How I manage frontline transplant-eligible multiple myeloma in Italy

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Abstract

The treatment of transplant-eligible multiple myeloma patients in Italy consists in an induction phase based on bortezomib plus thalidomide plus dexamethasone (VTd), followed by a single or tandem autologous stem cell transplantation (ASCT), followed by lenalidomide maintenance. This approach offers an overall response rate of 93% and a CR rate of 58% with acceptable toxicity. Lenalidomide maintenance adds a significant increase in disease control, with a progression free survival after ASCT of 53 months, and an overall survival of 86 months. Second primary malignancies represent the most concerning toxicity of lenalidomide maintenance with a 6.9% incidence. However, the benefit in terms of increased myeloma control largely outweigh this complication. The incorporation of daratumumab in this treatment schema will further improve these clinical results.

Introduction

Multiple myeloma (MM) accounts for 1% of all malignant diseases and 10% of all hematological neoplasms.[1] In the last two decades, the consolidation of the role of autologous stem cell transplantation (ASCT) and the incorporation of novel agents in the first line of therapy have significantly improved the quality of responses and the overall survival (OS).[2-4] Several studies have clearly demonstrated that ASCT is superior to standard therapy, also when the latter includes new drugs.[5-7] The upper limit of the transplant age has been progressively raised by the 60 years of the first ASCT studies,[8] to the 70 years currently adopted in the most recent protocols.[9] In several centers fit patients older than 70 years are considered for ASCT.[10] Therefore, since the transplant age threshold set at 70 years coincides with the average age of diagnosis of the disease, approximately half of MM are considered transplant eligible. In the following sections, I will discuss in detail the transplant approach adopted in Italy.

Management of transplant eligible patients in Italy

The goal of the first line of therapy consists in the achievement of the maximal depth of disease response, that translates into an optimal duration of disease control and OS. Presently, the first line of therapy consists in an induction phase, followed by a single or tandem ASCT, followed by a maintenance therapy. Each phase of the treatment program has specific characteristics.

Induction

Induction should have a remarkable quick effect, since patients frequently suffer from pain or renal failure, minimal nephrotoxicity, and low myelotoxicity, in order to not interfere with the subsequent stem cell mobilization. Induction should reverse end organ damage and improve the performance status. At present, the optimal induction combination consists in a triplet containing bortezomib plus an immunomodulatory drug (IMiD) plus dexamethasone.[11] In Italy bortezomib plus thalidomide plus dexamethasone (VTD) is by far the most commonly used triplet. The Italian collaborative group GIMEMA has conducted a phase III study comparing the combination VTD *versus* thalidomide plus dexamethasone (TD), at that time one of the standard treatments for induction. Patients were randomized in a 1:1 ratio to receive 3 cycles of VTD or TD, then tandem ASCT with 2 sequential doses of melphalan 200 mg/m^2 given 3 to 6 months apart, then 2 modified VTD or TD cycles, accordingly to the treatment arm. Dexamethasone maintenance was then used until disease progression, relapse, or toxicity.[12] The primary composite endpoint of the study consisted in the number of complete remisisons (CR) and near CRs (nCR) after the induction therapy. The trial enrolled 480 patients. After induction, a significant advantage for the VTD arm in terms of CR + nCR (31% *versus* 11%, p < 0.0001) was observed. After consolidation therapy, the CR plus nCR rate was again significantly higher in the VTD arm *versus* the TD arm (62% *versus* 45%, p=0.0002), and the ORR was 93% *versus* 79% in the VTD arm *versus* the TD arm, respectively (p<0.0001). CR rate was 58% in VTD and 41% in TD patients (p=0.0001). In the same period, the Spanish PETHEMA group conducted the PETHEMA/GEM study that compared 6 courses of VTD versus TD versus a combination of vincristine+BCNU+melphalan+cyclophosphamide+prednisone, and vincristine+BCNU+doxorubicin+dexamethasone, and bortezomib (VBMCP/ VBAD/B), as induction before ASCT.[13] The transplant phase consisted in a single ASCT conditioned with melphalan 200 mg/m^2. After transplant, patients were randomized to receive a 3-year maintenance with interferon α-2b versus thalidomide 100 mg per day orally versus thalidomide 100 mg per day orally plus one cycle of bortezomib on days 1, 4, 8, and 11 every 3 months. The primary endpoint consisted in CR rate after induction and after ASCT. The trial enrolled 380 patients. The overall response rate (ORR) was 85% in the VTD arm, 72% in the TD arm, and 75% in the VBMCP/VBAD/B arm. The CR rate after induction was higher in the VTD arm respect to the TD arm (35% *versus* 14%, p=0.001) or the VBMCP/VBAD/B arm (35% *versus* 21%, p=0.01).

The combination of bortezomib plus cyclophopsphamide plus dexamethasone (VCD) represents an acceptable alternative to VTD. The French phase III IFM2013-04 trial compared 4 VTD cycles to 4 VCD

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Key words: Multiple myeloma, bortezomib, autologous stem cell transplantation, lenalidomide.

