Is there still a role for stem cell transplantation in multiple myeloma?

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Running title: Stem cell transplant for multiple myeloma

Authors: Roberto Mina[1] and Sagar Lonial[1]

Affiliations: [1] Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA

Correspondence to: Roberto Mina, MD, Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA

Email: roberto.mina.rm@gmail.com

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ABSTRACT

High-dose chemotherapy and autologous stem cell transplant (ASCT) is a standard of care for newly diagnosed, transplant-eligible multiple myeloma (MM) patients.

The introduction of novel agents, from immunomodulatory drugs and proteasome inhibitors to monoclonal antibodies, now integrated in both induction and salvage regimens, has dramatically revolutionised the treatment landscape of MM, challenging the role of high-dose chemotherapy and ASCT to treat MM. These advances have led to a number of provocative questions: 1) what is the current role of SCT as compared to standard-dose therapy incorporating novel agents? 2) Should ASCT be performed upfront ("early") or later ("delayed") in the course of the disease? 3) Single or double ASCT? 4) Is allogeneic-SCT still an option for MM patients?

In this article, we provide an overview of available data, and evidence-based responses regarding the role of SCT in MM.

CONDENSED ABSTRACT

- High-dose melphalan and autologous stem cell transplant (ASCT) is the current standard approach for young, newly diagnosed myeloma patients as part of first line treatment.
- At relapse, salvage ASCT is a feasible and effective treatment option, whereas allogeneic-SCT have been considered an option for young, high-risk myeloma patients.

Introduction

Multiple myeloma (MM) is the second most common hematological malignancy and the most common indication for autologous stem cell transplantation (ASCT) in the US. [1,2]

The natural history of MM was first changed by the introduction of high dose chemotherapy and ASCT, [3,4] and then further improved upon by the use of novel agents, such as immunomodulatory drugs (IMiDs), thalidomide, lenalidomide and pomalidomide, proteasome inhibitors (PIs), bortezomib, carfilzomib and ixazomib, and most recently the monoclonal antibodies, elotuzumab and daratumumab. [5,6] These therapeutics innovations have led to a significant survival improvement, with median overall survival (OS) of MM patients now ranging between 6 and 10 years, depending on the age of patients at diagnosis. [2,7]

Given the wide availability of new targeted therapies for the treatment of MM, the role of SCT has been questioned in the last years, with several trials addressing the role and timing of transplant.

In this article we provide an overview of the available literature on the use of SCT to treat MM patients.

Stem cell transplant for newly diagnosed myeloma patients

Autologous stem cell transplant eligibility

High-dose melphalan followed by autologous stem cell rescue is currently a worldwide standard of care for newly-diagnosed (ND), transplant-eligible MM patients. [8,9] In Europe, chronological age has been used to define ASCT eligibility, particularly in clinical trials, with

65 years as a cut-off to define ASCT-eligible and -ineligible patients. However, recent analysis of both the European Blood and Marrow Transplantation (EBMT) and the Center for International Blood and Marrow Research (CIBMTR) registries, clearly showed a constant increase, from 1991/1995 to 2010, in the use of ASCT in older patients (over 65 years of age). [10,11]

The feasibility of high dose melphalan and ASCT among older patients, has been evaluated in several studies. [12-14] In a prospective study enrolling patients over 65 years of age, ASCT conditioned with melphalan 100 mg/m^2, demonstrated to be feasible and effective (5-year OS: 63%), especially among patients aged 66-70 years, whose treatment-related mortality (TRM) was lower than that of patients over 70 years of age (5% vs. 19%). [15] In the DSSM II trial, in which patients received a tandem ASCT conditioned with melphalan 140 mg/m^2, no difference in terms of TRM (1%) was reported between patients aged 60-65 and those over 66 years. [16] In another prospective trial comparing melphalan 140 mg/m^2 to melphalan 200 mg/m^2 in patients older than 65 years of age, the TRM at day +100 from transplant was 0% in both arms, confirming the feasibility of delivering high-dose melphalan to older patients. [17] Many studies have confirmed that chronological age is not, itself, a limitation to ASCT. Instead, organ function and comorbidities, as well as performance status, should be taken into consideration to define ASCT eligibility [18] and currently, in the US, ASCT is considered and may be appraised for patients up to the age of 80.

