Management of myeloma: an Italian perspective

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.

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 and 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, 5 and 6] However, the high transplant-related mortality greatly limited its use. [7 and 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, 10, 11 and 12] However, results from different groups are conflicting and allografting has become a less attractive option.[13, 14, 15 and 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.

"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]
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 ≥ 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 anti-apoptotic 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 and 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 and 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, 35 and 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 and 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 addition of a third drug results in prolonged overall survival without affecting quality of life.

"New Drugs" In Eldery and Medically Unfit Patients

The oral combination melphalan-prednisone has been regarded as the standard of care for both elderly and medically unfit patients not eligible for autologous stem cell transplantation for decades. The introduction of immunomodulatory drugs and proteasome inhibitors has radically changed the treatment paradigm and led to new standards of care. To date, five randomized phase III clinical trials have compared melphalan-prednisone with the combination melphalan-prednisone-thalidomide.[46, 47, 48, 49, 50 and 51] All these studies showed a prolonged time-to-progression with the

latter combination, although in only two this advantage also translated into an improved overall survival. In another trial, the combination of melphalan-prednisone with bortezomib was associated with an increased time-to-progression and overall survival as compared with melphalan-prednisone. Moreover, recent data showed the superiority of the four-drug combination melphalan-prednisone-thalidomide-bortezomib followed by bortezomib-thalidomide maintenance over melphalan-prednisone-bortezomib, and of melphalan-prednisone-lenalidomide followed by lenalidomide maintenance over melphalan-prednisone alone.[32 and 52] Importantly, reports showed a reduced toxicity profile of lenalidomide when associated with low doses of steroids rather than the standard doses.[40] The availability of different efficacious regimens may provide clinicians with the opportunity to tailor a specific approach for each patient in the light of comorbidities and biologic age. Moreover, regional differences in the choice of a given combination may be seen. The use of melphalan-prednisone in association with new drugs remains a predominantly European approach, whereas the use of lenalidomide with low-dose dexamethasone is more commonly used in North America.[40] Both approaches appear to lead to similar clinical outcomes.

Sequential Approaches for the Treatment of MM

The recent development of new agents with potent antimyeloma activity that target not only malignant plasma cells but also the myeloma microenvironment has opened a new era of clinical research. However, it does not currently appear that any combinations of these new biologically based drugs allow physicians to reach a cure. Many trials are currently in progress to define the optimal combinations of new drugs with older agents, with/without autologous transplantation, that may provide long-term disease control and translate into significantly prolonged overall survival. Two main approaches may be investigated: one may be that of using three- or even four-drug combinations including novel potent antimyeloma agents in the upfront setting to maximize tumor reduction and the other that of using newer and older agents in a more sequential schedule with the goal of converting the disease into a chronic phase that prolongs survival and improves quality of life.

Richardson et al recently reported the first prospective evaluation of a combination of lenalidomide-bortezomib and dexametasone in previously untreated myeloma patients. In this phase I/II study, the maximum planned doses were first established as 25 mg for lenalidomide, 1.3 mg/m^2 for bortezomib, and 20 mg for dexametasone. An impressive overall response rate of 100%, including high complete and very good partial remission rates, was reported.[53] Furthermore, after a median follow-up of 21 months, estimated 18-month progression-free and overall survival for this novel combination with/without autologous transplantation were 75% and 97%, respectively.

We recently evaluated the effect of sequential approaches in elderly patients and in those who were not eligible for autologous transplantation.[32 and 54] We investigated the role of bortezomib as induction before autologous stem cell transplantation, followed by lenalidomide as consolidation-maintenance in newly diagnosed elderly patients.[54] One hundred two patients, 65- to 75-years old, were enrolled. Induction consisted of four 21-day cycles of bortezomib (1.3 mg/m^2 days 1, 4, 8, 11), pegylated-liposomal-doxorubicin (30 mg/m^2 day 4), and dexamethasone (40 mg/d: cycle 1, days 1–4, 8–11, 15–18; cycles 2–4, days 1–4). Autologous stem cell transplantation included two procedures after melphalan 100 mg/m^2 and G-CSF–mobilized stem-cell rescue. Consolidation included four 28-day cycles of lenalidomide (25 mg/d days 1–21 every 28 days) with prednisone (50 mg every other day), followed by maintenance with lenalidomide (10 mg/d days 1–21) until relapse. Primary endpoints were safety and efficacy. In a recent analysis, after induction, 58% of the patients obtained at least a very good partial response including a complete response rate of 13%. Importantly, immunofixation-negative complete remission rates gradually increased to 38% after the two autologous stem cell transplants and up to 66% after consolidation with the combination lenalidomide-prednisone and maintenance with lenalidomide alone. At a median follow-up of 21 months, the 2-year progression-free survival and overall survival were 69%, and 86%, respectively.

