Management of Myeloma: An Italian Perspective

Benedetto Bruno, Francesca Gay, Mario Boccadoro, Antonio Palumbo

Abstract

Multiple myeloma remains a fatal plasma cell malignancy. However, new insights into the disease biology and immunology have identified molecular mechanisms, underling functional interactions between plasma cells and the bone marrow microenvironment that have become molecular targets of so-called "new drugs" such as thalidomide, lenalidomide, and bortezomib. Recently, the combinations of new drugs with melphalan and prednisone in elderly patients, and with autologous stem cell transplantation in induction and/or maintenance schedules in younger patients have significantly prolonged overall survival. Optimal combinations and timing are a matter of debate. Moreover, management of side effects is a key clinical target to improve long-term quality of life. Many randomized phase III studies are currently in progress to address these issues. Whether these new advancements in myeloma treatment will eventually translate into a long chronic phase or a monoclonal gammopathy of undetermined significance–like status for the majority of patients remains, however, still unanswered.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 11, No. S1, S82-6
Keywords: Multiple myeloma, New drugs

Introduction

Multiple myeloma represents the second most common hematological malignancy worldwide and causes about 11,000 and 19,000 deaths every year in the United States and Europe, respectively.[1,2] The introduction of "new drugs," such as thalidomide, bortezomib, and lenalidomide has significantly improved overall response rates, progression-free survival, and overall survival.[3] Relapsed patients rescued with these new drugs had longer survival from disease recurrence as compared with those who were not treated with these new therapies (30.9 versus 14.8 months, $P < .001$). Moreover, in the past decade, newly diagnosed patients had a 50% improvement in overall survival as compared with those diagnosed before December 1996, when thalidomide was first introduced (44.8 versus 29.9 months, $P < .001$).[3] Allografting has been regarded as the only potentially curative treatment.[4–6] However, the high transplant-related mortality greatly limited its use.[7,8] Reduced-intensity conditionings, where graft versus myeloma effects play a more important role than the intensity of the preparative regimen, have been explored.[9–12]

However, results from different groups are conflicting and allografting has become a less attractive option.[13–16] Here we present a brief description of the three agents, thalidomide, lenalidomide and bortezomib, that dramatically changed the treatment paradigm of multiple myeloma treatment and focus on a sequential treatment strategy that may translate into high complete remission rates and prolonged overall survival.

Divisione di Ematologia dell'Università di Torino, Azienda Ospedaliero-Universitaria San Giovanni Battista di Torino, Torino, Italy

Submitted: Jan 19, 2011; Revised: Mar 23, 2011; Accepted: Mar 25, 2011

Address for correspondence: Benedetto Bruno, MD, PhD, Divisione di Ematologia dell'Università di Torino, Azienda Ospedaliero-Universitaria San Giovanni Battista, Via Genova 3, 10126 Torino
Tel: +39 011 633 4354; fax: +39 01 1696 3737; e-mail contact: benedetto.bruno@unito.it

"New Drugs" and Their Mechanisms of Action

Thalidomide and Immunomodulatory Drugs. Initially, the anti-angiogenic characteristics of thalidomide and the correlation between bone marrow angiogenesis and disease activity formed the empirical basis for its clinical use of in refractory/relapsed myeloma. However, the evidence that bone marrow microvessel density were not significantly changed in responsive patients soon indicated that this drug is also endowed with other mechanisms of action. Thalidomide induces G_1 growth arrest and apoptosis in myeloma cells and shows immune-modulatory effects by inducing CD3+ T-cell proliferation, secretion of interferon gamma (IFN-γ) and interleukin 2 (IL-2), and natural killer cell expansion that could trigger myeloma cell lysis.[17] Importantly, thalidomide was soon shown to act in synergy with dexamethasone.[18] The very first evidence of the clinical efficacy of thalidomide was in patients with heavily pretreated multiple myeloma (MM) refractory to conventional or high-dose chemotherapy. Singhal et al[19] reported ≥ 25% reductions in serum or urine paraprotein levels in 32% of 84 patients. At the time of publication, side-effects included constipation, peripheral neuropathy, weakness, and morning somnolence whereas severe neutropenia was a rare event. This pioneering experience was later updated on a large series of patients and confirmed the encouraging data.[20]

2152-2650/$ - see frontmatter
doi: 10.1016/j.clml.2011.03.026

Thalidomide derivatives were later developed. Two major classes of chemical and functional analogues were developed and defined as selective cytokine inhibitory drugs and immunomodulatory drugs.[21] Among these latter, CC-5013, or lenalidomide, was shown to be up to 2000 times more potent in inducing T-cell proliferation and up to 100 times in enhancing IL-2 and IFN-γ secretion.[22] Richardson et al initially reported a phase I study on 27 patients with relapsed or refractory myeloma. Lenalidomide was given at four daily doses: 5 mg, 10 mg, 25 mg, and 50 mg.[22] Grade 3 myelosuppression was seen in all patients treated with 50 mg, and 25 mg was then considered the maximal tolerated dose. A $\geq$ 25% paraprotein reduction was observed in 17 of 24 patients. Importantly, most of them had received prior therapy with thalidomide.

