

* CHAPTER 26

HSCT for multiple myeloma in adults

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Multiple myeloma (MM) is the most common plasma cell disorder with an incidence of 4–5 new cases per 100.000 individuals/year. Unfortunately, MM remains incurable with conventional chemotherapy. Nevertheless the availability of new drugs, which target not only the PC but also the microenvironment, together with the well established use of high dose chemotherapy is changing the prognosis of these patients.

1. Indications for transplant

High dose therapy followed by auto-HSCT is considered the standard of care for patients diagnosed with multiple myeloma. Accordingly, MM is currently the most common indication for auto-HSCT in North America and Europe.

As far as allogeneic transplantation is concerned, it remains as the only curative therapeutic approach in MM patients. However, it is associated with a high mortality and morbidity (mainly due to GvHD). Accordingly, it should be used in carefully defined situations and, preferably, within the context of clinical trials.

2. Specific conditioning

Melphalan 200 mg/m² is considered the gold standard conditioning regimen prior to auto-HSCT. The IFM randomised trial (1) confirmed that patients receiving melphalan 200 displayed a better median overall survival as compared to patients treated with melphalan 140 mg/m² in combination with TBI (65 vs. 45% survival at 45 months). Other studies using intensification of the doses or addition of alkylating agents have not demonstrated significant improvements either in terms of response rate nor in outcome.

As far as allogeneic transplantation is concerned, there is a marked heterogeneity in the type of conditioning regimen used: varying from myeloablative conditioning (MC) regimens to a variety of reduced intensity non-myeloablative regimens (RIC). Moreover, within each modality of conditioning the dose and type of drugs or radiotherapy is highly variable.

3. Role and outcome of autologous transplant

High dose therapy followed by auto-HSCT prolonged overall survival as compared to standard dose therapy (SDT) in prospective randomised trials conducted by the French (IFM) and English (MRC) groups (2, 3) and has provided evidence for >10 year survivorship at least in a subset of patients. Nevertheless, the US study (SWOG 9321), the French MAG91 study and the Spanish PETHEMA group, although they confirmed the benefit of auto-HSCT in terms of response rate and EFS, did not find superiority in terms of survival as compared to SDT (4, 5, 6). These discrepancies

can be, at least in part, explained by: 1) differences in the studies' design (the Spanish study randomised patients responding to initial therapy while, in the others, randomisation was performed up-front), 2) differences in the conditioning regimens and, particularly, 3) differences in the intensity and duration of the chemotherapy arm (the dose of alkylating agents and steroids were higher in the SWOG and Spanish trials, which may explain why overall survival for conventionally treated patients was longer in these two studies as compared to IFM and MRC trials). Finally, two recent meta-analyses did not provide evidence of an overall survival advantage for HDT as compared to SDT (7, 8).

In spite of these discrepancies, HDT is currently considered as standard of care for younger patients with multiple myeloma, mainly based on the benefit on response rate and EFS. Nevertheless, the availability of highly efficient new drugs may challenge this statement. Thus, novel drugs combinations based on thalidomide, bortezomib or lenalidomide, have shown to be superior to VAD-like regimens as debulking agents prior to auto-HSCT, with response rates >80%, including up to 10–30% CR rates. The next question is whether or not auto-HSCT is able to up-grade the response obtained with novel agents. In six pilot studies based on bortezomib-induction regimens, it was observed that the CR rate was improved following auto-HSCT, which suggests that the two approaches (induction with novel agents and auto- HSCT) are complementary rather than alternative.

Regarding tandem auto-HSCT, its use will decrease for two reasons: 1) according to IFM (9) and Italian (10) experience only patients achieving a very good partial response with the first transplant benefit from the second and 2) a similar benefit is obtained upon using thalidomide as consolidation/maintenance therapy (11). In contrast, second transplant at relapse may be increasingly used, providing that the duration of the response to first transplant has lasted for more than 2–3 years.

4. Role and outcome of HLA-identical sibling transplant

Although HDT followed by autologous transplantation allows long-term survival, at least in a subset of patients, there is no clear plateau on the survival curve. Moreover, patients displaying poor prognostic features such as IgH translocations plus Rb or p53 deletions and advanced stage according to the International Staging System display poor prognosis after HDT. On the contrary, allogeneic transplantation remains the only curative therapeutic approach which may offer long-term disease free survival. Unfortunately, although TRM has been

