



# UNIVERSITÀ DEGLI STUDI DI TORINO

***This is an author version of the contribution published on:***

*Questa è la versione dell'autore dell'opera:*

*Drugs. 2015 Mar;75(4):367-75. doi: 10.1007/s40265-015-0367-0.*

***The definitive version is available at:***

*La versione definitiva è disponibile alla URL:*

*<http://link.springer.com/offcampus.dam.unito.it/article/10.1007%2Fs40265-015-0367-0>*

**The role of pre-transplant induction regimens and autologous stem cell transplantation in the era of novel targeted agents**

Francesca Gay<sup>1</sup>, Federica Cavallo<sup>1</sup> Antonio Palumbo<sup>1</sup>

<sup>1</sup>Myeloma Unit, Division of Hematology, University of Torino, Torino, Italy

RUNNING HEAD: Autologous transplantation in myeloma patients

**Correspondence:** Dr Antonio Palumbo, Divisione di Ematologia dell'Università di Torino, Azienda Ospedaliera S. Giovanni Battista, Via Genova 3, 10126 Torino, Italy. E-mail: [appalumbo@yahoo.com](mailto:appalumbo@yahoo.com); Tel.: +39 01166 35814; fax: +39 01169 63737.

## **Abstract**

Outcome of patients with multiple myeloma (MM) has greatly improved with the use of autologous stem cell transplantation (ASCT) and new agents, such as immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib). When compared to conventional chemotherapy, high-dose melphalan with ASCT significantly improved response rates and progression-free survival, while overall survival benefit was not consistent across all trials. ASCT is considered the standard treatment for patients who are younger than 65 years and who do not have limiting comorbidities. New, effective agents have been introduced as part of induction, consolidation and maintenance treatments within ASCT and in combinations with chemotherapy for patients not eligible for ASCT. The remarkable results obtained with these regimens are questioning the role of ASCT for newly diagnosed MM patients. This article aims to delineate the role of ASCT in the era of novel agents based on the results of recent clinical trials.

## **1.Introduction**

Autologous stem cell transplantation (ASCT) is the standard treatment for newly diagnosed multiple myeloma (MM) patients younger than 65 years and/or eligible for high-dose chemotherapy. Before the introduction of novel agents, such as immunomodulatory drugs (IMiDs; thalidomide and lenalidomide) and proteasome inhibitors (bortezomib), high-dose melphalan with ASCT significantly improved response rates and progression-free survival (PFS) in comparison with conventional chemotherapy, with conflicting results in terms of overall survival (OS) (1-4). Newer agents were later incorporated both in the transplant and non-transplant settings, and significantly improved patient outcome (5). The depth and the duration of response obtained with these new approaches correlated with a PFS benefit and, in several studies, also with an OS improvement. This was evident in both young patients receiving ASCT, and elderly patients receiving conventional chemotherapy in combination with new agents (6-10). It has been suggested that the optimal treatment strategy should aim at achieving sustained complete response (CR) (11).

Yet, long-term control of the disease has been shown also in patients not achieving high-quality responses, which may reflect changes in host immune status or a clonal heterogeneity of the disease at diagnosis. Thus patients may also benefit from a less intensive treatment, that can be able to control, if not eradicate, the disease. The remarkable results obtained in the non-transplant setting questioned the role of ASCT for newly diagnosed MM patients. On the other hand, there is increasing evidence that the selective pressure of treatment may be responsible for emergence of different MM sub-clones leading to drug resistance at more advanced stages (12). If this will be confirmed, it could be reasonable to give the most effective and intensive treatment, that is ASCT, at the early phases of disease, when the probability of reaching long-lasting remissions is higher. This article aims to delineate the role of ASCT in the era of novel agents based on the results of recent clinical trials.

## **2. New agents in the transplant setting.**

Novel agents have been incorporated in the pre-transplant induction and post-transplant consolidation and maintenance regimens. Data about the impact of induction therapy on transplantation are quite limited and further investigation is certainly needed.

### ***2.1 Induction regimens***

Vincristine-doxorubicin-dexamethasone (VAD) was used for many years as pre-transplant induction therapy, inducing an overall response rate (ORR) of 54% with a CR rate of 2% (13). Novel agents (thalidomide and bortezomib) were then tested in combination with dexamethasone as induction regimens before ASCT. Thalidomide plus dexamethasone (TD) increased response rates in comparison with VAD or thalidomide alone: the at least very good partial response (VGPR) rate was 30% with TD vs 15% with VAD ( $P=0.003$ ) (14); the ORR was 72% with TD vs 36% with thalidomide alone (15). Similarly, bortezomib plus dexamethasone (VD) showed an ORR of 78% in comparison with 63% with VAD ( $P<0.001$ ) (16). Two randomized phase III trials evaluated a short

course of lenalidomide and dexamethasone (Rd) as induction before ASCT, showing an ORR of 76%, including 29% of patients achieving at least a VGPR (17,18).