Proteosome Inhibitors. Bortezomib is the prototype of proteasome inhibitors.[23] Its molecular target is the 26S proteasome, a cytoplasm multisubunit protein complex which regulates the turnover of several intracellular proteins controlling fundamental cell functions such as cell cycle and apoptosis. Bortezomib shows high affinity and specificity for the catalytic activity of the 26S proteasome, the inhibition of which can block protein degradation. Nuclear factor κB (NF-κB) is a transcription factor bound to its inhibitory partner protein κB (IκB). Once IκB is phosphorylated in the cytoplasm is eventually degraded by the 26S proteasome complex with the release of NF-κB, that migrates into the cell nucleus and induces the synthesis of antiapoptotic proteins. The biological NF-κB functions are blocked by the inhibition of IκB degradation within the proteosome complex which sequesters NF-κB in the cytoplasm.[24,25] Orlowski et al initially reported a phase I study on 27 patients with advanced hematological malignancies.[26] Interestingly, 9 patients with advanced plasma cell disorders showed a response including a complete remission in a myeloma patient. Evidence of significant clinical activity was provided by Richardson et al in a phase II study of 202 heavily pretreated myeloma patients.[27] Responses were seen in 67 patients, including 7 complete remissions with negative immunofixation.

Toxicity Profiles

Toxicity of new drugs represents a clinical challenge. Venous thromboembolism soon emerged as the most serious side effect of thalidomide in untreated newly diagnosed myeloma patients.[28] Most thromboembolic episodes occurred early and distant from central venous catheters suggesting a systemic thalidomide-induced prothrombic state.[29] However, no baseline prothrombotic laboratory abnormalities could be identified. Prophylaxis is now routinely administered in newly diagnosed patients.[30] Other side effects, such as peripheral neuropathy, numbness, and paraesthesia appeared to correlate with drug dose and treatment duration and should promptly be recognized before neurological damage becomes irreversible.

Lenalidomide has shown a safer toxicity profile.[31] Myelosuppression may be a serious side effect requiring drug reduction or discontinuation. Every effort should be made to manage adverse events so that patients can remain on treatment to ensure the greatest treatment efficacy. Prolonged neutropenia can effectively be managed by dose modifications and addition of granulocyte–colony-stimulating factor (G-CSF), whereas thromboembolic prophylaxis should be considered for all patients.

Bortezomib-based regimens put patients at risk of peripheral neuropathy, which may be irreversible in a number of patients. In elderly patients, we reduced the incidence of peripheral neuropathy by about 70% by modifying the administration schedule of bortezomib from days 1, 4, 8, and 11 to days 1, 8, 15, and 22. This may be particularly effective for patients who have pre-existing neuropathy.[32,33]

"New Drugs" In Young Patients

Nowadays, the definition of a "young patient" is understood not only as patients who are younger than 60 to 65 years of age, but also as those who are older than 65 years but remain medically fit enough to endure intensive and repetitive treatments. After showing their efficacy in refractory/relapsed patients,[34–36] new drugs have extensively been used during the induction phase instead of the once standard vincristine-adriamycin-dexametasone (VAD)–based regimens, with the aim of increasing tumor cytoreduction and response rates before autologous transplantation. Most importantly, it is imperative to explore if the initial benefit of higher response rates will also translate into prolonged post-transplant overall survival. Results have so far been rather conflicting.

Lokhorst et al showed a post-transplant benefit in progression-free survival of the combination of thalidomide-adriamycin-dexametasone versus VAD in those patients who reached a very good partial remission but not in those who reached a complete remission after induction. However, there was no difference in overall survival between the two cohorts.[37] In contrast, Morgan et al reported a prolonged superior benefit in terms of complete remission post-transplant of a combination of cyclophosphamide-thalidomide-dexametasone over cyclophosphamide-VAD.[38]

Lenalidomide with high-dose dexametasone has been shown to be active in newly diagnosed patients.[39] Moreover, a recent randomized trial showed that lenalidomide with low-dose rather than high-dose dexametasone was associated with less toxicity and better overall survival.[40]

The proteosome inhibitor bortezomib as single agent or in combination with dexametasone has shown potent activity in newly diagnosed myeloma. Harousseau et al compared bortezomib-dexamethasone versus VAD.[41] Both pre- and post-transplant very good partial response rates were superior with bortezomib-dexamethasone as compared to VAD (38% versus 15%, and 54% versus 37%, respectively). However, the difference in progression-free survival did not reach statistical significance (36 versus 30 months, respectively). No overall survival benefit has been reported so far. The major adverse effect was the risk of neurotoxicity early in the disease course. Recent reports, however, show that reducing the dose of bortezomib to once weekly shows similar efficacy with significantly lower risk of neurotoxicity.[42]

Multidrug combinations have also been explored. Bortezomib-thalidomide-dexamethasone resulted in better response rates and progression-free survival compared to thalidomide-dexametasone or bortezomib-dexametasone in randomized trials.[43–44] Similarly, the combination of bortezomib-lenalidomide-dexamethasone produce high overall and complete remission rates in newly diagnosed patients.[45] Overall, three-drug combinations appear to improve response rates and progression-free survival compared to two-drug combinations. However, longer follow-up is needed to define if the