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

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Abstract

Despite significant improvements in survival for multiple myeloma patients through autologous stem-cell transplantation (SCT) and the introduction of novel drugs, the disease remains incurable for all but a small fraction of patients. Only allogeneic SCT is potentially curative, due in part to a graft-versus-myeloma effect. High transplant-related mortality with allogeneic SCT is currently the major limitation to wider use of this potentially curative modality. Mortality can be reduced through the use of lower-intensity conditioning regimens which allow engraftment of allogeneic stem cells, but this comes at a cost of higher rates of disease progression and relapse. Promising studies to improve outcomes of allogeneic transplants include the use of more intensive non-myeloablative conditioning regimens, tandem transplants, peripheral blood cells, graft engineering to improve the graft-versus-myeloma activity while reducing graft-versus-host disease (GVHD), post-transplant maintenance, and targeted conditioning therapies such as bone-seeking radioisotopes.

Keywords

multiple myeloma; allogeneic stem-cell transplantation

The treatment of multiple myeloma has dramatically improved in the last 10 years. High-dose therapy followed by autologous stem-cell support has emerged as a promising means for increasing remission rates and improving survival. As such, autologous stem-cell transplantation has become the standard of care for many patients with multiple myeloma. In addition, insights into the biology and genetics of myeloma cells have resulted in the rapid introduction of new drugs with unique mechanisms of action. These drugs – which include thalidomide, lenalidomide and bortezomib – have shown significant activity in multiple myeloma, and when these new agents are combined with more traditional drugs, the response and complete remission rates are as high as responses achieved with autologous stem-cell transplantation.[1,2] Despite these advances, long-term survival after treatment with stem-cell transplantation or the newly developed drugs is rare, and disease recurs in virtually all patients.

Stem-cell transplantation from allogeneic donors may be curative for 10–20% of patients with chemotherapy-resistant, refractory hematologic malignancies, and for up to 80% of

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patients who are transplanted in remission. Much of the high response and curative potential of allografts is attributed to a 'graft-versus-tumor' effect. In patients with multiple myeloma this effect has been well documented.[3–5] In contrast, stem-cell transplantation from autologous or syngeneic donors provides little or no immunologic effect against the myeloma cell. Thus autologous or syngeneic stem-cell transplants are mainly a form of supportive care and require intensive chemotherapy with or without radiation to accomplish eradication of the disease or alternative strategies designed to duplicate or mimic the graft-versus-myeloma effect. Long-term follow-up of recipients of autologous stem-cell transplants indicate a continuing risk of disease recurrence after 5 years, and arguably few if any patients are cured. In contrast allogeneic stem-cell transplants with long-term follow-up appear to result in durable remissions and a lower risk of recurrence after 5 years.

Although treatment with high-dose chemoradiotherapy followed by allogeneic stem-cell transplantation is capable of producing remissions and long-term survival for patients with multiple myeloma, the transplant-related mortality of 25–50%, even in 'good-risk' patients, limits the wide application of this approach. Patients who have failed a prior autologous transplant or who have advanced refractory disease are generally poor candidates for a full-dose allogeneic stem-cell transplant due to treatment-related mortality that exceeds 50%. Furthermore, since more than 80% of patients who develop multiple myeloma are >55 years of age and need a closely HLA-matched family member or unrelated individuals to serve as stem-cell donors, less than 10% of patients are able to receive an allogeneic stem-cell transplant.

GRAFT VERSUS MYELOMA

The main interest in allografting derives from the hypothesis that the immunocompetent cells in the donor graft are potent enough to eradicate residual multiple myeloma in the recipient. This effect is often associated with graft-versus-host-disease (GVHD). Because of small patient numbers and heterogeneity of risk factors in registry data, only a few conventional transplant studies to date have been able to identify a graft-versus-myeloma effect. A small retrospective report of 37 patients who received conventional allografts for multiple myeloma found that among 15 patients who achieved complete response, 11 had chronic GVHD while four did not.[6] Individual case reports have documented a graft-versus-myeloma effect in association with GVHD when immunosuppression was withdrawn.[7] Small series of patients with multiple myeloma who developed post-allograft relapses and who subsequently were infused with allogeneic leukocytes from their original stem-cell donors have clearly demonstrated a graft-versus-myeloma effect that was associated with GVHD.[3–5,8,9] In initial studies, 50–70% of patients receiving donor lymphocyte infusions for relapsed multiple myeloma have been reported to achieve complete responses.[5,10,11] A more recent survey of 25 patients at 15 centers reported complete responses in only seven patients (28%) who received one or more infusions of donor lymphocytes.[9] In a review of donor lymphocyte infusions for relapsed multiple myeloma, a graft-versus-myeloma effect was noted in 18/22 patients who developed GVHD compared to only 2/7 patients who did not develop GVHD ($P = 0.02$).[12] These studies suggest that clinical GVHD is not essential for a graft-versus-myeloma effect, but the relationship between the two is very strong. Retrospective studies of reduced-intensity transplants have shown a strong linkage between the development of chronic GVHD and a diminished risk of relapse (HR, 0.37, $P = 0.02$).[13,14] Furthermore, when one compares response rates to donor lymphocyte infusions among different diseases, it appears that the graft-versus-tumor effects in patients with multiple myeloma are less potent than in other diseases such as chronic myeloid leukemia, chronic lymphocytic leukemia, mantle-cell or follicular lymphoma.[15–17] This suggests that reduced-intensity allografting for multiple

