

Hematopoietic stem cell transplantation for multiple myeloma beyond 2010

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Autologous stem cell transplantation (ASCT) is considered the gold standard in the frontline therapy of younger patients with multiple myeloma because it results in higher complete remission (CR) rates and longer event-free survival than conventional chemotherapy. The greatest benefit from ASCT is obtained in patients achieving CR after transplantation, the likelihood of CR being associated with the M-protein size at the time of transplantation. The incorporation of novel agents results in higher pre- and posttransplantation CR rates. Induction with bortezomib-

containing regimens is encouraging in patients with poor-risk cytogenetics. However, longer follow-up is required to assess the impact of this increased CR on long-term survival. The results of post-transplantation consolidation/maintenance with new drugs are encouraging. All this indicates that, in the era of novel agents, high-dose therapy should be optimized rather than replaced. Because of its high transplantation-related mortality, myeloablative allografting has been generally replaced by reduced-intensity conditioning (reduced intensity conditioning

allogeneic transplantation). The best results are achieved after a debulky ASCT, with a progression-free survival plateau of 25% to 30% beyond 6 years from reduced intensity conditioning allogeneic transplantation. The development of novel reduced-intensity preparative regimens and peri- and posttransplantation strategies aimed at minimizing graft-versus-host disease, and enhancing the graft-versus-myeloma effect are key issues. (Blood. 2010;115(18):3655-3663)

Introduction

The outcome of patients with multiple myeloma (MM) treated with conventional chemotherapy is unsatisfactory.¹⁻³ A significant survival improvement has been observed for patients diagnosed in the more recent years.⁴⁻⁶ Because the strongest survival increase was noted in patients younger than 60 years, the improvement was attributed, at least in part, to the benefit of high-dose therapy/stem cell transplantation (HDT/SCT). In addition, the long-term results of autologous and allogeneic transplantation show that a number of patients enjoy prolonged progression-free survival (PFS), and a small proportion of them can be cured.⁷⁻¹¹ Indeed, MM is the most frequent indication for HDT/SCT in Europe and the United States.^{7,12} In recent years, the availability of new effective drugs, such as thalidomide, lenalidomide, and bortezomib, as well as the increased experience with the so-called dose-reduced intensity conditioning allogeneic transplantation (Allo-RIC), has resulted in a new scenario in which the role of HDT/SCT needs to be revisited. This review is focused on: (1) the impact of single and tandem autologous transplantation (ASCT) in the outcome of MM patients, (2) the results achieved with allogeneic transplantation (ie, myeloablative and Allo-RIC), and (3) the prospects for improvement with the incorporation of the new drugs in transplantation programs.

clear that refractory and relapsed myeloma patients are not the ideal candidates for autotransplantation, the aforementioned seminal studies showed: (1) the feasibility of the procedure, (2) the high antimyeloma activity, although generally transient, of HDT, and (3) that, even in a poor-risk population, up to one-fourth of the patients achieving complete remission (CR) remained in CR 10 years beyond ASCT.¹⁵

ASCT should be considered whenever possible in MM patients with sensitive relapse. Indeed, in a randomized trial designed to assess the optimal timing of ASCT, survival of patients who underwent a rescue transplantation was identical to that of those receiving ASCT up-front.¹⁶ However because of a longer time without symptoms, toxicity, and treatment, the authors recommended performing transplantation up-front.¹⁶

Patients with primarily refractory disease seem to benefit from early ASCT (Table 1).¹⁷⁻²¹ However, for a meaningful interpretation of the data, the 2 categories of patients considered as primary refractory (ie, primary unresponsive with progressive disease vs minimal response or with no change but without clinical progression, nonresponsive/nonprogressive) should had been analyzed separately. Thus, in the Spanish Programa de Estudio y Tratamiento de las Hemopatías Malignas (PETHEMA) experience, the median survival of 31 patients with primary unresponsive progressive disease who underwent an ASCT was only 21 months.²²

Autologous transplantation

Refractory and relapsed disease

The first studies on HDT/SCT in MM were performed in patients with advanced refractory disease. Although the response rate was encouraging, the median event-free survival (EFS) and overall survival (OS) were short.^{13,14} Although it is

Up-front therapy

Single ASCT versus conventional chemotherapy. Autologous transplantation is considered the gold standard as part of the initial therapy for patients with MM younger than 65 years. However, the results of trials comparing a single autologous transplantation

Table 1. ASCT in primary refractory multiple myeloma

Reference	No. of patients	Age, y	β_2 M, mg/L	CR, %	Median EFS, y	Median OS, y
Alexanian et al, ¹⁷ (1994)	27	45	2.8	8	3.5	6
Vesole et al ¹⁸ (1994)	72	50	—	15	1.7	4
Singhal et al ¹⁹ (2002)	43	54	3.3	40	2	—
Kumar et al ²⁰ (2004)	50	56	2.7	20	2.5	5
Alexanian et al ²¹ (2004)	89	52	3.7	16	7*	7*

ASCT indicates autologous stem cell transplantation; β_2 M, β_2 -microglobulin; CR, complete remission; EFS, event-free survival; OS, overall survival; and —, not applicable.

