Novel drugs for the treatment of multiple myeloma

Joan Bladé, Mª Teresa Cibeira and Laura Rosiñol

Hematology and Oncology Institute, Hematology Department, IDIBAPS, Hospital Clínic, Barcelona, Spain. E-mail: jblade@clinic.ub.es. *doi:10.3324/haematol.2009.021550*

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The outcome of patients with multiple myeloma (MM) treated with conventional chemotherapy with or without high-dose therapy/autologous stem cell transplantation (SCT) has not been satisfactory, with median survivals ranging from 2 to 3 years for older patients and from 5 to 6 years for younger patients.[1] In recent years, the availability of the novel effective drugs thalidomide, lenalidomide and bortezomib, with new mechanisms of action, has resulted in a real hope for a significant improvement in the long-term outcome. Moreover, novel drugs targeting new molecular pathways through many different mechanisms of action have been developed and are currently being investigated in clinical trials to further improve the outcome of patients with MM.[2,3]

Autologous SCT is an essential component of the initial therapy in younger patients with MM.[4] However, it must be considered that the achievement of immunofixation-negative complete remission is the most important factor associated with long-term survival in MM.[5-7] With the use of conventional induction regimens the post-transplant complete remission rate is about 35%, the median overall survival is 6 years and the proportion of patients achieving "operational cure" (i.e., surviving in continued complete remission beyond 10 years after autologous SCT) is less than 10%.[4] It is expected that the incorporation of novel agents will improve the above-mentioned results. In this regard, the associations of thalidomide plus dexamethasone and bortezomib plus dexamethasone have been investigated as novel pre-transplant induction regimens. There is growing evidence that thalidomide plus dexamethasone is a sub-optimal pre-transplant regimen because of its limited efficacy in patients with high-risk cytogenetics [del 17p, t(4;14), t(14;16)] and in those with extramedullary disease.[8-10] Although bortezomib-containing regimens can overcome, at least at in the short- and mid-term, the poor prognosis of high-risk cytogenetics,[8,9] the post-transplant complete remission rate with bortezomib plus dexamethasone is generally not superior to the 35% achieved with conventional chemotherapy.[11-13] The so-called triple regimens, such as bortezomib/adriamycin/dexamethasone and, particularly, bortezomib/thalidomide/dexamethasone, are more promising with pre- and post-transplant complete remission rates ranging from 19 to 31% and from 43 to 52%, respectively.[8,9] Post-transplant consolidation/maintenance with novel drugs is becoming a crucial step forward.[14] Thus, it has recently been reported that the post-transplant administration of all thalidomide, lenalidomide or bortezomib increases the complete remission rate and it has been shown, for the first time outside the allogeneic setting, that consolidation with bortezomib/thalidomide/dexamethasone after autologous SCT can induce long-lasting molecular remissions.[15] In this context, assessment of minimal residual disease, either by multiparameter flow cytometry[16] or molecular studies,[15] can help to establish what treatment is necessary and for how long. Finally, encouraging results with the use of bortezomib as part of high-dose therapy with melphalan 200 have been reported.[17] Despite the apparent benefit of the above-mentioned approaches incorporating novel drugs into the treatment for younger patients with MM, long-term results are needed to understand the real improvement in comparison with results in the previous era.[4]