myeloma is unlikely to be successful unless patients can first be treated to a state of minimal disease. Subsequent studies have confirmed this prediction.

NON-ABLATIVE ALLOGENEIC TRANSPLANTS

The high-intensity conditioning regimens customarily used before allogeneic transplants are designed to produce cytoreduction and immunosuppression sufficient to allow establishment of the donor graft. The demonstrated efficacy of donor lymphocyte infusions in relapsed allograft patients suggests that the allogeneic graft-versus-myeloma effect is important for cure. This has led to the exploration of reduced-intensity conditioning regimens, designed more for immunosuppression rather than cytoreduction, with the aim of establishing consistent donor engraftment while minimizing toxicity and damage to normal host tissues. Furthermore, reduced-intensity immunosuppression should minimize or eliminate the period of severe pancytopenia that always occurs after high-intensity conditioning. In theory, this technique could – once donor engraftment is achieved – allow the graft-versus-myeloma effects to operate while avoiding the high transplant-related mortality.

The most widely used reduced-intensity regimen was developed in Seattle, based on canine transplant studies, where it was shown that reliable allogeneic donor peripheral-blood stem-cell engraftment could be achieved with a very low dose of total body irradiation of 200 cGy and a combination of two potent immunosuppressive drugs, including mycophenolic acid and cyclosporine.[18] This strategy was applied to 18 patients undergoing allogeneic transplant for multiple myeloma. Seven patients had refractory disease and six had failed a prior autograft. Two of the first four patients rejected the donor graft, leading to the addition of fludarabine, which provided additional immunosuppression.[19] There were no further occurrences of rejection following the addition of fludarabine to the regimen. Although only one of 18 died of transplant-related toxicities, complete responses occurred in only two patients, and only three others achieved partial responses. None of the responses was durable. These results confirmed that in multiple myeloma the graft-versus-myeloma effects are relatively modest, and that additional cytoreduction would be needed prior to a reduced-intensity allograft in order to improve the responses.

As a means to accomplish cytoreduction, an autologous stem-cell transplant was added first, followed by a reduced-intensity allograft in patients with multiple myeloma who had not received a prior high-dose regimen. Patients undergo autologous peripheral-blood stem-cell collection, followed by melphalan 200 mg/m² and reinfusion of autologous stem cells to provide cytoreduction and some immunosuppression. In this way the high-dose therapy is separated in time from the introduction of the allograft. After 2–4 months, following recovery from the first autologous stem-cell transplant, patients received a regimen of 200 cGy total body irradiation, mycophenolic acid, and cyclosporine, with allogeneic peripheral-blood stem cells. Fifty-four patients aged 29–71 years (median age 52 years) received this tandem autologous, allogeneic transplant strategy. All patients were stage II or III, and 48% had refractory or relapsed disease. One patient died of cytomegalovirus pneumonia after the initial autologous stem-cell transplant, one patient progressed after the autograft, and 52 proceeded to allogeneic stem-cell transplant; 51/52 achieved full donor chimerism, with a single patient requiring donor lymphocyte infusions on day 84 for partial chimerism. The overall transplant mortality was 22%, and the complete remission rate was 57%. Four patients developed severe acute GVHD (grades 3–4), and chronic GVHD developed in 60%. [20] With a median follow-up of 60 months after allograft, the survival at 60 months was 69%, and the progression-free survival 40%.

There are approximately 400 patients who have received allogeneic stem-cell transplants after reduced-intensity regimens for multiple myeloma; results have been reported in full

manuscript or abstract form in 13 phase-II studies (Table 1) The types of regimens used have varied widely and include melphalan 100–140 mg/m² often with added fludarabine, total body irradiation 200 cGy, with fludarabine or sometimes with added cyclophosphamide or low-dose busulfan. Anti-thymocyte globulin or the anti-CD52 antibody alemtuzumab have been included with some regimens in order to facilitate engraftment and reduce GVHD. GVHD prophylaxis regimens have included cyclosporine, or tacrolimus and mycophenolic acid, or methotrexate. There is currently no consensus on which of these regimens is superior in terms of toxicity or efficacy. PBSCs mobilized with granulocyte-specific colony-stimulating factor (G-CSF) have been used for the majority of studies because of fewer graft failure/rejections and putatively greater graft-versus-myeloma effects when compared to bone-marrow. Unrelated donors were used in 121 transplants. Approximately 120 of these patients had the reduced-intensity allograft performed as part of a tandem strategy following an ablative autologous transplant.