*In patients achieving CR after ASCT.

versus conventional chemotherapy have not been uniform across the studies. Five trials comparing ASCT versus conventional chemotherapy have been published (Table 2).²³⁻²⁷ Two of them showed that ASCT significantly increased the CR rate, EFS, and OS.^{23,24} In contrast, the remaining 3 studies showed no benefit of ASCT in EFS and OS.²⁵⁻²⁷ Several reasons may have accounted for the discrepancies among these trials. First, in the Spanish PETHEMA trial,²⁵ only patients with chemosensitive disease were randomized and the French MAG study²⁶ included only patients 55 to 65 years of age. Whether randomization at diagnosis in the PETHEMA study or the inclusion of patients younger than 55 years in the MAG trial could have ended up with different results is uncertain. Second, dose intensity in the conventional arms of the PETHEMA (vincristine, bischloroethylnitrosourea [BCNU], melphalan, cytoxan, prednisone [VBMCP]/vincristine, BCNU, adriamycin, dexamethasone [VBAD])²⁵ and in the US Intergroup (VBMCP)²⁷ studies was higher than in the Intergroup Franophone du Myelome (IFM) and Medical Research Council trials.^{23,24} A systematic review and meta-analysis of randomized trials, including a total of 2411 patients, of ASCT versus conventional chemotherapy showed a significantly longer PFS in favor of ASCT, with no significant impact on OS.¹²

Single versus double (tandem) ASCT. The results of 2 trials comparing the efficacy of single versus double ASCT have been published.^{28,29} The IFM group reported that the median survival was prolonged by 10 months with tandem transplantation and that the OS at 7 years of follow-up for tandem and single ASCT was 42% and 21%, respectively.²⁸ A non-preplanned subset analysis showed that the patients who benefited from a second ASCT were only those failing to achieve at least a very good partial response (VGPR) with the first transplantation. In this subgroup, survival at 7 years was 43% and 11% with tandem and single transplantation, respectively. The Italian Bologna 96 study showed a significant prolongation in EFS with no impact on OS with tandem versus single ASCT.²⁹ A non-preplanned subset analysis of patients not achieving CR or near-CR also showed a significantly longer EFS with double ASCT that did not translate into a significant OS prolongation.²⁹ In addition, neither of these 2 studies was adequately powered to evaluate

the equivalence of 1 versus 2 transplantations in patients achieving at least a VGPR after the first transplantation. Finally, whether or not patients who do not achieve at least a VGPR with a first ASCT benefit from a second high-dose procedure should be answered in a clinical trial.

Impact of CR after ASCT

Whether ASCT is beneficial for the majority of MM patients or the benefit comes from certain subsets of patients remains an unsolved issue. It seems that CR achievement is the crucial step for a long-lasting response and prolonged survival. Thus, it has been shown that patients who achieve immunofixation (IFE)-negative CR after ASCT had an EFS and OS significantly longer than those who remained in PR.^{30,31} In a Spanish PETHEMA trial, Lahuerta et al have shown that the improvement in the depth of response, particularly the achievement of posttransplantation CR, was associated with a significantly longer EFS and OS.³² In a literature review and meta-analysis, the achievement of CR highly correlated with PFS and long-term survival.³³ The Spanish group has also shown that the achievement of a negative minimal residual disease by multiparameter flow cytometry (MFC) is a strongest predictor of EFS and OS compared with IFE-negative CR.³⁴ Furthermore, the Italian group has reported that 18% of patients in at least VGPR after ASCT achieved molecular remission by qualitative and quantitative polymerase chain reaction with intensification therapy using bortezomib/thalidomide/dexamethasone (VTD).³⁵ After a median follow-up of 27 months, no patient in molecular remission had relapsed.³⁵ These 2 studies indicate the importance of achieving the lowest possible tumor mass and support the need for more refined/sensitive CR criteria for MM, including not only negative IFE but also MFC and molecular complete remissions. It is probable that most of the long survivors in continued CR in both the Arkansas study with tandem ASCT (Total Therapy I)¹⁰ and in our single ASCT series¹¹ enjoy the aforementioned really “stringent” CR and are not only “operational” but also true cures.