Better results were achieved with three-drug combinations including thalidomide or bortezomib plus conventional chemotherapeutic agents, such as doxorubicin and cyclophosphamide (13,19,20). A significant improvement in ORR in comparison with VAD was reported with doxorubicin in combination with thalidomide-dexamethasone (TAD) (88% vs 79%,  $P=0.005$ ) (19) and doxorubicin in combination with bortezomib and dexamethasone (PAD) (78% vs 54%,  $P<0.001$ ) (13). Cyclophosphamide in combination with thalidomide-dexamethasone (CTD) significantly enhanced the ORR in comparison with cyclophosphamide-VAD (83% vs 71%,  $P<0.0001$ ) (20).

The three-drug combination bortezomib-thalidomide-dexamethasone (VTD) was compared with TD and multi-agent chemotherapy (21,22). A significant improvement in the CR rate was detected with VTD compared with TD (35% vs 14%,  $P=0.0001$ ) and with multi-agent chemotherapy (35% vs 21%,  $P=0.01$ ) (21). Another study compared the triplet VTD with TD and showed a higher CR rate with the three-drug regimen (31% vs 11%,  $P<0.001$ ) (22). A recent phase 2 trial showed a promising VGPR rate of 58% after induction with bortezomib-lenalidomide-dexamethasone (VRD) (23).

Two meta-analyses of data from phase III studies in ASCT-eligible patients with previously untreated MM demonstrated that bortezomib-containing induction regimens results in a significantly improved ORR compared with non bortezomib-containing regimens (24,25).

Two phase II studies did not show significant advantages with four-drug bortezomib-based regimens in comparison with three-drug combinations (26,27).

In all the trials previously reported, ASCT further improved the depth of response as shown in table 1. Table 2 reports safety data of selected induction regimens.

## ***2.2 Consolidation regimens***

In the past, a second ASCT was administered to consolidate the response achieved after a first course of high-dose melphalan followed by ASCT. Before the introduction of novel agents, several trials showed a prolonged event-free survival (EFS) with double ASCT vs single ASCT (28-30). Results of a subgroup analysis of one of those trials, reported an improved OS only in patients achieving less than a VGPR after the first ASCT (28). The role of double ASCT in the era of novel agents is not yet defined. In the HOVON-65/GMMG-HD4 study, patients were randomized to receive induction with PAD vs VAD followed by ASCT. Per protocol, one or two cycles of high-dose melphalan were planned. In patients who received single ASCT, the 5-year OS was 55% in both PAD and VAD arms ( $P=0.39$ ), while in those who received tandem ASCT the 5-year OS was 70% with PAD and 55% with VAD ( $P=0.07$ ), thus suggesting an advantage with the tandem option (13). Yet,  $P$ -values were not significant and results were derived from a subgroup analysis. In addition, patients were not randomized to receive either tandem or single ASCT, but the choice was dependent on country practice (13). Post-ASCT consolidation with bortezomib and IMiDs is currently under evaluation. In a randomized phase III trial, bortezomib was compared with no consolidation therapy in bortezomib naïve patients (31). The progression-free survival (PFS) from randomization was 27 months for the bortezomib group and 20 months for the control group ( $P=0.05$ ), while no difference in OS was seen (31). In another trial, VTD consolidation was administered in patients achieving at least a VGPR after double ASCT. This strategy further improved the depth of response: the CR rate increased from 15% to 49% and molecular remission rate increased from 3% to 18% (8,32). Of note, the two previous studies included newly diagnosed patients who did not receive novel-agent based induction. A consolidation approach using the same regimens employed during induction (VTD vs TD) was assessed after double ASCT (33). VTD consolidation increased the CR/nCR rate from 63% to 73%; most of the patients who improved to CR after VTD consolidation had achieved at least a VGPR after transplantation. The 3-year PFS was superior with VTD in comparison with TD (60% vs 48%,  $P=0.042$ ) (33). Similarly, a recently published trial showed an improvement in post-ASCT response rate with VRD consolidation

(VGPR 70% after ASCT to 87% after consolidation); as in the previous study, the same regimen was administered as pre-transplant induction (23). Four cycles of lenalidomide-prednisone have been adopted as consolidation after double ASCT in patients receiving PAD induction. This approach increased the CR rate from 33% to 48%; also in this study, the major benefit was noticed in patients who achieved VGPR after transplantation (34). These data show that intensification with bortezomib and/or IMiDs improves response rates, and the improvement was mainly seen in patients with sensitive disease. The total therapy (TT) study evaluated the impact of the addition of thalidomide (TT2) or bortezomib (TT3) to a multi-agent chemotherapy and high-dose melphalan program supported by double ASCT (35). In this TT study, novel agents were administered both in the pre-transplant and in the post-transplant settings. In the TT3 the cumulative frequency of CR increased during the different treatment phases reaching 56% at 2 years (36,37).

