



The impact of new drugs in the high dose strategy

M. ATTAL

For the Intergroupe francophone du myélome (IFM)
*Service d'hématologie, Hôpital Purpan, Toulouse, France

During the past ten years, major advances in the treatment have improved the outlook in myeloma. The antitumor activity of thalidomide, bortezomib and lenalidomide has been discovered. In elderly patients, the combination of these new drugs with conventional chemotherapy has been reported to induce a high response rate and to improve overall survival. In young patients, these new drugs have been evaluated to improve the outcome of high dose therapy supported with autologous transplantation. This abstract will focus on the impact of these new drugs in the transplantation setting: 1) during induction therapy, 2) combined with the high dose regimen, and 3) used as maintenance therapy post transplantation.

New drugs during the induction phase

Patients eligible for transplantation should avoid alkylating agents to enable an adequate stem cell collection. Currently, standard induction therapy is based on dexamethasone (DEX) alone or associated with vincristine and doxorubicin (the VAD regimen). *The association of thalidomide (THAL) and DEX* has been reported to significantly improve the response rate as compared with DEX alone or VAD. In a matched case-control analysis, Cavo *et al.* (Blood, 2005; 106:35) reported 52% of partial response (PR) including 8% of complete response (CR) after VAD, versus 76% of PR including 10% of CR after DEX-THAL ($p<0.001$). In a phase III trial, Rajkumar *et al.* (J Clin Oncol 2006; 24: 431) reported 41% of PR without CR after DEX, versus 63% of PR including 4% of CR after DEX-THAL ($p<0.001$). In a phase III trial, Goldschmidt *et al.* (Blood 2005; 106: abstract 424) reported 63% of PR including 3% of CR after VAD, versus 80% of PR including 7% of CR after TAD (THAL, Adriamycin, DEX) ($p<0.001$). *The association of bortezomib with DEX* has been evaluated in a pilot study of the Intergroupe Francophone du myélome and Harousseau *et al.* reported 67% of PR

including 21% of CR. This association is now compared with VAD in a large phase III trial (IFM 2005 01 trial). *The association of lenalidomide and DEX* has been evaluated in a pilot study and Rajkumar *et al.* (Blood 2005; 106: 4050) reported an unprecedented 91% of PR including 32 % of CR or near CR. Thus, although randomized trial are still ongoing, it is reasonable to speculate that the associations of these new drugs with DEX will increase the PR and CR rate before high dose therapy as compared with VAD. Furthermore, since an adequate stem cell collection has been obtained with these newer induction regimens, the death of VAD as induction therapy is yet written.

New drugs combined with the high dose regimen

In myeloma, the standard high dose regimen is melphalan alone in a dosage of 200 mg/m². Attempts to improve this regimen with the association of other drugs or TBI have failed to improve the antitumor response rate but have increased the hematological and non hematological toxicities. A synergistic effect between Bortezomib and melphalan has been demonstrated *in vitro* and *in vivo*. Furthermore, the toxicity profile of these 2 drugs is not overlapping. Thus, *the combination of bortezomib and high dose melphalan* was a logical approach. We conducted a pilot study of melphalan (200 mg/m² on day -2) and bortezomib (1 mg/m² on days -6, -3, +1, +4) supported with autologous blood stem cells (day 0). Twenty five patients (non responding after induction therapy, n=18; or failing to achieve a near CR after a first transplant, n=7) were enrolled. No toxic death occurred, the median durations of neutropenia (<500/mm³) and thrombocytopenia (<20000/mm³) were 7 and 1 day, respectively. The incidence of severe mucositis (grade 3/4) was 20%. Three months after transplantation an unexpected response rate was observed: 77% of near CR including 31% of true CR. Furthermore, 5/7 patients failing to achieve a near CR

after the first transplant prepared with melphalan alone achieved a CR (n=4) or a near CR (n=1). Finally, this pilot study strongly suggests that the association of bortezomib and melphalan could improve the CR rate as compared with melphalan alone without additive toxicity. Since the achievement of CR has been shown to be the most important prognostic factor for survival after high dose therapy, this association could improve the overall survival.

New drugs as maintenance therapy after transplantation

The role of maintenance therapy in myeloma remains controversial. Maintenance chemotherapy has failed to demonstrate any benefit. Most randomized studies and meta-analyses evaluating maintenance interferon showed a modest increase in progression free survival without any, or with minimal, survival benefit after conventional or high dose therapy. Corticosteroid maintenance was found to prolong the duration of response, however the impact on survival was controversial. Thalidomide is an oral agent, with immunomodulatory properties, active in one-third of patients with refractory disease, with doses as low as 50 mg, without myelosuppressive toxicity. Thus, thalidomide was an attractive candidate for use in maintenance situations, particularly after high dose therapy. In 1999, the *Intergroupe Francophone du Myélome* (IFM) initiated the first randomized trial (IFM 99 02) designed to evaluate *the role of thalidomide as maintenance treatment after transplantation*. Two months after autologous stem cell transplantation, 597 patients under the age of 65 years were randomly assigned to receive no maintenance (arm A), pamidronate (arm B), or pamidronate plus thalidomide (arm C). Thalidomide was administered for a median

duration of 15 months, in a mean dosage of 200 mg per day. A complete or very good partial response was achieved by 55 percent of patients in arm A, 57 percent in arm B, and 67 percent in arm C ($p=0.03$). The 3-year post-randomization probability of event-free survival was 36 percent in arm A, 37 percent in arm B, and 52 percent in arm C ($p<0.009$). The 4-year post-diagnosis probability of overall survival was 77 percent in arm A, 74 percent in arm B, and 87 percent in arm C ($p<0.04$). The proportion of patients who had skeletal events requiring a specific therapy (chemotherapy, irradiation or surgery) was 24 percent in arm A, 21 percent in arm B, and 18 percent in arm C ($p=0.4$). Thus, maintenance treatment with thalidomide improves the overall survival in patients with myeloma and should be recommended. Maintenance treatment with pamidronate does not decrease the incidence of bone events. However, thirty nine per cent of patients had to discontinue thalidomide due to drug-related adverse events. Peripheral neuropathy was the main reason for discontinuation. Thus, lenalidomide, an analog of thalidomide without neurological toxicities, might be an attractive candidate for use in maintenance situations. Lenalidomide is evaluated in the current IFM 2005-02 protocol.

Conclusions

If new drugs have considerably modified the prognosis of elderly patients, their impact in the high dose strategy could be even greater. With the new induction and high dose regimens, a 70% or 80% of CR or near CR rate can be expected and effective maintenance strategies will significantly prolong their duration. Whether such a CR rate, efficiently maintained, will be associated with a percentage of *cure* will be answered by ongoing studies.