Acute GVHD grades 2–4 occurred in 25–58% of patients. Chronic GVHD was reported in 7–70% of patients. Overall, transplant-related mortality has ranged from a low of 0% to a high of 41%. Survival has been 50–100% at 1 year, 26–74% at 2 years, 36–70% at 3 years, and as high as 69% at 4 years. Complete response rates have ranged from a low of 10% to as high as 73%.

The Arkansas group utilized melphalan 100 mg/m² to prepare 45 patients prior to reduced-intensity conditioning allografting. These patients had either failed two or three prior autologous transplants, or received the allograft as part of a tandem autologous–allogeneic transplant strategy (n = 12). The patients had a median age of 56 years, and donors were all HLA-matched; 12 were unrelated volunteer donors. Total body irradiation and fludarabine were added to the regimens of patients receiving transplants from unrelated donors. The day-100 transplant-related mortality was 15%, overall transplant mortality was 38%, and 64% achieved complete response or near-complete response. Overall survival at 3 years was poor, only 36%. There was a significantly better survival for patients transplanted as part of the planned tandem strategy versus failed autografts, 86% versus 31%, $P = 0.01$. [21] Several other studies of reduced-intensity allografts from family members or unrelated donors have confirmed that results are poor when patients have failed a prior autologous transplant or have chemotherapy-resistant disease. [22–24] Two German studies and a study from the MD Anderson center confirmed 2-year survivals of 26–50% for patients who had failed one or more autologous transplants. A study combining data from several centers, including approximately 120 patients, found that relapse from a prior autologous transplant was the most significant risk factor for transplant mortality (HR 2.80; $P = 0.02$), relapse (HR 4.14; $P < 0.001$), and death (HR 2.69; $P = 0.005$). [13] At least one trial comparing autologous to reduced-intensity allografts following relapse from a prior autologous transplant found no differences in progression-free and overall survival. [25] A more recent study has demonstrated that a second autologous transplant performed only after relapse or progression can result in major responses with prolonged survival. [26] Thus it remains to be determined whether or not a reduced-intensity allograft or a second autograft is the best choice once patients have failed a prior autograft. Conversely, complete response rates and early survivals were very good when a planned tandem reduced-intensity allograft approach was utilized as part of the initial treatment. [20,27–29]

In one study the anti-CD52 antibody alemtuzumab was added to total body irradiation and fludarabine in 20 patients with multiple myeloma undergoing reduced-intensity allografting as part of front-line therapy. [30] Fourteen of the 20 patients were given donor lymphocyte infusions post-transplant for residual or progressive disease. Although transplant mortality and survival at 2 years were acceptable at 15% and 71%, respectively, the complete response rate of 10% was disappointing. The low response rates may have been due to the

addition of alemtuzumab, which could have interfered with the graft-versus-myeloma effect. In another study anti-thymocyte globulin at doses of 2.5–12.5 mg/kg were added to a busulfan–fludarabine regimen. The incidences of transplant mortality and GVHD were relatively low at 17% and 27%, respectively, but the complete response rates were also low at 24%. [31] The studies of both Peggs et al [30] and Mohty et al [31] suggest that antibodies such as alemtuzumab or anti-thymocyte globulin to prevent GVHD must be used cautiously, and probably at reduced doses, since these antibodies may also abrogate the graft-versus-myeloma effect.

Recently the European Group for Blood and Marrow Transplant (EBMT) has summarized registry data containing 229 patients undergoing reduced-intensity allogeneic stem-cell transplants in 33 centers. [32] The regimens varied widely, but almost all utilized fludarabine, with a large majority of patients receiving low-dose total body irradiation, melphalan or cyclophosphamide. Approximately 50% of the reduced-intensity regimens also contained anti-thymocyte globulin or alemtuzumab. Transplant with peripheral-blood stem cells was performed in 80% of patients. Acute GVHD grades 2–4 occurred in 31% of patients, and extensive chronic GVHD was reported in 25%. Although the transplant-related mortality was low at 22%, the 3-year overall survivals and progression-free survivals were disappointing at 41% and 22%. Disease status and duration at transplant and the use of alemtuzumab for conditioning were found in multivariate analysis to be adverse risk factors for transplant mortality, progression-free survivals and overall survivals. The development of limited chronic GVHD was associated with better overall survivals and progression-free survivals (84% and 46%), while patients with extensive chronic GVHD had overall survivals and progression-free survivals of 58% and 30%. Interestingly, patients with no chronic GVHD had the worst outcomes, with overall survivals and progression-free survivals of 29% and 12%, with deaths due mainly to recurrent disease.