The sensitivity to the initial therapy measured by the M-protein size at the time of transplantation is the most important predictor of CR after ASCT.^{30,36,37} Thus, in patients with an M-protein less than 10 g/L, the likelihood of CR is between 52% and 67%; whereas in those with a serum M-protein higher than 10 g/L or 20 g/L, the probability of CR is 15% and 7%, respectively.^{31,36} The Mayo Clinic group reported that the M-spike at the time of transplantation was the only predictor for CR and developed a single function to predict the probability of achieving CR with ASCT.³⁷ In a meta-analysis, a strong association between maximal response to induction therapy and long-term survival was found.³³

Table 2. Randomized trials: single ASCT versus conventional chemotherapy

Reference	CR, %	Median PFS, mo	Median OS, mo
Attal et al ²³ (1996)	22 vs 5	28 vs 18	57 vs 42
Child et al ²⁴ (2003)	44 vs 9	32 vs 20	55 vs 42
Bladé et al ²⁵ (2005)	30 vs 11	42 vs 34	67 vs 65
Fermand et al ²⁶ (2005)	8.5 vs 7	25 vs 19	47.8 vs 47.6
Barlogie et al ²⁷ (2006)	17 vs 15	25 vs 21	58 vs 53

ASCT indicates autologous stem cell transplantation; CR, complete remission; EFS, event-free survival; and OS, overall survival.

Incorporation of novel drugs in the myeloma ASCT programs

Rationale

Conventional induction regimens followed by a single or double ASCT have resulted in 30% to 40% IFE-negative CR and a median survival of 6 years in the best circumstances but, unfortunately, with no survival plateau. The introduction of novel drugs (thalidomide, lenalidomide, and bortezomib) has provided the frame for improving the results of the pretransplantation induction therapy.^{38,39} The higher antimyeloma potency of the new induction regimens should theoretically end up with a higher pretransplantation tumor reduction, resulting in a higher posttransplantation CR rate and, ultimately, an improvement in the long-term survival and potential cures.

Novel induction regimens

During the last years, the combination of thalidomide/dexamethasone (TD) has increasingly replaced VAD⁴⁰ and has been approved by the US Food and Drug Administration for its use as pretransplantation induction regimen. Although the overall response rate to TD is between 58% and 76%, the CR rate is low.^{41,42} In addition, TD could not be an optimal regimen for patients with extramedullary disease because of the lack of activity of thalidomide on soft-tissue plasmacytomas.⁴³ Furthermore, of 3 reported studies comparing pretransplantation induction with TD versus VAD,⁴⁴⁻⁴⁶ TD resulted in an improved posttransplantation outcome in only one.⁴⁶ The incorporation of thalidomide in the Total Therapy II protocol resulted in significantly higher CR rate and EFS with no advantage in OS because of a shorter survival after relapse.⁴⁷ Of interest, a more recent update shows that the thalidomide arm of the Total Therapy II produced an improvement in both the OS and the response duration in patients with metaphase cytogenetic abnormalities.⁴⁸

Two phase 2 trials on the combination of bortezomib/dexamethasone (VD) as induction regimen have shown a pre- and posttransplantation CR rates of 12% and 33%, respectively.^{49,50} In a trial by the French IFM group, including 482 patients, posttransplantation IFE-negative CR rate and PFS were significantly higher with VD than with VAD.⁵¹

Thalidomide and bortezomib are being used in combination with dexamethasone or anthracyclines, resulting in the so-called triple regimens. The PAD regimen (bortezomib PS 341, adriamycin, dexamethasone) resulted in a pretransplantation overall response of 95% with 24% CR.⁵² The posttransplantation CR rate after induction with PAD was 43%. The accrual of a large trial from the Dutch-Belgian Hemato-Oncology Cooperative Group comparing PAD versus VAD has recently been completed, but the results are not yet mature.