reduced in the last years, conventional allogeneic transplantation is still associated with a high TRM. In the SWOG 9321 randomised trial, patients with a suitable donor received allogeneic transplantation after conditioning with melphalan 140 mg/m² plus TBI and the arm was closed due to a 1 year TRM of 53%. Interestingly, 7 year estimated progression free survival in this subset of patients was 39%, similar to that reported for patients receiving autologous transplant or SDT, and this was due to a low relapse rate among patients receiving allogeneic transplant. In order to decrease TRM different RIC regimens have been developed (allo-RIC). In a prospective randomised trial, the French group compared double auto-HSCT to auto-HSCT followed by allo-RIC among patients displaying poor prognostic features (high B₂microglobulin and monosomy of chromosome 13). Unfortunately, there were no event free survivors at 5 years either after double auto-HSCT or after auto-HSCT followed by allo-RIC (12). By contrast, the Italian group, using a similar approach, has recently described an improvement in terms of overall survival among patients receiving auto-HSCT followed by allo-RIC as compared to double auto-HSCT (13). In addition to differences in patient characteristics, the different GvHD prophylaxis and conditioning regimens used could explain these differences.

Currently available data suggest that the use of RIC rather than myeloablative conditioning regimens may decrease TRM, but no prospective comparison is so far available. In a retrospective study from the EBMT comparing MC vs. allo-RIC, TRM was 37 vs. 24% and cumulative incidence of disease progression were 27 vs. 54% for MC vs. allo-RIC, respectively, which resulted in similar overall survival (51 vs. 38%).

In high risk MM patients, including those displaying poor cytogenetic features (t(4;14), t(14;16) and t(14;20), Chr 13 deletion by conventional cytogenetics, p53 deletion, complex karyotype or hypodiploidy) or those with progressive disease during induction therapy, the use of novel agents as induction therapy followed by a tandem transplant, auto-HSCT and allo-RIC, represents an attractive approach, although these type of studies should be conducted within well controlled clinical trials.

Regarding rescue therapy, in a series of 54 patients, 14 patients obtained complete remission or partial response out of 19 patients with refractory disease undergoing auto-HSCT followed by RIC allogeneic transplant (14). Unfortunately, a significant proportion of these patients finally relapse, leading to a poor event free survival, especially among patients who had relapsed after a prior autograft or with active disease at the time of allogeneic transplantation (15) (Table 1).

Table 1: Results of randomised trials

Trials (Ref.)	EFS / PFS	OS	p
Standard dose chemotherapy (SDT) vs. autologous HSCT			
IFM(2)			S
SDT	18 months (10% 5 years)	37 months (12% 5 years)	
Auto-HSCT	27 months (28% 5 years)	not reached (52% 5 years)	
MRC(3)			S
SDT*	19 months	42 months	
Auto-HSCT *	31 months	54 months	
SWOG(4)			NS
SDT*	14% 7 years	39% 7 years	
Auto-HSCT *	17% 7 years	38% 7 years	
PETHEMA(5)			NS
SDT*	33 months	66 months	
Auto-HSCT *	42 months	61 months	
MAGG(6)			NS
SDT*	19 months	47 months	
Auto-HSCT *	25 months	47 months	
Single vs. double autologous HSCT			
IFM(9)			S
Single*	25 months (10% 7 years)	48 months (21% 7 years)	
Double*	30 months (20% 7 years)	58 months (42% 7 years)	
Cavo(10)			NS
Single	23 months	46 months	
Double	35 months	43 months	
Autologous vs. allogeneic HSCT			
IFM(12)			NS
Auto-HSCT (double)	30 months (0% 5 years)	41 months (44% 5 years)	
Auto-HSCT plus RIC-allo	25 months (0% 5 years)	35 months (33% 5 years)	
Bruno(13)			S
Auto-HSCT (double)*	29 months	54 months	
Auto-HSCT plus RIC-allo *	35 months	80 months	
SWOG(4)			NS
Auto-HSCT	17% 7 years	38% 7 years	
Allo-HSCT (MC)	22% 7 years	39% 7 years	

(p) differences for OS: (NS) non significant; (S) significant differences. (*) results expressed as median OS: overall survival; EFS: event-free survival; PFS: progression-free survival; MC: myeloablative conditioning

5. Role and outcome of matched unrelated donor (MUD) allogeneic transplant

In the unrelated donor setting, the use of fludarabine and melphalan as conditioning regimen plus ATG as graft-versus-host disease prophylaxis was associated with a 90%

response rate (40% complete and 50% partial) in a series of 21 MM patients. TRM was 26% at 1 year and 2 year overall and progression free survival were 74% and 53% (16). In another series of 17 patients, receiving MUD after fludarabine plus 2 Gy TBI, including 71% with chemotherapy resistant disease, 42% achieved complete remission and 17% partial response after transplant. Outcome was significantly better among those receiving tandem auto-HSCT followed by allo-RIC as compared to those who directly proceeded to allogeneic transplantation (51 vs. 11% progression free survival, respectively) (17).