### ***2.3 Maintenance regimens***

The optimal maintenance regimen should aim at prolonging the remission duration without affecting the patient's quality of life. Maintenance treatments with alkylating agents, steroids or interferon were tested in the pre-novel agents era (38-41). In one study, maintenance with prednisone every other day improved PFS and OS, (38) yet, in another study, no benefit was seen with single agent dexamethasone.(39) Data are therefore insufficient to recommend corticosteroids maintenance therapy.

In six different randomized trials, thalidomide maintenance was used post-ASCT: thalidomide-based maintenance arm was compared with alpha-interferon, dexamethasone, pamidronate, prednisone, or observation in the different trials (19,35,42-45). A recent meta-analysis showed a reduced risk of progression (HR 0.64,  $P < 0.001$ ) and death (HR 0.73,  $P = 0.002$ ) with thalidomide maintenance (46). However, a significant rate of grade 3-4 neuropathy (7-19%) limited the long-term use of this drug (the rate of discontinuation reached 52%) (47). The lack of tolerability of thalidomide likely resulted from the doses used in the source studies and these data suggest that

other options than continuous therapy with thalidomide should be recommended. Only one trial evaluated post-ASCT bortezomib maintenance. Patients randomized to PAD or VAD induction followed by ASCT received bortezomib or thalidomide maintenance respectively. In a landmark analysis, bortezomib maintenance significantly improved the CR/nCR rate from 31% to 49% and reduced the risk of progression ( $P=0.04$ ) and death ( $P=0.05$ ). The rate of grade 3-4 peripheral neuropathy was 5% with bortezomib maintenance and 8% with thalidomide maintenance, the incidence of grade 3-4 infections was 24% and 18% in the two groups, respectively (13). However, these data should be interpreted with caution considering that patients received different induction regimens. Three trials evaluated lenalidomide maintenance after ASCT (17,47,48). In two trials lenalidomide was employed after ASCT in newly diagnosed patients who received VAD or novel agent-based combinations at induction (47,48); in the IFM0502 trial, consolidation with lenalidomide was administered after ASCT, and lenalidomide was then given up to 2 years (47); whereas, in the CALGB 100104 trial no consolidation was planned and lenalidomide maintenance was continued until progression (48). In the GIMEMA MMRV-209 trial, all patients received induction with Rd, afterwards they were randomized to consolidation with ASCT or no ASCT, and finally to lenalidomide maintenance or no maintenance (17). The median follow-up period of these 3 trials was different (range 18-51.2 months) and this further limits the comparison of the results. Despite the differences in the trial designs and treatments, a significant reduction in the risk of progression was reported with lenalidomide maintenance compared with no maintenance (HR range 0.47-0.50) (17,47,48). Only the CALGB 1000104 trial also showed a significant reduction in the risk of death (48). The main grade 3-4 adverse events during maintenance with lenalidomide were neutropenia (23-51%), and infections (6-13%). Lenalidomide maintenance raised some concern second primary malignancies (SPM). The incidence of SPM with lenalidomide maintenance was 4.3-8% vs 2.6-4.3% with placebo/no maintenance (17,47,48). The use of lenalidomide after and with oral melphalan could be a possible explanation for the increased incidence of SPM, as



suggested by the results of a recent meta-analysis (49). In the different studies, however, the advantage associated with lenalidomide maintenance seems to outweigh the risk of SPM.

### **3.Non-transplant setting**

Impressive results were achieved also with novel agents used for the treatment of elderly patients not eligible for ASCT. This provided the rationale to compare novel agent-based regimens with the more intensive approach ASCT, commonly associated with a higher rate of toxicity. Here follows a brief description of the most common regimens including novel agents adopted in the non-transplant setting.

A meta-analysis of six randomized trials comparing melphalan-prednisone-thalidomide (MPT) with melphalan-prednisone (MP) improved the median PFS (20.3 vs 14.9 months,  $P<0.0001$ ) and OS (39.3 vs 32.7 months,  $P=0.004$ ) with MPT (50). The combination bortezomib-melphalan-prednisone (VMP) improved the median time to progression (24 vs 16.6 months,  $P<0.001$ ) and OS (56.4 vs 41 months,  $P<0.001$ ) in comparison with MP (51,52). A more intensive regimen including 2 novel agents was explored in a phase III trial. VMP plus thalidomide followed by bortezomib-thalidomide maintenance (VMPT-VT) was compared with VMP alone. The 3-year PFS (56% vs 41%,  $P=0.008$ ) and the 5-year OS (61% vs 51%,  $P=0.01$ ) were significantly improved with the four-drug combination (53,54). In another study bortezomib-thalidomide-prednisone (VTP) vs VMP inductions were followed by VT or bortezomib-prednisone (VP) maintenance. The median PFS was 32 months for VMP and 33 months for VTP ( $P=0.09$ ). VMP significantly prolonged the median OS in comparison with VTP (63 vs 43 months;  $P=0.01$ ) (55,56). Melphalan-prednisone-lenalidomide followed by lenalidomide maintenance (MPR-R) prolonged the median PFS by 17 months in comparison to MPR and MP alone (31 vs 14 vs 13 months,  $P<0.001$ ), highlighting the impact of post-induction maintenance in elderly patients (57). Continuous treatment with lenalidomide and dexamethasone showed prolonged PFS and OS in comparison with MPT (58). Tables 3 and 4 present efficacy and safety data of selected regimens in the non-transplant setting.