The M. D. Anderson group first reported the results achieved with VTD in 36 patients.⁵³ The overall response rate after 2 induction cycles was 92% with 19% CR. The posttransplantation response rate was 89% with 31% CR. Cavo et al⁵⁴ have recently reported that VTD was significantly superior to TD in terms of CR rate both before (21% vs 6%) and after (43% vs 23%) ASCT. The PFS was also significantly longer with VTD. The Spanish PETHEMA group is currently comparing TD versus VTD versus combination chemotherapy with VBMCP/vincristine, BCNU, adriamycin, dexamethasone (4 cycles) plus 2 cycles of bortezomib as pretransplantation induction therapy.⁵⁵ The preliminary results of

Table 3. Pre- and post-ASCT CR rate with novel induction regimens

Regimen	Pre-ASCT, %	Post-ASCT, %
Thalidomide/dexamethasone	6	23-34
Bortezomib/dexamethasone	12	33
PAD-1	24	43
VTD	21-30	43-49
Total Therapy III	—	56 (2 y)

ASCT indicates autologous stem cell transplantation; CR, complete remission; PAD, bortezomib PS 341, adriamycin, dexamethasone; VTD, bortezomib/thalidomide/dexamethasone; and —, not applicable.

this study show that the best regimen is VTD, with a pre- and posttransplantation CR rate of 30% and 49%, respectively. Encouraging results have been reported with RVD (lenalidomide, bortezomib, dexamethasone) in a phase I/2 trial, including 36% CR/near-CR response rate, even in high-risk groups,⁵⁶ and a large international transplantation trial using VRD as induction regimen has recently been activated. Finally, the Total Therapy III protocol used at the University of Arkansas with VTD-PACE induction plus tandem ASCT, consolidation with VTD or VRD and maintenance with TD resulted in a CR rate of 56% at 2 years.⁵⁷ The pre- and posttransplantation CR rates achieved with novel induction regimens are summarized in Table 3.

Unsolved questions in autologous transplantation

Will induction with new regimens improve the posttransplantation outcome?

Post-induction IFE-negative CR is higher when new agents are incorporated than with VAD-like regimens, cyclophosphamide/dexamethasone or combination chemotherapy (up to 30% vs ~ 10%).^{32,40,42,58} With this higher pretransplantation tumor reduction, a higher posttransplantation CR rate should be expected. Actually, ASCT increases the CR rate in approximately 20% of the patients, irrespective of the regimen used for induction (Table 3).⁴⁹⁻⁵⁵ The real impact of these increased CR rates on the long-term post-ASCT survival requires longer follow-up. Hopefully, the remarkable results of Total Therapy I,¹⁰ with 10-year OS of 33% and 7% of patients alive in continued CR after a median follow-up of 12 years (“operational” cures), will be improved. Of interest, induction with bortezomib-containing regimens results in a high CR rate and in an encouraging, at least in the short-term, outcome in patients with high-risk myeloma by overcoming the negative impact of poor cytogenetics.^{54,55,57} From the currently available data, it seems that a triple regimen, such as VTD or PAD, will result in superior results than a double combination, such as VD or TD. However, we have to wait until the results of the aforementioned large phase 3 studies are mature enough to be certain of whether or not a multidrug induction will produce significantly longer EFS, OS, and superior long-term outcome with a higher rate of “operational” or true cure rate than a gentler new drug approach. Finally, it must be considered that the experience with new agents is still limited, as shown in a recent report demonstrating that bortezomib, in contrast to the general belief, induces canonical nuclear factor- κ B activation.⁵⁹ This can modify the way we will use proteasome inhibitors in the future.

How can the efficacy of the high-dose regimens be improved?

The gold standard for HDT in MM remains melphalan 200 mg/m². Attempts with other drug combinations, such as cyclophosphamide, vepeside, and BCNU-carmustine⁶⁰; the trialkylator regimen thiotepa, busulfan, and cyclophosphamide⁶¹; an increased melphalan dose to 220 mg/m²; or the association of melphalan 140 mg/m² with total body irradiation (TBI)^{23,25,63} or busulfan⁶⁴ have not resulted in an improved outcome. It has recently been shown that the administration of ascorbic acid and arsenic trioxide preceding MEL-200 is safe and could enhance the antimyeloma activity of melphalan.⁶⁵ Interestingly, bortezomib synergizes with chemotherapy resulting from its effects on DNA repair enzymes. Thus, the combination of melphalan/prednisone with bortezomib in elderly patients has resulted in an impressive 30% IFE-negative CR in the nontransplantation setting.⁶⁶ In a phase I trial investigating the bortezomib dose (1-1.6 mg/m²) and sequence (24 hours before or 24 hours after melphalan administration), the combination of MEL-200 along with the aforementioned bortezomib dose and schedule resulted in a PR rate or better of 93% (14 of 15 patients), with a toxicity profile and engraftment kinetics similar to that observed in an historical control receiving MEL-200 alone.⁶⁷ The IFM group used bortezomib on days -6, -3, 1, and 4 along with MEL-200 on day -2 in 35 patients with high-risk MM, and the results on engraftment and response were encouraging.⁶⁸ Thus, the door for enhancing the efficacy of MEL-200 with imaginative combinations with new agents is open.