6. Other sources: role and outcome of haploidentical transplant and cord blood transplant

Data using alternative sources of progenitor cells in MM patients are too limited to draw any firm conclusion.

7. Nature and role of any additional cellular or chemotherapy post-transplant

Donor lymphocyte infusions (DLI) given for relapsed myeloma following allogeneic transplantation induce responses in 30–50% of patients, the most common approach being the use of escalating dose at a usual starting dose of 1×10^7 CD3/kg (10^6 in the unrelated setting). In a recent multicentre analysis, the most important prognostic factors for response to DLI after RIC were the development of acute and chronic GvHD. Interestingly, the combination of DLI with thalidomide or bortezomib may improve the response rate and contribute to modulate the immune response, although further studies are required to confirm these data (18).

8. Nature and role of minimal residual disease monitoring after transplant

A high relapse rate has been reported among MM patients receiving transplantation even in the allogeneic setting. For this reason, MRD monitoring might allow individualised treatment strategies. In this regard, PCR may contribute to identify patients at high risk of relapse; thus, in a series of MM patients undergoing transplantation, among 16 PCR negative patients no relapses were observed as compared to 100% among 13 patients with positive PCR (19). Unfortunately, a high proportion of patients develop extramedullary relapses without bone marrow involvement (20) indicating that, although the disease may be under control in the bone marrow milieu, extramedullary spread may occur. For this reason, MRD monitoring in bone marrow may not allow an early identification of all patients at risk of relapse and other tools, such as PET/MRI should be considered for a better follow-up of these patients.

References

1. Moureau P, Facon T, Attal M, et al. IFM. Comparison of 200 mg/m² melphalan and 8 Gy total body irradiation plus 140 mg/m² melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: Final analysis of the IFM 9502 randomized trial. *Blood* 2002; 99: 731-735.
2. Attal M, Harousseau JL, Stoppa AM, et al. A prospective randomised trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *Intergroupe Francais du Myelome. N Eng J Med* 1966; 335: 91-97.
3. Child JA, Morgan GJ, Davies FE, et al. Medical Research Council adult Leukemia Working Party. High dose chemotherapy with hematopoietic stem cell rescue for multiple myeloma. *N Eng J Med* 2003; 348: 1875-1883.
4. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high dose chemoradiotherapy for multiple myeloma: Final results of a phase III US intergroup trial S9321. *J Clin Oncol* 2006; 24: 929-936.
5. Blade J, Rosignol L, Sureda A, et al. PETHEMA. High dose therapy intensification compared with continued standard chemotherapy in multiple myeloma patients responding to the initial chemotherapy: Long term results from a prospective randomised trial from the Spanish cooperative group PETHEMA. *Blood* 2005; 106: 3755-3759.
6. Femand JP, Katsahian S, Divine M, et al. Group Myeloma Autogreffe. High dose therapy and autologous blood stem cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65: Long term results of a randomised control trial from the MAG. *J Clin Oncol* 2005; 23: 9227-9233.
7. Levy V, Katschian S, Femand JP, et al. A meta-analysis on data from 575 patients with multiple myeloma randomly assigned to either high-dose therapy or conventional therapy. *Medicine (Baltimore)* 2005; 84: 250-260.
8. Koreth J, Cutler CS, Djulbegovic B, et al. High dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma. A systematic review and meta-analysis of randomised controlled trials. *Biol Blood Marrow Transplant* 2007; 13: 183-196.
9. Attal M, Harousseau JL, Facon T, et al. IFM. Single versus double autologous stem cell transplantation for multiple myeloma. *N Eng J Med* 2003; 349: 2495-2502.
10. 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: 2434-2441.
11. Attal M, Harousseau JL, Leyvraz S, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. *Blood* 2006; 108: 3289-3294.
12. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. *Blood* 2006; 107: 3474-3480.
13. Bruno B, Rotta, M, Patriarca F, et al. A Comparison of Allografting with Autografting for Newly Diagnosed Myeloma. *N Engl J Med* 2007; 356: 1110-1120.
14. Maloney D, Molina A, Sahebi F, et al. Allografting with nonmyeloablative conditioning