For many years the gold-standard therapy for patients not eligible for autologous SCT has been melphalan and prednisone (MP) or dexamethasone-based regimens. The overall response rate was not higher than 50% with a complete remission rate of less than 5% and a median survival of about 3 years.[1] The new agents thalidomide, lenalidomide and bortezomib have been associated with either melphalan and prednisone (MPT, MPR, MPV) or dexamethasone resulting in significantly improved response rates and progression-free survival in almost all studies and in a significant prolongation of overall survival in some of them.[18] Five trials have compared MPT versus melphalan and prednisone. In all of them the response rate and progression-free survival were superior with MPT. In three of these studies, the overall survival was also significantly longer with MPT. The progression-free and overall survival rates in patients older than 75 years with MPT using thalidomide at a daily dose of 100 mg are of particular interest.[18] The MPV combination was superior to melphalan and prednisone with regards to overall response rate and complete remission rate as well progression-free survival and overall survival.[19] Importantly, MPV was superior to melphalan and prednisone in all prognostic subgroups, including those with high-risk cytogenetics.[19] The first reported results of a large trial comparing MPR followed by lenalidomide maintenance (MPR-R) *versus* MPR and melphalan and predisone with no maintenance showed that the overall response and complete remission rates were significantly higher with MPR than with melphalan and prednisone and that the progression-free survival of patients treated with MPR-R was significantly longer than that of patients in the two other arms. However, the progression free survival achieved with MPR and melphalan and prednisone was about 13 months in both arms.[20] Lenalidomide with so-called low-dose dexamethasone (a weekly dose of 40 mg) is also an attractive induction option for patients not eligible for autologous SCT, with an overall response rate of 70%, including immunofixation-negative complete remissions in 14% of patients.[21] Lenalidomide with low-dose dexamethasone was associated with better short-term overall survival and with lower toxicity compared with lenalidomide plus high-dose dexamethasone.[21] Thalidomide plus dexamethasone seems suboptimal when compared with combinations of melphalan and prednisone with the three new available agents or with lenalidomide plus dexamethasone.[18] A large international trial by the *Intergroup Francophone du Myeloma* comparing lenalidomide plus dexamethasone *versus* MPT is ongoing. Outside clinical trials, the choice of the initial ther-

apy should depend on the age of the patient, clinical status and disease characteristics, as outlined in Table 1.[18] Finally, we want to remark that, although the improvement with the incorporation of novel drugs is clinically relevant, it is still far from satisfactory. Thus, the median duration of the complete remissions obtained with the above new combinations is only 2 years and it is unknown whether or not some "operational" cures can be achieved. So, in the elderly there is also a clear need for further improvement.

The treatment of patients with relapsed or refractory disease is an even more difficult challenge. All novel drugs have been investigated in patients with advanced disease. Regimens containing immunomodulatory drugs, particularly bortezomib or lenalidomide plus dexamethasone, are good rescue regimens and were first approved for patients with relapsed/refractory myeloma.[22-24] However, the duration of response is limited and all patients will eventually develop progressive disease. There is, therefore, a need for novel drugs or drug combinations to increase the duration of response and to treat relapsed and refractory disease. Numerous new drugs are currently being investigated (Table 2). Among what can be considered the next generation of novel drugs, the most promising are the immunomodulatory drug pomalidomide, which can be active even in patients refractory to lenalidomide, the proteasome inhibitor carfilzomib, active in patients resistant to bortezomib and with an acceptable safety profile, and the histone deacetylase inhibitors, particularly vorinostat (SAHA) and panobinostrat (LBH 589).[2,3]

Unfortunately, most of the new drugs under development have shown limited efficacy when used as monotherapy.[2,3] A promising approach is the addition of a new agent as a third drug to a well established regimen such as bortezomib/dexamethasone or lenalidomide/dexamethasone to obtain an additive or a synergistic effect in the so-called triple rescue regimens. In this issue of Haematologica, Ocio *et al.*[25] report the results of their investigation of the effect of the addition of panobinostat, a histone deacetylase inhibitor to either bortezomib/dexamethasone (PBD) or lenalidomide/dexamethasone (PLD) *in vitro* in myeloma cell lines, *ex-vivo* in freshly obtained myeloma cells by flow cytometry and *in vivo* in two different mouse models, one developing subcutaneous plasmacytomas and the other with disseminated myeloma. The addition of panobinostat resulted in a synergistic anti-myeloma potentiation in all: MM cell lines, fresh myeloma cells and plasmacytoma murine models. Of note, panobinostat had significant effects in both mouse models: the disseminated-induced model representing bone marrow disease and the subcutaneous plasmacytoma resembling extramedullary disease. The possible activity in extramedullary human myeloma is encouraging and deserves clinical investigation. The remarkable effect of these panobinostat triple combinations correlated with greatly increased gene deregulation, as compared with the sum of the genes deregulated by the three drugs when applied individually. This study provides the rationale for clinical trials with the triple combinations PDB or PLD in patients with relapsed/refractory myeloma.