Is there a role for posttransplantation consolidation/maintenance therapy?

Despite many attempts, the role of maintenance in MM remains controversial and none of the investigated treatments has been established. Thalidomide maintenance prolonged OS in 2 transplantation series.^{69,70} In the study by the IFM, the thalidomide arm was superior in response rate, EFS, and OS.⁶⁹ Interestingly, the survival benefit was only observed among patients who failed to achieve at least VGPR after ASCT, suggesting that the benefit was the result of a “consolidation” effect leading to a further reduction in tumor mass. The addition of thalidomide in the Total Therapy II program significantly prolonged the EFS⁴⁷ as well as the CR duration and OS in the subset of patients with metaphase cytogenetic abnormalities⁴⁸ and compared favorably with Total Therapy I, with single-agent interferon maintenance, in terms of CR duration, EFS, and OS.⁷¹ In the Total Therapy III program, including consolidation with VTD or VRD and maintenance with TD, an unprecedented CR rate of 56% at 2 years of initiation of therapy was achieved.⁵⁷ In a preliminary report, Palumbo et al⁷² reported a CR rate of 72% with lenalidomide/prednisone consolidation plus lenalidomide maintenance after induction with PAD and tandem ASCT with MEL-100 in patients 65 to 75 years of age. Interestingly, it has been shown, for the first time outside the allogeneic setting, that consolidation with VTD after ASCT can induce durable molecular remissions.³⁵ The encouraging results of the latter studies have led to the design of a number of phase 3 transplantation trials, including consolidation/maintenance based on the novel drugs thalidomide, lenalidomide, and/or bortezomib. Hopefully, these trials will help us to establish the role of consolidation/maintenance in patients with MM.

Do patients who achieve CR with primary therapy benefit from ASCT intensification?

It could be speculated that patients achieving CR with either conventional chemotherapy or a single transplantation are the

most likely to obtain long-term benefit, and perhaps cure, with further intensification with ASCT or with a repeated ASCT, respectively. However, the M. D. Anderson group has consistently reported that patients who achieve CR with conventional chemotherapy and who do not receive a transplantation have the same prolonged PFS and OS as those attaining CR after ASCT.^{31,73} In the same direction, patients who achieve CR or VGPR with a single transplantation do not benefit from a second ASCT.²⁹ On the other hand, a Mayo Clinic study showed that patients who were in CR at the time of ASCT had a similar survival as those achieving CR after ASCT only.⁷⁴ Thus, whether patients in CR with primary therapy would benefit from ASCT intensification is unknown. With the availability of novel agents yielding high CR rates as primary treatment, the question has become clinically relevant, and only a randomized trial would conclusively answer it. Such a study should ideally include sequential minimal residual disease studies with MFC and molecular analysis to establish from what CR level further treatment is beneficial or not. In this sense, the Arkansas group has recently reported on the importance of not only achieving CR but also sustaining CR by applying a time-dependent statistical methodology to the patients included in Total Therapy I, II, and III.⁷⁵ These results support the investigation of CR consolidation, especially in high-risk patients, to determine what treatment and for how long beyond CR it is still necessary.

Is there still a role for ASCT in the era of novel agents?

ASCT is an important tool to further decrease the tumor mass after induction therapy. Theoretically, the higher degree of response achieved with the new induction regimens should be the first step toward a higher CR rate after transplantation, the “sine qua non” condition for an improved survival. On the other hand, melphalan has an unquestionable efficacy in MM, and its high-dose administration in the transplantation procedure is an excellent way to optimize its antimyeloma activity. Furthermore, the mechanisms of action of the novel agents are different from that of high-dose melphalan; thus, the 2 treatment steps should be considered complementary. This is in line with the recent concept of the so-called “cancer stem cells.” This is a small population of cells able to self-renew and responsible for the tumor to sustain.⁷⁶ These cancer stem cells are biologically distinct from the bulk of differentiated cancer cells that characterize the disease. Novel antimyeloma agents, such as bortezomib, efficiently inhibit myeloma cells but appear to have little activity against myeloma stem cells “in vitro.” These novel drugs could indeed produce dramatic responses on the bulk of differentiated plasma cells but can have limited activity against myeloma stem cells responsible for disease persistence and regrowth.⁷⁶ In this scenario, intensification with high-dose melphalan appears most appropriate and, rather than replaced, ASCT must be further explored in the era of novel agents. To answer this question, a large international trial of induction with VRD followed by randomization to ASCT versus VRD consolidation with ASCT at relapse has just been activated.