#### **4.Does the introduction of novel agents challenge the role of transplantation?**

The first trial that tried to answer this question compared MPT vs reduced-intensity ASCT in an elderly population of patients. Patients randomized to reduced-intensity ASCT received induction with VAD and no novel agent was administered, which was a limitation of that study. In addition, a higher rate of toxic deaths was reported during the first three months of treatment in the reduced-intensity ASCT arm (therefore related to the induction regimen and not to ASCT itself) and this may have negatively affected the final results. MPT showed a significant reduction in the risk of progression (HR 0.54, P=0.0002) and the risk of death (HR 0.59, P=0.027) in comparison with reduced intensity ASCT (59). Despite its limitations, this study questioned the role of ASCT in the era of new drugs. The comparison of studies conducted in patients younger than 65 years versus those conducted in patients older than 65 years is however difficult. Recently, the first prospective randomized trial comparing combination chemotherapy including novel agents vs ASCT has been performed. Patients received Rd induction therapy and were then randomized to MPR or tandem ASCT. The median PFS was significantly longer for patients randomized to tandem ASCT than for those randomized to MPR (43.0 vs 22.4 months, P<0.001). Tandem ASCT also improved the 4-year OS rate (81.6% vs. 65.3%, P=0.02) (17). In a similar study, 390 patients received Rd induction regimen and were then randomized to receive tandem ASCT or cyclophosphamide–lenalidomide–dexamethasone, followed by lenalidomide or lenalidomide plus prednisone maintenance therapy. Preliminary results showed a reduced risk of progression for patients who received ASCT (3-year PFS: 60% vs 38%, P=0.003) (18). Two ongoing large studies are currently enrolling patients. In the IFM/DFCI2009 study, 1,000 patients are receiving VRD induction and are then randomized to continue VRD treatment or to receive ASCT plus VRD consolidation. Subsequently, patients will receive lenalidomide maintenance (CT.gov NCT01191060; NCT01208662). In the EMN02 study 1,500 patients are receiving VCD induction and are then randomly assigned to VMP or ASCT, and

further randomized to receive consolidation/ no consolidation with VRD, followed by lenalidomide maintenance (CT.gov NCT01208766).

In the majority of the previously described trials, patients who did not receive ASCT upfront will receive ASCT at relapse. These trials will therefore also try to define the best timing of ASCT, upfront or at first relapse. Before the introduction of novel agents, several randomized trials confirmed the PFS benefit with early ASCT in comparison with conventional chemotherapy. However, in 3 randomized studies, OS was similar whether ASCT was performed early or as salvage therapy at relapse (2-4). Despite similar OS (64.6 vs 64 months,  $P=0.92$ ), early ASCT improved the average time without symptoms (27.8 vs 22.3 months) and reduced treatment-related toxicities and discontinuation compared with late ASCT in one trial (3). Yet, in most of these trials, patients in the control arm did not have full access to novel agents.

In the era of new agents, to date only the results of two trials comparing early vs delayed ASCT are available. A recent pooled analysis including these two randomized trials was performed. The pooled analysis evaluated not only PFS and OS, but also PFS2 (survival from randomization to progression on or after second line therapy), to better analyze the role of delayed transplantation. The pooled analysis showed an improvement in PFS (3-year 59% vs 35%,  $P<0.001$ ) in PFS2 (3-year 77% vs 68%,  $P=0.012$ ) and OS (4-year 83% vs 72%,  $P=0.096$ ) – although the latter was not statistically significant - in patients receiving early ASCT (60)

## **5. Conclusions and future perspectives**

The introduction of effective regimens including bortezomib and IMiDs has greatly improved the outcome observed with ASCT in young MM patients. The data from the prospective trials performed to date suggest that the best available strategy to achieve high CR rate, to prolong response duration and survival consists in a sequential approach including induction with 3-drug, bortezomib-based combinations followed by ASCT and consolidation/maintenance with IMiDs or proteasome inhibitors. A major drawback of the majority of the previously described trials is the

fact that none of them was powered to assess OS. OS results may be affected by effective second-line therapy that dilutes the ability to dissect out the role of transplant vs no transplant. The impact of ASCT vs no ASCT could be also partly related to the number of therapeutic options available in different parts of the world. Obviously in the setting of limited treatment options, ASCT may play a more important role than in parts of the world where patients have a wider variety of treatments. Despite these considerations, available results suggest that upfront ASCT still remains a necessary component of therapy if compared with conventional chemotherapy plus IMiDs. The role of ASCT in comparison with bortezomib plus chemotherapy or IMiDs is currently under evaluation. The results of ongoing studies (IFM/DFCI2009 and EMN02) are awaited and will help clarify the role of ASCT in the era of new drugs.