Autologous stem cell transplant versus non transplant-based strategies

The two first large trials to compare high-dose chemotherapy and ASCT with standard-dose chemotherapy were conducted by the Intergroup Francophone du Myèlome (IFM) and the Medical Research Council (MRC) (Table 1). [3,4] In both trials, high-dose chemotherapy ad ASCT

significantly prolonged progression-free survival (PFS) and OS as compared to standard-dose chemotherapy without transplantation. It should be noted that, at the time, limited salvage options were available for these patients, accounting for the early improvement in OS for both trials.

Several trials have been conducted thereafter to support the benefit of high-dose chemotherapy and ASCT as compared to standard-dose chemotherapy, although only 1 trial was able to detect a significant OS advantage among patients undergoing ASCT. [19-23]However, all the studies comparing ASCT with standard-dose chemotherapy published before 2010 did not include novel agents as part of the initial treatment of NDMM patients. With the incorporation of IMiDs and PIs in the upfront treatment of MM patients, the need for ASCT as part of first-line treatment has therefore been challenged.

To date, 4 phase III trials have compared high-dose chemotherapy and ASCT to novel-agents-based regimens without ASCT. The first study, published by Palumbo et al. (RV-MM-209), enrolled 402 NDMM patients who, after a lenalidomide-dexamethasone (Rd) induction, were randomized to either 2 courses of high-dose melphalan (200 mg/m^2) followed by ASCT, or 6 cycles of melphalan, prednisone and lenalidomide (MPR). Patients in the ASCT arm had significantly longer PFS (median, 43 vs. 22 months; p<0.001) and 4-year OS (82% vs. 65%; p=0.02). [24] Similar results were presented by Gay et al. in the EMN-441 phase III trial, in which 389 NDMM patients, treated with Rd induction, were randomized to receive either tandem ASCT or 6 cycles of cyclophosphamide, lenalidomide and dexamethasone (CRD). Again, patients in the ASCT group displayed a prolonged median PFS (43 vs. 29 months; p<0.001) and 4-year OS (86% vs. 73%; p=0.004) in comparison with patients in the no ASCT arm. [25] In a pooled analysis of the two trials, the advantage of ASCT as compared to a lenalidomide-based approach without ASCT, in terms of 5-year PFS (55% vs. 45%; p=0.01),

PFS2 (71% vs. 62%; p=0.02) and OS (87% vs. 71%; p=0.03) was confirmed also in patients in CR. [26]

The addition of bortezomib to lenalidomide and dexamethasone (RVD) significantly improved median PFS (43 vs. 30 months; p=0.002) and OS (75 vs. 64 months; p=0.025) as compared to Rd alone. Therefore, RVD has become a standard of care for NDMM patients. [27]

A formal comparison between ASCT and RVD was performed in the IFM 2009 trial. Seven hundred patients, after 3 RVD induction cycles, were randomized to 1 course of high-dose melphalan (200 mg/m^2) and ASCT followed by 2 further RVD cycles or 5 RVD cycles without ASCT, and all patients received lenalidomide maintenance. A higher rate of CR (59% vs. 48%; p=0.03) and minimal residual disease negativity (79% vs. 65%; p<0.001) among patients in the ASCT arm was observed, translating into a 35% reduction in the risk of progression or death (median PFS 50 vs. 36 months; HR 0.65, p<0.001) in favour of patients transplanted in comparison with those who received RVD only. No difference in terms of OS was noted at 4 years; however, a longer follow-up might be needed to highlight an OS difference between the two arms, especially in light of the wealth of salvage treatment options that may cloud the OS benefit. [28] Moreover, in all trials PFS is improved with early ASCT, suggesting improved depth of response and better disease control for most patients.

In the European EMN02/HO95 trial, comparing 1 or 2 courses of melphalan 200 mg/m^2 and ASCT to bortezomib, melphalan and prednisone (VMP) consolidation after a bortezomib-based induction, patients randomized in the ASCT group displayed a higher rate of at least very good partial response (VGPR; 86% vs. 74%; p<0.001) and a longer 3-year PFS (66% vs. 58%; p=0.037) as compared to patients in the VMP arm. [29]

All the trials comparing ASCT to novel agent-based treatments without transplant for NDMM patients conducted so far, continue to favour ASCT over a non-transplant approach in terms of high quality responses and PFS, with two trials also reporting a significant OS advantage for

patients undergoing ASCT. For these reasons, ASCT still remains the standard of care for ND, transplant-eligible myeloma patients.