Allogeneic transplantation

Myeloablative conditioning

The allogeneic transplantation has the advantage over the autologous transplantation that the graft does not contain tumor cells and the

Table 4. Myeloablative versus RIC allogeneic transplantation

Procedure	No. of patients	TRM, %	CR rate, %	PFS, % at 3 y	OS, % at 3 y
Myeloablative	196	37	53.4	18.9	50.8
RIC	320	24	33.6	34.5	38.1
<i>P</i>		.002	< .001	< .001	NS

Data are from the European Group for Blood and Marrow Transplantation experience, 1998 to 2002.⁷

RIC indicates reduced intensity conditioning; TRM, transplantation-related mortality; CR, complete remission; OS, overall survival; PFS, progression-free survival; and NS, not significant.

potential for a graft versus myeloma (GVM) effect.^{77,78} However, the allogeneic transplantation in MM has 2 major shortcomings: a transplantation-related mortality ranging from 30% to 50% and a high posttransplantation relapse rate.^{7,8,79,80} Nevertheless, 10% to 20% of patients undergoing an allogeneic transplantation are long-term disease-free, many of them in molecular remission.^{7,8,79,80} The European Group for Blood and Marrow Transplantation (EBMT) reported a significant decrease in transplantation-related mortality (TRM) over time (ie, 30% between 1994 and 1998 vs 46% in the previous period).⁸ In a more recent analysis, the TRM with myeloablative allogeneic transplantation during the period 1998 to 2002 was still 37% (Table 4).⁷ The main attempts to reduce the TRM have been: (1) the use of peripheral blood progenitor cells and (2) T-cell depletion. In the EBMT series, including 770 patients who underwent a myeloablative allograft, the TRM was not different between peripheral blood stem cell (n = 401) and bone marrow (n = 369) recipients.⁸¹ Concerning T-cell depletion, the results have been disappointing. In the Dutch-Belgian Hemato-Oncology Cooperative Group, a series of 53 patients in which T cell–depleted allogeneic transplantation was part of the front-line therapy, median survival from transplantation was only 25 months.⁸² In a series of 66 patients from the Dana-Farber Cancer Institute, who received a T cell–depleted allogeneic graft, the nonrelapse TRM was 35%, with a PFS at 4 years of 23%.⁷⁸

The GVM effect of donor lymphocyte infusion (DLI) has led to the use of DLI in the treatment of both persistent disease or relapse after allogeneic transplantation. The GVM effect of DLI is associated with the development of graft-versus-host disease (GVHD)⁸³ as well as with an antibody response to highly expressed myeloma-associated antigens.⁸⁴ The response rate to DLI ranges from 45% to 61%, with the CR rate of 20% to 30%.^{83,85} Unfortunately, the proportion of patients in whom the response lasts for more than 1 year is only approximately 20%.^{83,85}

Myeloablative allogeneic versus autologous transplantation

In a retrospective case-control study by the EBMT, comparing the results of allogeneic and autologous transplantation, the survival was significantly longer in patients who underwent the autologous procedure.⁸⁶ However, the relapse rate was higher with ASCT and the prospects for a long-term outcome were better with the allogeneic transplantation. Of interest, Corradini et al⁹ reported that molecular remission was achieved in only 7% of patients undergoing autologous transplantation versus 50% in the allogeneic setting. The same authors highlighted the impact of molecular remission after allogeneic transplantation on the risk of relapse.⁹ Thus, none of 16 patients with a negative molecular status after allogeneic

transplantation had relapsed at 5 years after transplantation, whereas all 13 patients who remained molecular positive relapsed within the 5 years after allogeneic transplantation.

Reduced-intensity conditioning allogeneic transplantation

The Allo-RIC was introduced in an attempt to decrease the transplantation-related toxicity while retaining the beneficial GVM effect.⁸⁷⁻⁹³ The conditioning regimens consisted of: (1) fludarabine/melphalan with or without in vivo T-cell depletion with antithymocyte globulin (ATG) or alemtuzumab or (2) low-dose TBI with or without fludarabine. The results of early studies on Allo-RIC can be summarized as follows: (1) a TRM of approximately 20%, (2) an incidence of acute and chronic GVHD approximately 30% and 50%, respectively, (3) a CR rate up to 50%, (4) a negative effect of T-cell depletion with ATG or alemtuzumab, and (5) a low tumor burden at the time of transplantation as the main factor associated with long-term survival.