### **Acknowledgments**

The authors thank Drs Chiara Cerrato and Francesca Donato for their assistance in collecting data and revising the final manuscript, and the editorial assistant Giorgio Schirripa.

### **Authorship**

FC, FG, and AP collected and analyzed the data, and wrote the manuscript.

### **Disclosures**

No funding was received for the preparation of this manuscript.

Conflict-of-interest disclosures: FC has received honoraria from Celgene, Janssen-Cilag, Onyx, and has served on the advisory committee of Celgene; FG has received honoraria from Celgene and Janssen-Cilag, and served on the advisory committee for Celgene and Byotest; AP has received honoraria from Celgene, Janssen-Cilag, Bristol-Myers Squibb, Millennium, Merck, Onyx, and has served on the advisory boards of Celgene and Janssen-Cilag.

## Reference

1. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, et al. A prospective randomized trial of Autologous Bone Marrow Transplantation and chemotherapy in Multiple Myeloma. *N Engl J Med.* 1996;335:91-97.
2. Dunavin NC, Wei L, Elder P et al. Early versus delayed autologous stem cell transplantation in patients receiving therapies for Multiple Myeloma. *Leuk Lymphoma.* 2013;54(8):1658-1644.
3. Femand JP, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood.* 1998;92(9):3131–3136.
4. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol.* 2006;24(6):929-936.
5. Kumar SK, Rajkumar SV, Dispenzieri A, et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood.* 2008;111(5):2516-20.
6. van de Velde HJ, Liu X, Chen G, Cakana A, Deraedt W, Bayssas M. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. *Haematologica.* 2007;92(10):1399-1406.
7. Gay F, Larocca A, Wijermans P, et al. Complete response correlates with long-term progression-free and overall survival in elderly myeloma treated with novel agents: analysis of 1175 patients. *Blood.* 2011;117(11):3025-3031.

8. Ladetto M, Pagliano G, Ferrero S, et al. Major tumor shrinking and persistent molecular remissions after consolidation with bortezomib, thalidomide, and dexamethasone in patients with autografted myeloma. *J Clin oncol* 2010 ; 28(12):2077-84.
9. Paiva B, Martinez-Lopez J, Vidriales MB, et al. Comparison of immunofixation, serum free light chain, and immunophenotyping for response evaluation and prognostication in multiple myeloma. *J Clin Oncol*. 2011;29(12):1627-33.
10. Rawstron AC, Child JA, de Tute RM et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. *J Clin Oncol* 2013; 31(20):2540-7.
11. Hoering A, Crowley J, Shaughnessy JD Jr, et al. Complete remission in multiple myeloma examined as time-dependent variable in terms of both onset and duration in Total Therapy protocols. *Blood*. 2009;114(7):1299-1305.
12. Morgan GJ, Kaiser MF. How to use new biology to guide therapy in multiple myeloma. *Hematology Am Soc Hematol Educ Program*. 2012;2012:342-9.
13. Sonneveld P, Schmidt-Wolf I.G.H, van der Holt B. et al. Bortezomib Induction and Maintenance Treatment in Patients With Newly Diagnosed Multiple Myeloma: Results of the Randomized Phase III HOVON-65/GMMG-HD4 Trial. *J Clin Oncol*. 2012;30(24):2946-55.
14. Cavo M, Di Raimondo F, Zamagni E et al. Short-term thalidomide incorporated into double autologous stem cell transplantation improves outcomes in comparison with double autotransplantation for multiple myeloma. *J Clin Oncol*. 2009;27(30):5001-7.
15. Weber D, Rankin K, Gavino M, et al. Thalidomide alone or with dexamethasone for previously untreated multiple myeloma. *J Clin Oncol*. 2003;21(1):16-19.
16. Harousseau JL, Attal M, Avet-Loiseau H et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to

- autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol*. 2010;28(30): 4621-9.
17. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med*. 2014;371(10):895-905.
  18. Palumbo A, Gay F, Spencer A, et al. A Phase III Study Of ASCT Vs Cyclophosphamide-Lenalidomide-Dexamethasone and Lenalidomide-Prednisone Maintenance Vs Lenalidomide Alone In Newly Diagnosed Myeloma Patients. *Blood*. 2013;122: abstract 763.
  19. Lokhorst HM, Bronno Van der Holt B, Zweegman S et al. A randomized phase 3 study on the effect of thalidomide combined with adriamycin, dexamethasone, and high-dose melphalan, followed by thalidomide maintenance in patients with multiple myeloma. *Blood*. 2010; 115(6):1113-20.
  20. Morgan GJ, Davies FE, Gregory WM et al. Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. *Haematologica*. 2012;97(3):442-50.
  21. Rosiñol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. *Blood*. 2012;120(8):1589-96.
  22. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet*. 2010;376(9758):2075-2085.
  23. Roussel M, Lauwers-Cances V, Robillard N, et al. Front-Line Transplantation Program With Lenalidomide, Bortezomib, and Dexamethasone Combination As Induction and Consolidation Followed by Lenalidomide Maintenance in Patients With Multiple Myeloma:

- A Phase II Study by the Intergroupe Francophone du Myélome. *J Clin Oncol.* 2014;32(25):2712-7.
24. Sonneveld P, Goldschmidt H, Rosiñol L et al. Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials. *J Clin Oncol.* 2013; 31(26):3279-87.
  25. Nooka AK, Kaufman JL, Behera M, et al. Bortezomib-containing induction regimens in transplant-eligible myeloma patients: a meta-analysis of phase 3 randomized clinical trials. *Cancer.* 2013; 119(23):4119-28.
  26. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood.* 2012;119(19):4375-4382.
  27. Ludwig H, Viterbo L, Greil R, Randomized phase II study of bortezomib, thalidomide, and dexamethasone with or without cyclophosphamide as induction therapy in previously untreated multiple myeloma. *J Clin Oncol.* 2013;31(2):247-55.
  28. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med.* 2003 Dec 25;349(26):2495-502.
  29. Sonneveld P, van der Holt B, Segeren CM, et al. Intermediate-dose melphalan compared with myeloablative treatment in multiple myeloma: long-term follow-up of the Dutch Cooperative Group HOVON 24 trial. *Haematologica.* 2007;92(7):928-35.
  30. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol.* 2007;25(17):2434-41.
  31. Mellqvist UH, Gimsing P, Hjertner O, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase III trial. *Blood.* 2013;121(23):4647-54.



32. Ferrero S, Ladetto M, Drandi D, et al. Long-term results of the GIMEMA VEL-03-096 trial in MM patients receiving VTD consolidation after ASCT: MRD kinetics' impact on survival. *Leukemia*. 2014 Jul 16. doi: 10.1038/leu.2014.219. [Epub ahead of print].
33. Cavo M, Pantani L, Petrucci MT, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy following autologous hematopoietic stem-cell transplantation in patients with newly diagnosed multiple myeloma. *Blood*. 2012;120(1):9-19.
34. Gay F, Magarotto V, Crippa C, et al. Bortezomib induction, reduced-intensity transplantation, and lenalidomide consolidation-maintenance for myeloma: updated results. *Blood*. 2013;122(8):1376-83.
35. Barlogie B, Pineda-Roman M, van Rhee F, et al. Thalidomide arm of Total Therapy 2 improves complete remission duration and survival in myeloma patients with metaphase cytogenetic abnormalities. *Blood*. 2008;112(8):3115-21.
36. Barlogie B, Tricot G, Anaissie E, Shaughnessy J, Rasmussen E, van Rhee F, et al. Thalidomide and hematopoietic-cell transplantation for multiple myeloma. *N Engl J Med* 2006;354:1021–30.
37. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. *Br J Haematol*. 2007;138(2):176-185.
38. Berenson JR, Crowley JJ, Grogan TM, et al. Maintenance therapy with alternate-day prednisone improves survival in multiple myeloma patients. *Blood*. 2002;99:3163–8.
39. Shustik C, Belch A, Robinson S, et al. A randomized comparison of melphalan with prednisone or dexamethasone as induction therapy and dexamethasone or observation as maintenance therapy in multiple myeloma: NCIC CTG MY.7. *Br J Haematol*. 2007;136:203–11.

40. Myeloma Trialists' Collaborative Group. Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. *Br J Haematol.* 2001;113:1020–34.
41. Fritz E, Ludwig H. Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomized trials among 3948 patients. *Ann Oncol.* 2000;11:1427–36.
42. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood.* 2006;108:3289–94.
43. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. *J Clin Oncol.* 2009;27:1788–93.
44. Stewart AK, Trudel S, Bahlis NJ, et al. A randomized phase 3 trial of thalidomide and prednisone as maintenance therapy after ASCT in patients with MM with a quality-of-life assessment: the National Cancer Institute of Canada Clinical Trials Group Myeloma 10 Trial. *Blood.* 2013;121:1517–23.
45. Maiolino A, Hungria VT, Garnica M, et al. Thalidomide plus dexamethasone as a maintenance therapy after autologous hematopoietic stem cell transplantation improves progression-free survival in multiple myeloma. *Am J Hematol.* 2012;87:948–52.
46. Ludwig H, Durie BG, McCarthy P, et al. IMWG consensus on maintenance therapy in multiple myeloma. *Blood.* 2012;119(13):3003-15.
47. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide Maintenance after Stem-Cell Transplantation for Multiple Myeloma. *N Engl J Med.* 2012;366(19):1782-1791.
48. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after Stem-Cell transplantation for Multiple Myeloma. *N Engl J Med.* 2012;366(19):1770-1781.

49. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. *Lancet Oncol.* 2014 Mar;15(3):333-42.
50. Fayers PM, Palumbo A, Hulin C, et al. Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. *Blood.* 2011;118(5):1239-1247.
51. San Miguel JF, Schlag R, Khuageva NK et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. *N Engl J Med.* 2008;359(9):906-17.
52. San Miguel JF, Schlag R, Khuageva NK, et al. Persistent overall survival benefit and no increased risk of second malignancies with bortezomib-melphalan-prednisone versus melphalan-prednisone in patients with previously. *J Clin Oncol.* 2013; 31(4):448-55.
53. Palumbo A, Bringhen S, Rossi D, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: a randomized controlled trial. *J Clin Oncol.* 2010;28(34):5101-9.
54. Palumbo A, Bringhen S, Larocca A, et al. Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: updated follow-up and improved survival. *J Clin Oncol.* 2014;32(7):634-40.
55. Mateos MV, Oriol A, Martínez-López J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: a randomised trial. *Lancet Oncol.* 2010;11(10):934-941.

56. Mateos MV, Oriol A, Martínez-López J, et al. Update of the GEM2005 trial comparing VMP/VTP as induction in elderly multiple myeloma patients: do we still need alkylators? *Blood*. 2014 Aug 7. pii: blood-2014-05-573733. [Epub ahead of print]
57. Palumbo A, Hajek R, Delforge M, et al. Continuous Lenalidomide Treatment for Newly Diagnosed Multiple Myeloma. *N Engl J Med*. 2012;366(19):1759-1769.
58. Benboubker L1, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. *N Engl J Med*. 2014;371(10):906-17.
59. Facon T, Mary JY, Hulin C, et al. Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99-06): a randomised trial. *Lancet*. 2007;370(9594):1209-1218.
60. Cavallo F, Spencer A, Gay F, et al. Early autologous stem cell transplantation improves survival in newly diagnosed multiple myeloma patients. *Haematologica*. 2014; abstract S-1338.

**TABLE 1.** Transplant setting: efficacy of selected sequential approaches. Improvement in response rates observed with induction, transplant, consolidation-maintenance regimens and survival data

REGIMEN	PATIENTS	CR (%)	PFS	OS
VD induction MEL 200 <sup>16</sup>	240	6* 40°*	50% at 36 months	81% at 36 months
PAD induction MEL 200 V maintenance <sup>13</sup>	413	7 21 36	50% at 35 months	61% at 60 months
PAD induction MEL 100 RP consolidation R maintenance <sup>34</sup>	102	12 33 48 53	43% at 60 months	63% at 60 months
VTD induction MEL 200 VTD consolidation <sup>33</sup>	160	23* 49* 61*	62% at 60 months	90% at 36 months
TD induction MEL 200 TD consolidation <sup>33</sup>	161	6* 40* 47*	49% at 60 months	88% at 36 months
RD induction MEL 200 R maintenance <sup>17</sup>	399 141 126	8 16 36	50% at 55 months	79% at 60 months
TAD induction MEL 200 T maintenance <sup>19</sup>	268	3 14 31	50% at 34 months	50% at 73 months
VTD induction MEL 200 <sup>21</sup>	130	35 46	50% at 56 months	74% at 48 months
VRD induction MEL 200 VRD consolidation R maintenance <sup>23</sup>	31	23 47 50 -	77% at 36 months	100% at 36 months

CR, complete response; Mel 100, melphalan 100 mg/m<sup>2</sup>; MEL 200, melphalan 200 mg/m<sup>2</sup>; OS, overall survival; PAD, bortezomib-adriamycin-dexamethasone; PFS, progression-free survival; R, lenalidomide; RD, lenalidomide-dexamethasone; RP, lenalidomide-prednisone; T, thalidomide; TAD, thalidomide-adriamycin-dexamethasone; TD, thalidomide-dexamethasone; V, bortezomib; VD, bortezomib-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.

° ≥near CR; \* Data in the per protocol population. In all the other studies, data refer to the intention-to treat population; - Data not available.