Early versus delayed autologous stem cell transplant

Before the introduction of novel agents, the role of early ASCT as compared to that of a delayed ASCT was addressed in 3 trials. In the study published by Fermand et al., a trend towards a better PFS (p=0.07) and a longer interval without treatment, symptoms and treatment-related toxicities, was observed for early over delayed ASCT, but no OS advantage. [20] A North American cooperative study comparing high-dose therapy and ASCT to standard-dose therapy, offered a delayed ASCT to patients in the standard-dose arm; of these, approximately 50% of patients with a follow-up received ASCT at relapse. At 7 year, the overall survival was equal between the patients in the two arms (38% vs 39%). [22] In the randomized CIAM study, specifically designed to compare early versus delayed ASCT, a preliminary analysis, reported in abstract form, showed no OS difference between the two arms. [30]

Two retrospective analysis compared early (within 12 months from diagnosis) versus delayed (beyond 12 months) ASCT. Kumar et al. analysed 290 patients treated with an IMiD-based induction and subsequently receiving ASCT. They showed a similar median time to progression (TTP, 20 vs. 16 months; p: NS) from ASCT, as well as no difference in terms of 4-year OS (73% in both groups) between early and delayed ASCT. However, the reasons for the delayed ASCT are not clear, and a higher percentage of patients in the delayed ASCT group had deeper responses to induction therapy. [31] Furthermore, this analysis may have limited value given the short TTP in both arms. Similar results were reported by Dunavin et al. in an analysis of 167 patients undergoing early or delayed ASCT; despite a trend towards a longer

median TTP in the early ASCT group (28 vs. 23 months; p=0.055), no differences in terms of OS were noted between the two groups at 3 (90% vs. 82%) and 5 years (63% vs. 63%); again, the median TTP is shorter than those seen in trials with modern maintenance approaches [32] These trials showed the feasibility of a delayed ASCT; however, given the lack of a randomization and the absence of stratification for baseline characteristics, is not clear which subgroup of patients can actually benefit the most from a delayed ASCT.

In a pooled analysis of the RV-MM-209 and EMN-441 studies, only 53% of patients who did not receive ASCT as part of first line treatment were able to receive ASCT at relapse. Patients who underwent ASCT upfront not only had a longer PFS, but also benefited from a longer 4-year PFS2 (71% vs 54%; p<0.001) and OS (84% vs 70%; p<0.001) as compared to those who received a delayed ASCT. [33] It must be noted that the patients in the non-transplant arm received a suboptimal induction and consolidation (Rd-MPR/CRD) approach as compared to current 3-drug regimens including a PI and an IMiD.

Nonetheless, this pooled analysis shows that a fraction of patients who do not receive ASCT upfront may not be able to receive it at relapse. A possible explanation for this phenomenon is related to ageing of patients, deterioration of performance status and comorbid conditions, and type of relapse. However, in the more recent IFM 2009 trial, a higher rate (79%) of patients who did not undergo ASCT upfront were instead able to receive a salvage ASCT, and this probably reflects in the lack of OS survival observed between the two arms. Longer follow-up is needed to evaluate the impact of delayed ASCT on PFS2 and OS. [28]

Single versus tandem autologous stem cell transplant

The role of a tandem ASCT as upfront treatment in NDMM patients and its superiority over a single ASCT has been investigated, with conflicting results, and still remains a matter of discussion (Table 2).

A first evidence of the superiority of tandem ASCT over single ASCT, came by the IFM study published in 2003, demonstrating a longer median EFS (36 vs. 25 months; p=0.03) and OS (58 vs. 48 months; p=0.01) in patients receiving tandem ASCT. In a subgroup analysis, authors reported that patients who benefited the most from tandem ASCT were those who failed to achieve a VGPR after the first ASCT, which may be expected as induction therapy did not include novel agents. [34]

