenous bortezomib.

Bortezomib in multiple myeloma
Renal failure is a common appearance and end organ damage of multiple myeloma (MM). It may complicate the treatment and management of the disease. Pharmacological dose escalating studies of bortezomib have shown that the pharmacokinetics of bortezomib is independent of renal clearance and not influenced by the degree of renal impairment. The reversal rate of renal impairment in patients with MM has been shown to be about 30-44% in patients using bortezomib-based treatments, which had been better than that achieved by combinations not including bortezomib. Most of the earlier studies including randomized controlled trials have reported similar toxicity profiles for bortezomib in patients with normal and impaired renal functions. A recent study data support the activity of bortezomib in patients with renal impairment. Overall and severe adverse event, dose modification, and treatment discontinuation rates are higher in those patients. Patients with renal failure experience more thrombocytopenia and diarrhea. Particularly diarrhea may be a problem by leading to serious adverse events in those patients with MM using bortezomib as monotherapy.

A CHAIN OF CLINICAL EVIDENCES WITH BORTEZOMIB

Bortezomib has been investigated in number of randomized trials for the efficacy and safety in patients with relapsed/refractory myeloma conditions.

- In the SUMMIT trial (2003), 202 patients with relapsed and refractory myeloma were treated with single agent. Bortezomib for up to 8 cycles with an overall response rate of 35% using the European Group for Blood and Marrow Transplantation (EBMT) criteria. The response rate was increased to 50% with the addition of dexamethasone on the day of and the day after each injection of bortezomib. Responses were independent of the type or number of previous treatments, b2-microglobulin and chromosome 13 deletion status - factors which have previously influenced response to other types of chemotherapy.

- In the CREST study (2004), 54 patients with relapsed myeloma following one line of therapy were randomized to receive bortezomib at either 1.0 Mg/m² or 1.3 Mg/m². Overall response rates were 33% and 50%, respectively. Again when dexamethasone was added, response rates were higher at 44% and 62%, respectively. The incidence of adverse events was 20% lower in the group receiving 1.0 mg/m² suggesting that patients with unacceptable toxicities receiving 1.3 Mg/m² may be able to tolerate a reduced dose of bortezomib and still achieve good response rates.

- The assessment of proteasome inhibition for extending remissions (APEX) trial was a randomized phase III trial set
up to compare bortezomib with high dose dexamethasone in 669 patients with multiple myeloma who had relapsed after one or more therapies. The results showed a significant survival benefit in the bortezomib group and the trial was terminated early with the dexamethasone patients crossing over to the bortezomib arm. Overall response rates were 38% in the bortezomib arm versus 18% with dexamethasone alone ($P < 0.001$). The results were updated at American Society of Hematology (ASH) in December 2005 based on a median follow up of 15.8 months with a response rate of 43% to single agent bortezomib and 9% of patients achieving a complete response. Response rates were higher in those who had only received one prior line of therapy. At one year, overall survival was 80% in those who had received bortezomib compared with 67% in the dexamethasone arm, with a six month survival advantage for patients treated with bortezomib. It was concluded from this phase III data that bortezomib is superior to high dose dexamethasone as second line treatment for relapsed myeloma.[37]

- In 2005 Wu, et al. evaluated the efficacy and toxicity of bortezomib for treatment of relapsed or refractory MM in community practice. Bortezomib can induce marked and durable response in advanced MM. Overall, bortezomib was well tolerated and the toxicity was acceptable.[38]

- Freimann, et al. (2007) explored the use of bortezomib to treat patients with relapsed/refractory MM in routine clinical practice. This study in daily oncology practice confirmed findings from clinical trials, demonstrating high response rates and predictable adverse events in patients with relapsed/refractory MM treated with bortezomib.[39]

- Orlowski, et al. (2007) compared the efficacy and safety of a combination of pegylated liposomal doxorubicin (PLD) plus bortezomib with bortezomib monotherapy in patients with relapsed or refractory MM. This randomized phase 3 study demonstrated that PLD with bortezomib is superior to bortezomib monotherapy for the treatment of patients with relapsed or refractory MM. The combination therapy is associated with a higher incidence of grade 3/4 myelosuppression, constitutional symptoms, and GI and dermatologic toxicities.[40]

- Anargyrou, et al. (2008) investigated bortezomib in 35 patients with relapsed/refractory MM. Bortezomib administration resulted in the normalization of the serum ang-1/ang-2 ratio. This revealed that part of bortezomib's anti-myeloma effect may be accomplished via anti-angiogenetic action through the Tie2- angiopoietin system. The study concluded that in patients with relapsed/refractory MM presented a low ang-1/ang-2 ratio, while response to bortezomib administration was accompanied by normalization of this ratio.[41]

- The investigators of Minnie Pearl Cancer Research Network in 2008 evaluated the efficacy and toxicity of weekly bortezomib in the treatment of patients with recurrent/refractory MM. A total of 40 patients with MM who had received either 1 or 2 previous treatment regimens were treated with bortezomib at a dose of 1.6 mg/m² intravenously for 4 consecutive weeks, followed by 1 week without treatment. Responses were measured using International Myeloma Working Group criteria. The study projected a schedule of weekly bortezomib to be effective and well tolerated in patients with previously treated MM. Although the response rate and duration appear comparable to those achieved with twice-weekly bortezomib, the relative efficacy of these 2 schedules cannot be determined definitively on the basis of this phase 2 study. A weekly schedule of bortezomib is a reasonable option for patients who have logistic difficulties receiving a twice-weekly schedule, and is an attractive schedule for incorporation into combination regimens.[42]

- **Bortezomib vs. Thalidomide:** Satoh, et al. (2011) studied the efficacy and safety of bortezomib for treatment of MM in comparison with thalidomide by reference to adverse events, and searched for laboratory markers that could be used for prognostication of patients. Bortezomib showed a higher rate of effectiveness than thalidomide for refractory MM, and its effects were rapid. The overall survival of bortezomib-treated patients tended to be longer than that of thalidomide-treated patients. The efficacy of bortezomib was unrelated to patient age, the number of previous therapeutic regimens, or the disease period. After medication with bortezomib, patients in whom it had been effective tended to show an increase of the serum alkaline phosphatase (ALP) level. Thrombocytopenia (86.2%) and leukopenia (69.0%) were observed at high frequencies, but no previously unreported adverse events or fatalities were associated with bortezomib therapy.

The study evaluated that bortezomib has therapeutic efficacy for MM as a first-line medical treatment and/or for patients with thalidomide resistance, and can improve prognosis and survival. Since serum ALP elevation was observed in many patients for whom bortezomib was effective, this may be a predictor of bortezomib efficacy.[43]

**SUMMARY**

Based on encouraging results from the several phase II and phase III trials have demonstrated impressive role of bortezomib-based regimens’ efficacy in the frontline treatment of MM. However, the disease remains irredeemable. Further, the potential of newer proteasome inhibitors and their combinations is to be explored for morbidity and mortality tendencies in relapsed/refractory myeloma.
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