Bone marrow endothelial cells secrete CXCL12, also known as stromal derived factor 1-alpha (SDF-1α). This factor is a ligand of CXCR4 and plays a pivotal role in myeloma bone marrow homing. Thus, the CXCL12/CXCR4 axis stimulates myeloma cell chemotaxis and motility and increases the expansion and migration of plasma cells *in vivo*, which is crucial for bone marrow homing in human myeloma and in some murine myeloma models. CXCL12 not only regulates migration but also up-regulates metalloproteinases such as MMP-9, which stimulates bone marrow angiogenesis resulting in myeloma progression. In fact, serum levels of CXCL12 correlate nicely with bone marrow angiogenesis.[26] On the other hand, it has been suggested that hypoxia and hypoxia-inducible transcription factors (HIF) can play a role in the aberrant plasma cell expression of CXCL12. In this issue of Haematologica, Martin *et al.*[26] report that prolonged exposure to hypoxia strongly up-regulated CXCL12 expression in myeloma plasma cells, with HIF-2 playing a crucial role in this response. Over-expression of HIF in myeloma plasma cells strongly induced angiogenesis *in vivo* and the administration of a CXCL12 antagonist decreased HIF-induced angiogenesis. In consequence, it has been suggested that targeting HIF-2 might be an interesting strategy in the attempt to inhibit angiogenesis and disease progression in MM.

Cancer testis antigens (e.g., MAGE-C1/C17 and MAGE-A3), a class of tumor-specific proteins, could be suitable for targeted therapies such as T-cell-mediated immunotherapy.[27] Their expression is regulated by epigenetic mechanisms such as promoter methylation and histone acetylation.[28] Multiple myeloma likely represents the malignancy with the richest cancer testis antigen expression of all human cancers. Surprisingly, the possible role of cancer testis antigens in MM has not been investigated. In this issue of Haematologica, Atanackovia *et al.*[29] describe the role of MAGE-C1/C17 and MAGE-A3 in the proliferation, cell adhesion, chemosensitivity and apoptosis resulting

Table 1. Up-front therapy in elderly patients.

"Aggressive" disease	Melphalan – prednisone - bortezomib
"Non-aggressive" disease	Melphalan – prednisone - thalidomide
Poor cytogenetics	Melphalan- prednisone - bortezomib
Renal failure	Bortezomib - dexamethasone
History of peripheral neuropathy	Lenalidomide-based
Very elderly (thalidomide 100 mg/day)	Melphalan – prednisone - thalidomide
Logistics	Melphalan- prednisone - thalidomide/ lenalidomide-based

Table 2. New generation of anti-myeloma drugs.

• Immunomodulatory drugs Pomalidomide
• Proteasome inhibitors Carfilzomib NPI_0052
• Histone deacetylase inhibitors SAHA (vorinostat®) LBH 589 (panobinostat®)
• Tanespimycin
• Perifosine
• Plitidepsin (aplidin®)

from gene-specific silencing in myeloma cell lines. It was shown that the above-mentioned cancer testis antigens play an important role in reducing the rate of spontaneous and chemotherapy-induced apoptosis and might constitute important targets for novel anti-myeloma specific therapies. The authors hypothesize that such an approach could be particularly useful in the setting of minimal residual disease following currently available anti-myeloma therapy.

Until recently, the treatment of MM was empirically based and consisted mainly of alkylating agents, glucocorticoids and high-dose therapy followed by hematopoietic stem cell support. During the last decade, the new drugs thalidomide, lenalidomide and bortezomib were incorporated into the anti-myeloma armamentarium resulting in significant short- and mid-term improvements. For the next decade we can anticipate the consolidation of the novel treatment approaches which have resulted in the best long-term outcomes as well as the incorporation of a new generation of drugs with more specific molecular targets in our myeloma treatment programs.

Dr. Joan Bladé and Dr. Laura Rosiñol are, respectively, Senior Consultant and Specialist at the Department of Hematology, Hospital Clinic, Barcelona, Spain. Dr. Mª Teresa Cibeira is a Research Fellow at the same institution.

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