In the Italian trial published by Cavo et al, patients receiving tandem ASCT had a higher rate of CR (47% vs. 33%) and a significantly prolonged median EFS (35 vs. 23 months; p=0.001), but similar OS (median, 71 vs. 65 months; p=0.9) as compared to patients who received a single ASCT. [35] Similarly, in a randomized study by Fermand et al conducted in NDMM patients, double over single ASCT has yet to show an OS advantage. [36] Sonneveld et al. compared a non-myeloblative approach (two cycles of melphalan 70 mg/m^2) to the same regimen followed by ASCT in a phase III study; despite a higher CR rate (32% vs. 13%; p<0.001) and prolonged median PFS (27 vs. 24 months; p=0.006), no difference in OS (50 vs. 55 months) was observed between the two arms. [37]

More recently, in a pooled analysis of four European trials, median PFS (50 vs. 38 months; p<0.001) and 5-year OS (75% vs. 63%; p=0.002) were longer in patients receiving a second transplant as compared to patients in whom a single ASCT was planned. [38]

Similar results have been reported by a preliminary analysis of the European EMN02/HO95 trial, in which patients who received a tandem ASCT had a significantly longer 3-year PFS (74% vs. 62%; p=0.005) as compared to those who received a single ASCT. [39]

To address the role of consolidation therapy after a first ASCT, the phase III STAMINA trial randomized NDMM patients who previously underwent a first ASCT, to either a second ASCT or RVD consolidation, followed by lenalidomide maintenance. [40] At 38 months, the investigators found no differences in terms of PFS (57% vs. 57%) and OS (86% vs 82%) between the two groups.

Taking into consideration the conflicting results published so far, a second ASCT appears a feasible and reasonable option, especially for high-risk MM patients and those who fail to achieve at least a VGPR after the first transplant. Ongoing and future randomized trials should ultimately define the role of a tandem ASCT in the general population.

Early allogeneic stem cell transplant

Allogeneic SCT (allo-SCT) is regarded as a potentially curative approach for MM due to the graft versus myeloma (GvM) effect mediated by the donor immune system. [41] However, despite its biological rationale, the role allo-SCT for the treatment of MM is limited.

Two meta-analysis including studies that compared allo-SCT to ASCT as initial treatment for NDMM failed to demonstrate a superiority, in terms of PFS and OS, of allo-SCT over ASCT; this is despite higher rates of CR among patients in the allo-SCT group, that also experienced a higher TRM than the ASCT group, and early and late relapses continue to be a major cause for treatment failure. [42,43]

To combine a highly effective cytoreductive procedure yet taking advantage of the GvM effect, a tandem auto/mini-allo-SCT approach, using a reduced intensity conditioning (RIC) regimen, has been designed and compared to the standard tandem ASCT for the initial treatment of myeloma patients (Table 3).

In two trials only, both of which not randomized and designed before the novel agents era, patients who underwent a tandem auto/allo-SCT had a clear PFS and OS advantage in comparison with patients receiving a tandem ASCT. These results were not confirmed by other studies, in which neither PFS nor OS were prolonged with auto/allo-SCT as compared to tandem ASCT. [44-51] Of notice, the majority of those trials did not incorporate the use of novel agents in the induction and consolidation/maintenance phase.

To date, allo-SCT is not routinely recommended as part of initial treatment of NDMM patients, due to the increased toxicity and the lack of a clear benefit for most patients. However, for young, selected and motivated patients with high-risk MM, allogeneic transplant may be considered, preferentially in the context of a clinical trials. [8,9]

Salvage stem cell transplant for relapsed and/or refractory myeloma patients

Salvage autologous stem cell transplant

Several retrospective studies have evaluated the role of salvage ASCT (sASCT) in the relapse setting, demonstrating that a second, even a third, ASCT is a feasible and effective treatment option among patients who have previously received ASCT. [52-54]

A retrospective analysis of the EMBT registry, showed that sASCT is safe (1-year non relapse mortality[NRM]: 2%) and effective (3-year OS: 46%). This study also demonstrated that patients with a long relapse-free interval from previous ASCT (>36 months), had longer PFS (p=0.045) and OS (p=0.019) as compared to patients with a shorter relapse-free interval (<36 months). [55]

Similar results were confirmed in a retrospective analysis by Lemieux et al., in which 93% of patients achieved at least an objective response after sASCT, 46% of them reaching a VGPR.

No treatment-related death were observed, and median PFS after sASCT was 18 months. Again, the duration of response (DOR) from previous ASCT (>24 months) was associated with longer PFS and OS.