- following cytoreductive autografts for the treatment of patients with multiple myeloma *Blood* 2003; 102: 3447-3454.
15. Kröger N, Perez-Simon J, Myint H, et al. Influence of timing allogeneic stem cell transplantation after dose-reduced melphalan/fludarabine conditioning in multiple myeloma. *Biol Blood and Marrow Transplant* 2004; 10: 698-708.
 16. Kröger N, Sayer H, Schwerdtfeger R, et al. Unrelated stem cell transplantation in multiple myeloma after a reduced-intensity conditioning with pretransplantation antithymocyte globulin is highly effective with low transplantation-related mortality. *Blood* 2002; 100: 3919-3924.
 17. Georges G, Maris M, Maloney D, et al. Nonmyeloablative unrelated donor hematopoietic cell transplantation to treat patients with poor-risk, relapsed, or refractory multiple myeloma. *Biology of Blood and Marrow Transplantation* 2007; 13: 423-432.
 18. Van de Donk N, Kröger N, Hegenbart U, et al. Prognostic factors for donor lymphocyte infusions following non-myeloablative allogeneic stem cell transplantation in multiple myeloma. *Bone Marrow Transplant* 2006; 37: 1135-1141.
 19. Corradini P, Cavo M, Lokhorst H, et al. Molecular remission after myeloablative allogeneic stem cell transplantation predicts a better relapse-free survival in patients with multiple myeloma. *Blood*. 2003; 102: 1927-1929.
 20. Pérez-Simón J, Sureda A, Fernández-Avilés F, et al. Reduced intensity conditioning allogeneic transplantation is associated with a high incidence of extramedullary relapses in multiple myeloma patients. *Leukemia* 2006; 20: 542-545.

Mutiple Choice Questionnaire

To find the correct answer, go to <http://www.esh.org/ebmt-handbook2008answers.htm>

1. **Regarding auto-HSCT, which of the following sentences is wrong?**
 - a) Patients receiving melphalan 200 mg/m² display a better median overall survival as compared to patients treated with melphalan 140 mg/m² in combination with TBI
 - b) Two recent meta-analyses have not provided evidence of an overall survival advantage auto-HSCT as compared to standard dose therapy
 - c) Novel drugs combinations based on thalidomide, bortezomib or lenalidomide, have shown to be superior to VAD-like regimens as debulking treatment prior to auto-HSCT, with response rates >80%, including up to 10–30% CR rates
 - d) Auto-HSCT does not improve the response rate obtained with bortezomib-based induction regimens

2. Regarding auto-HSCT, one of the following answers is incorrect:

- a) MM is currently the most common indication for auto-HSCT in North America and Europe
- b) In the Spanish (PETHEMA) and American (SWOG) trials, the dose of alkylating agents and steroids used in the chemotherapy arm were higher than in the French (IFM) and UK (MRC) trials, which may explain why the survival was similar to that obtained with auto-HSCT...
- c) According to two randomised trials, patients achieving complete remission with the first auto-HSCT do benefit from the second transplant
- d) Second transplant in relapsing patients offers no benefit to those patients in whom the duration of the response to first transplant has lasted less than 1 year

3. Choose the correct answer:

- a) In the SWOG 9321 randomised trial, patients with a suitable donor received allogeneic transplantation after conditioning with melphalan 140 mg/m² plus TBI and the arm was closed due to a 1 year TRM of 53%
- b) Seven year estimated overall survival in this subset of patients was 39%, similar to that reported for patients receiving auto-HSCT or standard dose chemotherapy, and this was due to a low relapse rate among patients receiving allogeneic transplant
- c) The IFM compared double auto-HSCT to auto-HSCT followed by RIC-allo among patients displaying poor prognostic features (high B₂microglobulin and monosomy of chromosome 13). There were no event free survivors at 5 years in either arm
- d) In the IFM trial, the conditioning regimen among patients receiving allo-RIC consisted of fludarabine and melphalan

4. Regarding allogeneic transplantation one of the following answers is incorrect:

- a) Median overall survival among patients receiving double auto-HSCT was 54 months as compared to 80 months among those receiving auto followed by allo-RIC in a multicentre prospective randomised Italian trial conducted by Bruno et al.

- b) This study included only patients displaying poor cytogenetics
- c) In a retrospective study from the EBMT comparing myeloablative conditioning vs. allo-RIC or RIC, the TRM was lower with RIC-allo but the cumulative incidence of disease progression was higher, which resulted in similar overall survival in both subgroups
- d) In that study, the use of Campath in a subset of patients receiving RIC-allo was associated with a significant increase in the risk of relapse

5. Regarding allogeneic transplantation which of the following answers is correct:

- a) Response rates ranging from 70 to 90% has been reported even among patients with refractory MM undergoing auto followed by RIC-allo transplant
- b) DLI given for relapsed myeloma following allogeneic transplantation induce responses in >80% of patients
- c) The most common approach is the use of escalating dose at a usual starting dose of 1×10^8 CD3/kg (10^7 in the unrelated setting)
- d) The combination of DLI plus thalidomide or bortezomib may improve the response rate as compared to DLI alone