Tandem autologous/Allo-RIC transplantation

Considering the importance of a low tumor mass at the time of transplantation for the success of Allo-RIC, the use of ASCT to reduce the tumor burden followed by Allo-RIC has been investigated. Kröger et al⁹⁴ used a conditioning regimen consisting of fludarabine/melphalan/ATG. In this study, the incidence of acute and chronic GVHD was 38% and 40%, respectively, with a TRM of 11% at 100 days. The CR rate was of 73%. In a subsequent study from the same group, including 22 patients who received an unrelated allograft, the incidence of GVHD was almost identical and the CR rate after the allogeneic procedure was 40%.⁹⁵ Thus, Allo-RIC from unrelated donors is feasible and its results seem comparable with those achieved with HLA-identical siblings. The long-term results of 2 studies of ASCT with MEL-200 followed by Allo-RIC from identical siblings conditioned with the “Seattle approach” of 2 Gy TBI are summarized in Table 5.^{96,97} Of interest, the development of chronic GVHD was not associated with the achievement of CR or with disease relapse. An encouraging PFS plateau between 25% and 30% beyond 6 years from Allo-RIC was observed in both studies.^{96,97}

Double autologous versus tandem auto/Allo-RIC transplantation

Three studies have been published comparing the efficacy of a tandem double ASCT versus single autograft followed by Allo-RIC in patients with newly diagnosed MM with an available sibling

Table 5. Tandem ASCT followed by Allo-RIC

Reference	No. of patients	Median follow-up, y	aGVHD (II-IV)/cGVHD, %	CR rate, %	EFS, mo	OS at 5 y
Rotta et al ⁹⁶ (2009)	102	6.6	42/74	57	36	NR
Bruno et al ⁹⁷ (2009)	100	5	38/74	53	37	NR

ASCT indicates autologous stem cell transplantation; allo-RIC, reduced-intensity conditioning allogeneic transplantation; aGVHD, acute graft-versus-host disease; cGVHD, chronic graft-versus-host disease; CR, complete remission; EFS, event-free survival; OS, overall survival; and NR, not reached.

Table 6. Double ASCT versus ASCT/Allo-RIC

Reference	No. of patients	CR rate, %	EFS, mo	OS, mo
Garban et al ⁹⁸ (2006)	166 vs 51	32.5 vs 32.6	31.7 vs 35	42.7 vs 35
<i>P</i>		NS	NS	.07
Bruno et al ⁹⁹ (2007)	82 vs 80	26 vs 55	29 vs 35	54 vs 80
<i>P</i>		.004	.02	.01
Rosiñol et al ¹⁰⁰ (2008)	85 vs 25	11 vs 40%*	26 vs 19.6	58 vs NR
<i>P</i>		.01	NS	NS

ASCT indicates autologous stem cell transplantation; allo-RIC, reduced-intensity conditioning allogeneic transplantation; CR, complete remission; EFS, event-free survival; OS, overall survival; NS, not significant; and NR, not reached.

*Response improvement with second transplantation.

donor.⁹⁸⁻¹⁰⁰ The TRM ranged from 10% to 16% in the 3 studies. The French IFM study⁹⁸ reported no benefit in terms of CR, EFS, and OS from Allo-RIC versus a second autologous transplantation. In contrast, the Italian group⁹⁹ found an increased CR rate and a significant survival advantage in favor of Allo-RIC, along with a survival plateau beyond 4 years from allografting. In the Spanish PETHEMA study,¹⁰⁰ there were no significant differences in EFS and OS between the 2 groups. However, the curves of Allo-RIC patients showed an encouraging plateau beyond 3 years of follow-up (Table 6). The different results achieved in these 3 studies can be explained through the differences in the inclusion criteria and conditioning regimens (Table 7).