Conflict of interest: VM has received honoraria and travel grants from Janssen, Celgene, Bristol-Myers Squibb, Amgen and Takeda.

Contributions: VM, GM, CC conceived the work and wrote the paper.

Acknowledgments: The author thanks Mr. And Mrs Ferrari for their funding. The author thanks also Amo La Vita ONLUS for their support.

Licensee PAGEPress, Italy
Hematology Reports 2020; 12(s1):8954
doi:10.4081/hr.2020.8954

cycles as induction before ASCT.[14] Three hundred and forty patients were enrolled. The primary endpoint was the post-induction VGPR rate. In the VTD arm 66.3% of patients achieved at least a VGPR *versus* 56.2% in the VCD arm (p=0.05). The CR rate was 13.0% in the VTD arm, and 8.9% in the VCD arm (p=0.22), ORR was significantly higher in the VTD arm, 92.3% *versus* 83.4% in the VCD arm (*P*=.01). Despite its minor cytoreductive efficacy, VCD can be considered for patients at high risk of peripheral neuropathy.

Since the optimal backbone for induction is represented by bortezomib and dexamethasone plus an IMiD, the rational evolution of this triplet was the replacement of thalidomide with lenalidomide (VRD). In the French phase III IFM 2009 study, transplant-eligible patients have been randomized between 3 VRD cycles followed by a single ASCT and a consolidation with 2 VRD cycles *versus* 8 VRD cycles without transplantation. All patients received lenalidomide maintenance for one year.[6] The primary endpoint was PFS. The study enrolled 700 patients. After the consolidation phase, and before maintenance start, the CR rate was 78% in the VRD-ASCT arm *versus* 69% in the VRD arm (p=0.03).

Despite the advantages of VRd, for regulatory reasons, at present, VTd is the standard induction in Italy.

Transplant

The transplant phase consists in two steps: peripheral blood stem cell (PBSC) mobilization and collection, and ASCT. There are two main options for PBSC mobilization. The first consists in the administration of chemotherapy, mostly cyclophosphamide 2-4 gr/sqm, followed by filgrastim injections until an adequate level of CD34+ cells in blood is achieved. The second is a steady-state approach, only based on filgrastim injections. Since the PBSC number obtained with this procedure is generally lower than the chemo-based approach,[16] it is frequently necessary to combine it with plerixafor, a chemokine-receptor 4 antagonist that enhances the PBSC mobilization activity of filgrastim.[17] The optimal stem cell dose for each transplant is 4-6 x 10^6 CD34+/Kg, while the minimum dose required for a safe transplant is 2 x 10^6 CD34+/Kg.[18] Notably, patients candidate to a tandem ASCT should collect the required amount of PBSC before the start of the transplant phase, since a second collection after ASCT is hardly feasible, in particular if done close to previous transplant.[19]

The optimal conditioning regimen for ASCT in MM is melphalan 200 mg/sqm. Patients with renal failure require a dose reduction of melphalan, but the procedure can be safely performed also in patients with dialytic replacement therapy.[20] Several attempts have been done to find a more efficient preparative regimen, but, to date, without success. In a phase II study intravenous busulfan plus melphalan has been compared with standard melphalan. Despite an increase in PFS, the response rate was similar to that observed in the control arm, and the toxicity was significantly increased.[21] The incorporation of bortezomib in the melphalan 200 mg/sqm conditioning has been evaluated in the phase III IFM 2014-02 trial, and compared with melphalan 200 mg/sqm standard regimen. The primary endpoint of the study was the CR rate at day 60 after transplant, and both arms had similar results (44% CR rate in bortezomib-melphalan arm versus 46% in the melphalan arm).[22,23]

In the GIMEMA trial, the CR or near CR (nCR) rate after consolidation was significantly higher in the VTD arm versus the TD arm (62% vs. 45%, p = 0.0002), and the ORR was 93% versus 79% in the VTD arm versus the TD arm, respectively (p<0.0001). With regard to survival endpoints, the 3-year PFS was longer in the VTD arm versus the TD arm (68% versus 56% p=0.0057), with a favorable hazard ratio (HR) (HR 0.63, p = 0.0061).[12] A recent update of this trial, with a median follow-up for surviving patients of 124 months, has shown that the 10-year PFS was 34% in the VTD, and 17% in the TD arms, respectively (HR 0.62, CI 0.50-0.77; p<0.0001). Ten-year OS was 60% in the VTD arm versus 46% in the TD arm (HR 0.68, CI 0.51-0.90; p=0.007). Median OS was not reached in the VTD arm, and 110 months in the TD arm.[24] Ten-year PFS of high risk cytogenetic patients, defined by the presence of either del(17p) or t(4;14), was 40% for standard risk VTD, 20% for standard risk TD, 17% for high risk VTD, and 3% for high risk TD patients. Ten-year OS of high-risk cytogenetic patients was 67% for standard risk VTD, 52% for standard risk TD, 42% for high risk VTD, and 22% for high risk TD patients.