In a matched-pair analysis comparing sASCT to conventional chemotherapy in patients previously treated with ASCT, sASCT significantly extended median OS (56 vs. 25 months; p=0.04) as compared to conventional chemotherapy. [56]

The only prospective evaluation of sASCT has been conducted in the context of the Myeloma X trial; at relapse, after a bortezomib-based re-induction, patients were randomized to sASCT or cyclophosphamide. sASCT significantly extended median PFS (19 vs. 11 months; p<0.001), but no OS (65 vs. 56 months; p=0.19), as compared to cyclophosphamide. However, the use of salvage cyclophosphamide alone is not considered a standard treatment approach given the wide availability of novel agents at relapse.

A retrospective analysis showed that a sASCT is safe (TRM: 6%) and effective (CR rate: 44%; median PFS 14 months) even in patients who received maintenance therapy after the upfront ASCT. [57]

These studies demonstrate that sASCT is a safe and effective treatment option for RRMM patients. Both the American and European guidelines regard sASCT as a feasible treatment option among relapsed patients with a previous, adequate stem-cell collection. [8,9,58]

However, given the growing number of effective anti-myeloma drugs, it is important to carefully select those patients who might benefit the most from a sASCT (e.g. prolonged remission from first ASCT, adequate performance status).

Salvage allogeneic stem cell transplant

Data on allo-SCT in the relapse setting is scarce, mainly provided by retrospective analysis and single-center institutions. A European analysis of the EBMT registry on the use of allo-SCT among MM patients, showed a steady increase in the use of allo-SCT, particularly later in the course of the disease, with a parallel increase in the use of RIC over myeloablative conditioning. Among 3405 MM patients receiving allo-SCT after ASCT, 5-year PFS and OS were 15% and 32%, respectively, while NRM was 29%, confirming high toxicity and relapse rate, with limited benefit. [59]

In a retrospective study including 169 MM patients relapsed after a first ASCT, 68 patients who had an available donor and underwent RIC allo-SCT, were compared to 94 patients without a donor. [60] At two year, PFS was prolonged in the donor group (42%) as compared to the no-donor group (18%; $p<0.001$) but at a the cost of a significantly higher incidence of NRM (22% vs. 1%; $p<0.001$). This is likely to be reflected in the lack of OS difference between the two groups (54% vs. 53%; $p=0.33$).

Freytes et al. evaluated 289 patients receiving either a second ASCT or an allo-SCT after a first ASCT. At 1 year, the NRM was significantly higher in the allo-SCT group as compared to the second ASCT one (13% vs. 2%; $p<0.001$), whereas 3-year PFS (6% vs. 12%) and OS (20% vs. 46%) was longer among patients receiving a second ASCT.

Kroger et al. showed allo-SCT to be effective as salvage treatment for patients relapsing after ASCT, with a ORR at day +100 after transplant of 95%, including 46% of patients achieving a CR. Of notice, NRM was significantly lower (10% vs. 53%, $P = 0.001$) in patients with a human leucocyte antigen (HLA)-matched compared to -mismatched SCT. At 5 year, PFS was 20%, though 41% of matched patients in CR were alive and free from progression. [61] This study demonstrated that a careful selection of patients and donors can optimize efficacy and safety of allo-SCT, yet does not make a sufficiently convincing case for allo-SCT in the salvage setting.

To date, there is no clear advantage for a salvage allo-SCT over ASCT, particularly considering the constantly improving treatment armamentarium and the availability of targeted drugs and immunological approaches to treat MM. Thus, the role of allo-SCT at relapse remains limited to clinical trials.

Stem cell transplant for patients with high-risk multiple myeloma

MM is characterized by a variety of recurrent cytogenetic and molecular abnormalities. Of them, t(4;14), t(14;16), t(14;20) del17p and gain 1q and 1p deletion, have been associated with a poor prognosis. [62]

In a pooled analysis of 4 European phase III trials, high risk patients, defined as harbouring either t(4;14) or del17p, or failing to achieve a CR after the induction phase, greatly benefit from a tandem ASCT as compared to patients who received a single ASCT only, both in terms of PFS (median, 42 vs. 21 months, HR:0.41; p=0.006) and 5-year OS (70% vs. 17%, HR 0.22; p<0.001). [38]

