Multiple Myeloma. New drugs and transplant: before, during and after.
(Mieloma multiplo. Nuovi farmaci e trapianto: prima, durante e dopo.)

Benedetto Bruno

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

Multiple myeloma is a fatal plasma cell malignancy. New insights into its biology have identified mechanisms that have become molecular targets of so-called “new drugs” such as thalidomide, lenalidomide and bortezomib. The central role of high-dose therapy followed by autologous peripheral cell transplantation (AHCT), which remains a standard for younger and/or medically fit patients, has consequently evolved. Currently, cyto-reductive induction therapies before AHCT have incorporated several combinations of both the immunomodulatory derivatives thalidomide or, more recently, lenalidomide, and theproteasome inhibitor bortezomib. Though optimal combinations and treatment duration are a matter of debate, the use of these induction combinations has led to high response rates. Following the cyto-reduction obtained pre-transplant, AHCT can further improve depth of response. Patients younger than 65 years of age without relevant co-morbidities that contraindicate high-dose therapy are ideal candidates for AHCT. Though not all studies have uniformly reported the same advantages, randomized trials have demonstrated superior response rate and overall survival in patients treated with high dose therapy compared with conventional chemotherapy. [1] Whether single and double AHCT have similar outcomes remain to be determined.

Before the introduction of new drugs, the combination vincristine-doxorubicin-dexamethasone (**VAD**) and dexamethasone alone had been used for many years as pre-transplant induction therapy. So called **VAD**-based regimen often became reference treatments in phase III study where toxicity and efficacy of new induction treatments, which incorporated new drugs as single agents, were first explored. Initially, a prospective phase III study compared thalidomide and dexamethasone (**TD**) with **VAD** and showed higher response rates after induction in the **TD** arm. However, the benefit was not confirmed 6 months after autologous transplant, since very good partial response rates were almost identical. [2] Two randomized trials demonstrated that **TD** was better than high dose dexamethasone (**HD**) in terms of higher response rates and prolonged time to progression in

patients treated with **TD**, but this did not translate into overall survival improvement. [3,4] Main toxicities related to thalidomide were deep vein thrombosis and peripheral neuropathy. In the light of these trials, the Food and Drug Administration (FDA) granted approval for **TD** for the treatment of newly diagnosed multiple myeloma. In 2 parallel German-Dutch phase III multi-centre trials compared standard **VAD** regimen with **TD** plus doxorubicin (**TAD**): higher very good partial response rates after induction and after AHCT were observed with **TAD**.[5] In a phase III study, the combination of bortezomib and dexametasone (**VD**) was compared with **VAD** as induction therapy before single or double AHCT. Importantly, in both arms, lenalidomide was given as consolidation/maintenance after AHCT. Response rates of at least very good partial response were significantly higher in the **VD** arm than in the **VAD**. An advantage was also maintained after the first and the second AHCT. However, the progression free survival did not reach statistical significance between the two arms. [6] Lenalidomide with high-dose dexametasone (**RD**) was compared with lenalidomide and low-dose dexamethasone (**Rd**) in a prospective control trial which included either eligible or ineligible patients for AHCT. Though response rate was significantly higher with **RD** compared with **Rd**, toxicity and early mortality were higher with **RD**. A landmark analysis showed that the 3-year overall survival of patients who received AHCT after RD or Rd was 92% whereas in patients who did not receive AHCT was 79%.[7]

The encouraging results of induction therapies with new drugs as single agents and preclinical findings, which showed that immunomodulatory drugs could increase the anti-myeloma activity of bortezomib, formed the rational for combination therapies. Results of a phase III study of bortezomib-thalidomide-dexametasone (**VTD)** versus **TD** as induction therapy before and consolidation therapy after double AHCT have recently been reported. [8] After three 21-day induction cycles, **VTD** was superior to **TD** in terms of response rates. Higher response rates in the **VTD** arm were also observed after two AHCT and subsequent consolidation therapy. The estimated 3-year PFS for the **VTD** group of patients was significantly longer than for those assigned to **TD** and double AHCT, 68% vs 56% respectively. Longer follow up is needed to possibly confirm a long-term survival advantage. In Total Therapy 3, **VTD** combined with cisplatin, doxorubicin, cyclophosphamide, and etoposide was given as induction therapy before and consolidation after double AHCT, while maintenance therapy with **VTD** was continued for one year after AHCT. Total Therapy 3 significantly improved 2-year EFS and duration of complete remission as compared to Total Therapy 2 which associated **TD** with double AHCT. [9] A triplet combination of lenalidomide-bortezomib-dexamethasone (**RVD**) has been explored in small series of newly diagnosed

patients. [10,11] A phase I-II study on a series of 66 patients, who included eligible and ineligible patients for AHCT, received up to 8 cycles of **RVD**. Moreover, **RVD** maintenance was allowed in responding patients. After the first 4 cycles, the rates of at least near-complete remission and very good partial remission were 6% and 11%. Importantly, in about two thirds of the patients, deeper response was observed after the forth cycle and a further improvement was also reported during maintenance.

The most common toxicities associated with thalidomide include constipation, somnolence, and peripheral neuropathy, frequently sensory or sensory-motor. Dose reduction or drug discontinuation commonly improves symptoms. By contrast, its analogue lenalidomide induces neutropenia and thrombocytopenia and only rarely peripheral neuropathy. Major clinical challenge of up-front treatment with these agents is the risk of thromboembolic complications. Prophylaxis guidelines have recently been proposed by the International Myeloma Working Group. [12] Peripheral neuropathy, primarily sensory, which may seriously impair quality of life, remains an important side effect during bortezomib treatment. To decrease incidence and severity, dose reduction, given on a twice-weekly basis, or once-weekly administration at a higher dose have been proposed.

Overall, the proven clinical efficacy of these new agents, that target not only malignant plasma cells but also the myeloma microenvironment, does not currently allow to reach a cure. This provides the clinical rationale for using them in sequential approaches as induction before and as consolidation/maintenance after AHCT with the goal of converting the disease into a chronic phase that prolongs survival and improves quality of life. Consolidation treatment is designed to improve response following AHCT. Increase in response rates have been reported with the use of both bortezomib and lenalidomide. Moreover, some studies reported molecular remissions in a subset of patients. [13] Maintenance treatment as a means to prolong response duration and extend overall survival remains controversial. Recently, two independent phase III study indeed showed a longer progression free survival in patients treated with lenalidomide maintenance rather than placebo after single or double AHST. [14,15] However, concern has been risen by an unexpected incidence of second primary malignancies during lenalidomide treatment.

In summery, the incorporation of “new drugs” during induction therapy has practically become standard treatment in younger myeloma patients eligible for AHCT. Consolidation/maintenance therapy has resulted in longer progression free survival in several

studies. However, convincing evidence that this will translate into a benefit in overall survival is lacking. Therefore, much longer follow up is needed to address this issue. At present, whether the recent advancements in myeloma treatment will eventually allow a cure remains unanswered.

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