A debated point is represented by the need to perform a single as opposed to a double ASCT. The EMN02/HO95 phase III trial addressed this question. A part of this trial was committed to compare the role of tandem ASCT respect to the single ASCT. It has been shown that tandem transplantation improved the depth of the response by 25%, and more than 50% of the patients achieved at least a CR.[7] PFS was not reached in the tandem ASCT arm versus 45 months in the single ASCT arm, and the 3-year PFS was 73%, and 60%, respectively (HR=0.66, CI=0.45-0.96; P=0.030).[25] Interestingly, the increase in PFS observed in the tandem arm was particularly evident in the subgroups of patients with high risk disease, either defined as bone marrow plasma cells >60% (HR=0.41, CI=0.22-0.77; p=0.006), elevated LDH (HR=0.52, CI=0.28-095; p=0.034), or high risk cytogenetics (HR=0.49, CI=0.24-1.02; p=0.057).

Consolidation

In some trials, the transplant phase is followed by a short-term period of non-intensive therapy. In the GIMEMA trial patients received either VTD or TD, according to their originally assigned arm.[12] VTD consolidation was able to upgrade the CR and nCR rate from 63% to 73%, while TD consolidation from 55% to 61%.[26]

In the EMN02/HO95 patients were randomized to two VRd consolidation cycles followed by lenalidomide maintenance *versus* direct start of lenalidomide maintenance.[7] The median PFS of patients in the consolidation arm was 59 months, respect to 46 months of the no consolidation arm (HR 0.77, CI 0.63-0.95; p=0.014).

At present, in Italy consolidation is not widely used, since this treatment is not reimbursed by the Italian healthcare system.

Maintenance

At least three studies have demonstrated the advantage of post-ASCT lenalidomide maintenance.

The IFM 2005-02 study enrolled MM patients with at least a stable disease after ASCT.[27] Patients were randomized to daily lenalidomide 10 mg for the first 3 months, afterwards increased to 15 mg if tolerated, or placebo. The primary endpoint was PFS. The study enrolled 614 patients. The median PFS was 41 months in the lenalidomide arm and 23 months in the control arm (HR 0.50; p<0.001). The CALGB 100104 study has a similar design to the previous study. This trial enrolled patients who achieved at least a stable disease after ASCT. Patients were randomized to daily lenalidomide 10 mg for the first 3 months, afterwards increased to 15 mg if tolerated, or placebo.[28] The primary endpoint was time to progression, defined as time to progressive disease or death from any cause after transplantation. The trial enrolled 460 patients. The median PFS was 39 months in the lenalidomide arm and 21 months in the con-

trol arm (HR 0.37, CI 0.26-0.53; p<0.001). Both studies highlighted an increased risk of developing a second primary malignancy in patients receiving lenalidomide treatment. In a meta-analysis of individual patient data including 3218 subjects, it has been shown that 5-year cumulative incidences of all second primary malignancies were 6.9% in lenalidomide maintenance patients and 4.8% in control patients (HR 1.55, CI 1.03-2.34; p=0.037).[29] The 5-year rate of solid second primary malignancies was 3.8% in lenalidomide patients, and 3.4% in control patients (HR 1.1, CI 0.62-2.00; p=0.72), while the 5-year rate of hematologic second primary malignancies was 3.1% in lenalidomide patients, and 1.4% in control patients (HR 3.8, CI 1.15-12.62; p=0.029). An important meta-analysis on lenalidomide maintenance included data from the IFM 2005-02, CALGB 100104, and GIMEMA MM-PI-209 trials.[30] A total of 1208 patients were included, 605 received lenalidomide maintenance, and 603 placebo or observation. The median PFS was 53 months for the lenalidomide group and 24 months for the placebo or observation group (HR 0.48, CI 0.41-0.55). Median OS was not reached in the lenalidomide group, and was 86 months in the placebo or observation group (HR, 0.75, CI 0.63-0.90; p = 0.001). Seven-year OS rate was 62% with lenalidomide maintenance and 50% with placebo or observation. This meta-analysis confirmed the increased number of second primary malignancies in patients on lenalidomide maintenance. However, the benefit in terms of improved myeloma control in lenalidomide maintenance patients was unquestionably superior to the intrinsic risk of developing a second primary malignancy.

Conclusion and future perspective

Presently, myeloma treatment of transplant eligible patients in Italy consists in 4-6 VTD cycles, followed by one or two ASCT, followed by lenalidomide maintenance. In case of high-risk disease, a tandem ASCT is recommended. This approach offers excellent results in terms of PFS and OS. However, the availability of more effective induction regimens, such as VRd or the combination of daratumumab with VTd or VRd are extremely promising in terms of long-term disease control.[6,9,31] The possible rescue of relapsed patients with newer immunotherapeutic approaches, such as CAR-T, bispecific antibodies and antibody-drug conjugates, along with new drugs paves the way to a very long term disease control.

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