More recently, in a subset analysis of high-risk MM patients treated in the context of the EMN02/HO95 trial, showed a positive impact on PFS of double as compared to single ASCT (HR: 5.7; p=0.024). This, however, is in contrast with the STAMINA trial, that demonstrated no benefit for tandem ASCT, even among high-risk patients. A possible explanation for this discrepancy is the different induction regimen of the two studies, bortezomib-cyclophosphamide-dexamethasone (VCD) in the EMN02/HO95 study, RVD (predominantly) in the STAMINA trial. The different induction therapy may at least partially account for the PFS benefit seen in the European trial in favour of tandem ASCT. At present, the benefit of tandem ASCT for high-risk patients remains unclear, particularly if RVD induction is used.

To evaluate the role of allo-SCT in high-risk FISH patients, Roos-Weil et al. conducted a retrospective analysis on 143 MM patients who underwent allo-SCT, either as part of the initial strategy or as salvage treatment, comparing their outcomes to those of standard risk patients. [63] The authors found no difference in 3-year PFS (30% vs. 17%; p=0.9), relapse rate (53% vs. 75%; p=0.9) and OS (45% vs. 39%; p=0.8) between high-risk and standard risk FISH patients. TRM was 25% at 2 years, and 47% and 43% of patients developed any grade acute and chronic graft versus host disease (GVHD), respectively. Interestingly, the occurrence of chronic GVHD was associated to prolonged PFS. In the study conducted by the IFM and including high-risk patients, no PFS/OS benefit was observed in patients undergoing tandem ASCT or ASCT/allo-SCT. [46]

Kroger et al. retrospectively analysed the outcomes of 73 high-risk myeloma patients treated with either a tandem ASCT or tandem auto/allo-SCT; while no significant differences were noted in terms of molecular remission rate (50% vs. 40%) and 5-year PFS (24% vs. 30%; p=0.7) between the two groups, patients in the tandem auto/allo-SCT had a significantly higher 1-year NRM (23% vs. 2%) as compared to those in the tandem ASCT group.

Based on these data, the International Myeloma Working Group (IMWG) recommended consideration of a tandem ASCT for NDMM with high-risk cytogenetic features. [62] Allo-SCT, though not routinely recommended, may be considered for young patients with a high-risk MM in the context of a clinical trials.

Conclusion

Even in the era on novel agents, ASCT remains a standard of care for ND, transplant-eligible MM patients. ASCT improves the depth and the quality of responses, and prolongs survival as compared to standard-dose therapy, and is therefore an essential component of a complex treatment strategy that integrates the use of novel agents in the induction,

consolidation/maintenance, with high-dose chemotherapy and ASCT. Taking into consideration the efficacy and safety of ASCT, as well as data from randomized studies showing that a significant proportion of patients might not receive ASCT at relapse, we recommend performing ASCT as part of the initial treatment, as the disease is never as sensitive as it is at the time of presentation. However, a plan for a delayed ASCT at first relapse, with early stem cell harvest, in young patients without high-risk myeloma, may be considered based on patient's preferences. The limited benefit of tandem ASCT over a single ASCT remains unclear. The most robust data suggest that high-risk patients and patients with a sub-optimal response after the first ASCT might benefit from a second transplant, though they are most likely to get greater benefit from newer consolidation and maintenance approaches. [64] At relapse, sASCT represents an effective treatment option; however, given the wide availability of new drugs, physicians should consider the type and the duration of response obtained after prior ASCT, in order to select those patients who will benefit the most from a sASCT. Currently, there is no data to support the use of upfront allo-SCT. At relapse, allo-SCT may be considered as a treatment option for high-risk, young and motivated patients in the context of a clinical trial. However, newer immune, antibody and cellular-based approaches, will likely be used early in the course of the disease to eradicate clones of resistant disease.

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Table 1.