**Table 2.** Transplant setting: Safety (grade 3-4 adverse events) of selected pre transplant induction and post transplant consolidation-maintenance regimens

REGIMEN	NEUTROPENIA (%)	THROMBOCYTOPENIA (%)	ANEMIA (%)	THROMBOEMBOLISM (%)	PN (%)	INFECTION (%)	SPM (%)
<i>INDUCTION</i>							
VD <sup>16</sup>	5	3	4	2	7	9	-
PAD <sup>13-34</sup>	3-10	10-17	3-8	4-5	16-24	17-26	-
VTD <sup>21,22</sup>	10	8	-	3-12	10-12	3-21	-
TD <sup>22</sup>	-	-	-	15	4	4	-
TAD <sup>19</sup>	-	-	-	3	31§	-	-
RD <sup>17</sup>	9	3	6	3	-	6	0.3
VRD <sup>23*</sup>	35	13	3	-	-	-	-
<i>CONSOLIDATION</i>							
VTD <sup>33</sup>	-	5**	-	1	1	1	-
TD <sup>33</sup>	-	0**	-	1	0	3	-
RP <sup>34</sup>	19	15	-	3	-	-	-
<i>MAINTENANCE</i>							
V <sup>13</sup>	0	4	1	1	5	24	-
T <sup>13</sup>	1	2	1	1	8	18	-
R <sup>17,47,48</sup>	23-51	4-14	2-5	2-3	1	6-8	4.3-8

PAD, bortezomib-adriamycin-dexamethasone; PN, peripheral neuropathy; R, lenalidomide; RD, lenalidomide-dexamethasone; RP, lenalidomide-prednisone; T, thalidomide; TAD, thalidomide-adriamycin-dexamethasone; TD, thalidomide-dexamethasone; V, bortezomib; VD, bortezomib-dexamethasone; VRD, bortezomib-lenalidomide-dexamethasone; VTD, bortezomib-thalidomide-dexamethasone.

\* Data about induction or consolidation, as reported in the original study; \*\* All grade events; - Data not available; § Grade 2 to 4.

**TABLE 3.** Non transplant setting: efficacy of selected regimens

REGIMEN	PATIENTS	CR (%)	PFS	OS
MPT induction <sup>50</sup>	1685	25 <sup>°</sup>	50% at 20 months	50% at 39 months
VMP induction <sup>52</sup>	344	30	50% at 24 months*	68% at 36 months
VMP induction <sup>55,56</sup>	130	20	50% at 32 months	50% at 63 months
VMPT induction VT maintenance <sup>54</sup>	254	38 42	50% at 35 months	61% at 60 months
MPR induction R maintenance <sup>17</sup>	152	10 33 <sup>°</sup>	50% at 31 months	70% at 36 months
VTP induction <sup>55</sup>	130	28	50% at 33 months	50% at 43 months
Rd continuously <sup>58</sup>	535	15	50% at 26 months	59% at 60 months

CR, complete response; MPR, melphalan-prednisone-lenalidomide; MPT, melphalan-prednisone-thalidomide; OS, overall survival; PFS, progression-free survival; R, lenalidomide; Rd, lenalidomide-dexamethasone; VMP, bortezomib-melphalan-prednisone; VMPT, bortezomib-melphalan-prednisone-thalidomide; VP, bortezomib-prednisone; VT, bortezomib-thalidomide; VTP, bortezomib-thalidomide-prednisone.

<sup>°</sup> ≥ Very good partial response rate; \* Time to progression..

TABLE 4. NON TRANSPLANT SETTING: SAFETY (GRADE 3-4 ADVERSE EVENTS) OF SELECTED INDUCTION AND MAINTENANCE REGIMENS

REGIMEN	NEUTROPENIA (%)	THROMBOCYTOPENIA (%)	ANEMIA (%)	THROMBOEMBOLISM (%)	PN (%)	INFECTION (%)	SPM (%)
<i>INDUCTION</i>							
MPT <sup>50*</sup>	16-48	3-14	3-14	2-12	2-9	10-28	-
VMP <sup>51,54,56</sup>	28-40	20-37	10-19	<1-2	4-13	7-10	2
VTP <sup>56</sup>	22	12	8	2	9	<1	2
VMPT <sup>54</sup>	38	22	10	5	4	13	-
MPR <sup>17</sup>	35 <sup>°</sup>	11 <sup>°</sup>	3 <sup>°</sup>	1	-	9 <sup>#</sup>	7§
<i>MAINTENANCE</i>							
VT <sup>54,55</sup>	0-3	0	0	1	4-7	2	-
VP <sup>56</sup>	0	0	0	0	2	2	-
Rd <sup>58</sup>	28	8	18	8	1	29	3
R <sup>17</sup>	2 <sup>°</sup>	6 <sup>°</sup>	2 <sup>°</sup>	2	-	3 <sup>#</sup>	7§

MPR, melphalan-prednisone-lenalidomide; MPT, melphalan-prednisone-thalidomide; R, lenalidomide; Rd, lenalidomide-dexamethasone; VMP, bortezomib-melphalan-prednisone; VMPT, bortezomib-melphalan-prednisone-thalidomide; VP, bortezomib-prednisone; VT, bortezomib-thalidomide; VTP, bortezomib-thalidomide-prednisone.  
 - Data not available; \*Data retrieved from the source studies; § For the whole MPR-R regimen; # Grade 3 events only; ° Grade 4 events only.