Myeloablative versus Allo-RIC transplantation

The high TRM associated with conventional conditioning allogeneic transplantation has resulted in an almost universal switch from conventional to Allo-RIC. The EBMT group has reported a retrospective study comparing the results achieved in 196 patients who received a myeloablative conditioning versus those of 320 patients who underwent an Allo-RIC allografted between 1998 and 2002 (Table 4).⁷ Although the CR rate and PFS were favorable to the conventional conditioning, the OS was not significantly different: the higher TRM with conventional conditioning was compensated by a lower relapse rate. The main shortcoming of this study is that the 2 populations were not entirely comparable because the patients in the Allo-RIC group were older (median, 51 vs 45 years), had more resistant disease, and had been more heavily pretreated. In addition, there was an increased use of T-cell depletion in the Allo-RIC group, which was associated with a lower CR rate and an increased relapse rate.

Unsolved questions in allogeneic transplantation

Which is the best allogeneic transplantation approach?

The TRM of approximately 20% higher with myeloablative conditioning has resulted in a shift to Allo-RIC. However, the final

Table 7. Double ASCT versus ASCT/Allo-RIC: differences in study design

Reference	Inclusion criteria	Conditioning
Garban et al ⁹⁸ (2006)	High-risk (high β_2M , 13q-)	Fludarabine/busulfan/ATG
Bruno et al ⁹⁹ (2007)	All patients	TBI (2 Gy)
Rosiñol et al ¹⁰⁰ (2008)	No CR/nCR with first ASCT	Fludarabine/ MEL-140

ASCT indicates autologous stem cell transplantation; allo-RIC, reduced-intensity conditioning allogeneic transplantation; TBI, total body irradiation; ATG, antithymocyte globulin; CR, complete remission; and nCR, near complete remission.

outcome with the 2 conditioning approaches seems to be similar because the higher TRM with myeloablative conditioning is compensated by a lower relapse rate. Therefore, the only way to answer the question would be a randomized trial. With the current data, Allo-RIC from either related or unrelated donors seems the most promising allogeneic approach, but there may still be a role for myeloablative allografting in selected patients (ie, younger patients with poor cytogenetics).¹⁰¹

Who are the patients most likely to benefit from Allo-RIC?

Patients with sensitive disease after a debulky autologous transplantation are the most likely to benefit from Allo-RIC. In our opinion, the patients already in CR after either primary therapy or ASCT should not be submitted to the risk of any allogeneic procedure. Patients with sensitive relapse could also benefit from Allo-RIC. However, it is doubtful that patients with advanced disease benefit from Allo-RIC. In any event, taking into account the TRM of 10% to 20%, the chronic GVHD of 50% to 70%, and the controversial results on a meaningful survival plateau, Allo-RIC should only be conducted in controlled clinical trials, including patients with high-risk myeloma for whom other therapies are insufficient.¹⁰²

Double ASCT or tandem ASCT/Allo-RIC?

The results of the 3 prospective trials on double autologous versus auto/Allo-RIC are controversial.¹⁰² Our results in patients not achieving CR or near-CR with an autologous transplantation are similar to those reported in the Italian study in favor of Allo-RIC. The differences among these studies can be explained through the different study design (Tables 6-7).⁹⁸⁻¹⁰⁰ Hopefully, the results of the large prospective studies of the EBMT and the US Bone Marrow Transplant Clinical Trials will help to clarify the role of auto/Allo-RIC.

How can the results of Allo-RIC be improved?

The following points are essential for improving the outcome of patients undergoing Allo-RIC: (1) use a prior debulky autologous transplantation, (2) limit the procedure to patients with sensitive disease, (3) use the best conditioning with fludarabine/melphalan or low-dose TBI with or without fludarabine and with no T-cell depletion, and (4) optimize DLI (ie, with low-dose thalidomide) for suboptimal responses.¹⁰³ The incorporation of bortezomib in the allogeneic procedure could decrease acute GVHD while retaining the GVM effect,^{104,105} and trials including bortezomib in the conditioning and after engraftment are ongoing. It has been shown that lenalidomide is highly effective in patients relapsing after allogeneic transplantation.¹⁰⁶ Interestingly, lenalidomide increased the CD4⁺FoxP3⁺ cells, a specific marker of regulatory T cells.¹⁰⁶ The immunostimulatory effect

of lenalidomide deserves further investigation in the allogeneic transplantation setting. It is obvious, to actually improve the long-term outcome of patients undergoing Allo-RIC, that there is a need for developing novel reduced-intensity preparative regimens¹⁰⁷ as well as peri- and posttransplantation strategies (ie, expansion of T regulatory cells) aimed at minimizing the GVHD and enhancing the GVM effect.¹⁰⁸

Acknowledgments

This work was supported in part by Instituto Carlos III (Spanish Institute of Health; grants 06/0020/0005 and 08/0147).

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