During the induction phase, transplant-related mortality was 3%. Severe grade 3–4 adverse events were thrombocytopenia, neutropenia, peripheral neuropathy, and pneumonia. During the consolidation-maintenance phase, adverse events included primarily neutropenia, thrombocytopenia, pneumonia, and cutaneous rash. To our knowledge, this has been the first sizeable phase II study conducted in newly diagnosed myeloma patients to evaluate the clinical effectiveness of a sequential treatment approach which included new agents with different mechanisms of actions. Bortezomib was used during induction to cyto-reduce the disease before a tandem autologous transplant; lenalidomide was then used to consolidate-maintain post-transplant response. This suggests that a sequential approach may be effective in gradually increasing response rates. Although the importance of "death of response" is not universally accepted, the achievement of higher complete remission or very good partial remission rates is associated with a strong positive impact on overall survival.[35]

A bortezomib-based regimen was investigated in untreated elderly patients by the Spanish group.[42] Two hundred sixty patients were first randomly assigned to receive six cycles of bortezomib-melphalan-prednisone or bortezomib-thalidomide-prednisone as induction therapy, and then randomly assigned to maintenance therapy with bortezomib-prednisone or bortezomib-thalidomide. The primary endpoint was response rate after induction and maintenance phases. Complete remission rates were 28% and 20% after induction, respectively, whereas the rates were 44% in the bortezomib-thalidomide group and 39% in the bortezomib-prednisone group after maintenance therapy.

A phase III study on untreated patients ineligible for autologous transplantation by Palumbo et al compared the efficacy of the four-drug combination of bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide with bortezomib-melphalan-prednisone without maintenance.[32] A total of 511 patients were randomized. The primary endpoint was progression-free survival. The 3-year estimates of progression-free survival were 56% in patients receiving the four-drug combination with maintenance and 41% in those receiving the three-drug combination without maintenance ($P = .008$). Complete response rates were 38% and 24% ($P < .001$), respectively, whereas the 3-year overall survivals were comparable, at 89% and 87% ($P = .77$), respectively.

Two additional phase II studies in elderly patients that evaluated the clinical efficacy of melphalan plus prednisone combined with bortezomib or lenalidomide showed gradual disease responses; 30% of the treated patients achieved maximum monoclonal immunoglobulin reduction after 6 months of therapy. These data support treatment plans which include sequential exposure to different drugs to maximize depth of response.[52 and 55]

The role of maintenance has also been explored in young patients undergoing autografting. Thalidomide alone or in combination with corticosteroids used as maintenance after autologous stem cell transplantation has shown promising results in three randomized studies.[56, 57 and 58] In another study, maintenance with thalidomide improved progression-free survival but not overall survival.[59] Long-term treatment with thalidomide and bortezomib inevitably increases the risk of peripheral neuropathy whereas lenalidomide appears more tolerated without the risk of cumulative toxicity. Finally, one study reported a significant increase in complete response rates with a sequential approach, which included consolidation with bortezomib and/or immunomodulatory drugs, although this increase was primarily seen in patients who reached at least a very good partial remission. Thus, consolidation may play its best role in responsive patients.[60]

In summary, although randomized phase III trials comparing different induction and consolidation-maintenance schemas are needed, in our view, the sequential use of new drugs in both young and elderly patients may represent an efficacious treatment paradigm to obtain high complete remission rates and prolonged response duration that may eventually translate into a significant overall survival advantage.

Moreover, serious clinical challenges may lie ahead. MM has been associated with both solid tumors and hematological malignancies such as acute myeloid leukemia and myelodisplastic

syndromes.[61] Recently, preliminary data on phase III trials from the Intergroupe Francophone du Myelome, the Cancer and Leukemia Group B, and the Gruppo Italiano Malattie e Matologiche dell'Adulto Myeloma groups, reported a higher than expected incidence of hematological malignancies in the arms that included lenalidomide.[62, 63 and 64]
Results are not conclusive, however, the incidence of secondary tumors should carefully be monitored during the long-term follow-up examinations.

Conclusion

During the past decade, the introduction of new agents with potent antimyeloma activity has changed the treatment paradigm for myeloma cases. A significant improvement in overall survival has undoubtedly been reported in many trials after the incorporation of new drugs as salvage therapy. However, a further overall survival advantage with the use of these agents with/without autologous transplantation as induction therapy remains to be determined in long-term prospective clinical trials. Moreover, some issues in the long-term toxicity management, including the potential emergence of secondary malignancies, of new agents need to be addressed. Sequential use of new therapies with maintenance may represent a novel approach for patients who have MM, and current evidence is moving clinical practice in this direction. The best clinical benefits of the several ongoing clinical trials should become apparent in the next few years.

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