Phase III studies comparing autologous stem cell transplant to non-transplant approaches based on novel agents

Author	Study design	Response	PFS (median, months)	OS (median, months)	Ref.
Palumbo, 2014	MPR x 6 cycles vs. high-dose Melphalan + ASCT (x2)	-	43 vs. 22 P<0.001	4-year: 82% vs 65% P=0.004	[24]
Gay, 2015	CRD x 6 cycles vs. high-dose Melphalan + ASCT (x2)	-	43 vs. 29 P<0.001	4-year: 86% vs 73% P=0.004	[25]
Cavo, 2016	VMP x 4 cycles vs. high-dose Melphalan + ASCT (x1 vs. x2)	≥VGPR: 86% vs. 74% p<0.001	3-year PFS 66% vs. 58% p=0.037	-	[29]
Attal, 2017	RVD x 5 cycles vs. high-dose Melphalan + ASCT (x1) + RVD x 2 cycles	CR: 59% vs. 48% p<0.001	50 vs. 36 P<0.001	4-year: 81% vs 82% p: ns	[28]

CR, complete response; VGPR, very good partial response; MPR, melphalan, prednisone, lenalidomide; CRD, cyclophosphamide, lenalidomide, dexamethasone; RVD, lenalidomide, bortezomib, dexamethasone; VMP, bortezomib, melphalan, prednisone.

Table 2.

Selected studies comparing single versus double autologous stem cell transplant

Author, study group / trial	**Study design**	**PFS** (median, months)	**OS** (median, months)	**Ref.**
Attal, 2003	Mel140 mg/m^2 + TBI 8 Gy + ASCT vs. Mel140 mg/m^2 + ASCT1 → Mel140 mg/m^2 + TBI 8 Gy + ASCT2	25 vs. 36 p=0.03	48 vs. 58 p=0.1	34
Fermand, 2003	Mel140 + ASCT vs. Mel140 mg/m^2 + ASCT1 → Mel140 mg/m^2 + VP16 + TBI 12 Gy + ASCT2	31 vs. 33 -	-	36
Cavo, 2007	Mel200 mg/m^2 + ASCT vs. Mel200 mg/m^2 ASCT1 → Mel140 mg/m^2 + Bu 1 mg/Kg + ASCT2	25 vs. 35 p=0.01	65 vs. 71 p=0.9	35
Mai, 2016	Mel200 mg/m^2 + ASCT x 1 vs. Mel200 mg/m^2 + ASCT x 2	25 vs. 29 p: ns	75 vs. 79 p: ns	65
Cavo, 2016	Mel200 mg/m^2 + ASCT x 1 vs. Mel200 mg/m^2 + ASCT1 x 2	45 vs. NR 3-year: 60% vs. 73% p=0.03	-	39
Staudtmaer, 2016	Mel200 mg/m^2 + ASCT1 → lenalidomide maintenance Vs. Mel200 mg/m^2 + ASCT x 2 → lenalidomide maintenance	38-months: 57% vs. 52% p=ns	38-months: 82% vs. 83% p=ns	40

Mel, melphalan; NA, not available.

Table 3.

Selected studies comparing tandem autologous versus autologous/allogeneic-RIC stem cell transplant in NDMM patients

Author	Population	Conditioning regimens		Follow-up (median, months)	PFS (median, months)	OS (median, months)	TRM	Ref.
		ASCT	Allo-SCT					
Garban, 2006 Moreau, 2008	NDMM patients del13 + or B2M > 3 mg/dl	Mel200, Mel200	Bu-Flu	56	22 vs. 19 p=0.58	48 vs. 34 p=0.07	NA vs. 11%	45,46
Bjorkstrand, 2001 Gharton 2013	NDMM patients	Mel200	Flu-TBI 200 CGy	86	8-year 12% vs. 22% P=0.027	8-year: 39% vs 49% p=0.03	3-year, 3% vs. 13%	44,49
Bruno, 2007 Giaccone, 2011	NDMM patients	Mel200	TBI 200 cGy	96	35 vs. 29 p=0.02	80 vs. 54 p=0.01	2% vs. 10%	47,48
Rosinol, 2008	NDMM not in nCR/CR after 1st ASCT	Mel200 or CVB	Flu-Mel	62	31 vs. NR p: 0.08	58 vs. NR p=0.9	5% vs. 16%	50
Krishnan, 2011	NDMM after a prior ASCT	Mel200	TBI 200 cGy	40	3-year: 46% vs. 43% p=0.7	3-year: 80% vs. 71% p=0.2	NA	51

NDMM, newly diagnosed multiple myeloma; del13, deletion 13q; B2M, beta-2 microglobuline; Mel200, melphalan 200 mg/m^2,Flu, fludarabine; NA, not available; nCR, near complete response; CVB, cyclophosphamide, etoposide, BCNU.