More recently, the EBMT has compared reduced-intensity conditioning with standard ablative conditioning for allografting in multiple myeloma. [33] Between 1998 and 2002, 196 patients conditioned with ablative regimens were compared with 321 patients undergoing reduced-intensity conditioning. Transplant-related mortality was significantly lower for the reduced-intensity group ($P = 0.001$). There was, however, no statistical difference in progression-free survivals or overall survivals between the two groups. This was due to a rate of relapse for the reduced-intensity group that was more than double the rate for standard conditioning patients ($P = 0.001$).

RANDOMIZED TRIALS

No prospective randomized trials have been published comparing ablative with non-ablative conditioning regimens for the transplant of patients with multiple myeloma. However, a number of studies have been reported or are under way comparing tandem autologous transplants to a tandem autologous–non-ablative-allograft approach. The randomization for these studies was ‘genetic’, in that patients with available related donors were typed, and if an HLA-identical donor was identified, they were offered a non-ablative transplant as the second transplant. While not truly randomized, they provide some comparative data on the relative risks and benefits of the two techniques.

A French trial using two parallel studies compared outcomes in 284 patients with multiple myeloma who were high risk by virtue of elevated β_2 -microglobulin and deletion of chromosome 13 by fluorescence in-situ hybridization (Table 2). [34] All patients first had an autologous transplant with high-dose melphalan. The 65 patients with HLA-matched donors underwent an allogeneic transplant on one protocol after conditioning with busulfan, fludarabine and a high dose of anti-thymocyte globulin 12.5 mg/kg. They were compared to

219 patients without donors who were treated on another protocol with a second autologous transplant with melphalan 220 mg/m². Transplant mortality was 5% for the tandem auto group compared to 11% for the auto–allo group. The complete response and very good partial response rates were 51% and 62% respectively for the tandem auto and auto–allo groups. With a relatively short follow-up of a median 2 years, the overall survivals and event-free survivals were not statistically different: 35% versus 41% and 25% versus 30% for the tandem auto and auto–allo studies, respectively. Although these results indicate that patients with high-risk features do not benefit from a tandem auto-reduced-intensity allograft approach, the regimen utilized a high dose of ATG 12.5 mg/kg. This resulted in a low incidence of chronic GVHD (7%) but a relatively low complete response rate (33% of evaluable patients). This study agrees with another report analyzing the outcome of reduced-intensity allografting in patients with or without del13.[35] This study demonstrated that del13 was an independent, adverse risk factor for overall survivals and progression-free survivals after reduced-intensity allografting due primarily to a greater risk of relapse. Whether or not any allograft procedure can overcome this adverse risk factor remains to be determined.

A recent study prospectively assigned 162 patients with stage II or III multiple myeloma to induction with vincristine, adriamycin, and dexamethasone for 2–3 cycles, followed by autologous peripheral-blood stem-cell collection following cyclophosphamide and granulocyte colony stimulating factor.[36] All patients then received high-dose melphalan followed by autologous peripheral-blood stem cells. Patients with an HLA-identical sibling (n = 80) were assigned to receive a reduced-intensity allogeneic transplant using the Seattle regimen, while patients without a matched sibling (n = 82) were assigned to receive a second course of high-dose melphalan and autologous stem-cell transplant. Only 58 and 46 patients in the auto–allo and auto–auto groups completed their assigned treatments. The complete response rate was 26% with the tandem auto and 55% with the auto–allo group ($P = 0.004$). The transplant mortality was 2% and 10% for the tandem auto and auto–allo groups, respectively ($P =$ not significant). Based on intention to treat, and with a 45-month median follow-up, the median overall survivals were 54 months and 80 months for the tandem auto versus auto–allo groups, respectively ($P = 0.01$). The progression-free survivals were 29 months versus 35 months for the auto–auto and auto–allo groups respectively ($P = 0.02$). An important strength of this trial is that the treatment assignment was based solely on donor availability, and analysis was performed by intention to treat. These results suggest a possible advantage for the auto–allo approach, although longer follow-up is needed. In the multivariate analysis high lactate dehydrogenase and low platelet count at diagnosis were both independent predictors of survival and progression-free survival. This could suggest that allogeneic transplant may not be able to overcome high-risk prognostic factors.

It is clear that reduced-intensity allogeneic transplant regimens can result in reliable donor engraftment with a relatively low mortality compared to high-dose regimens. The immunologic effect of the allograft is, however, relatively modest, resulting in a reduced rate of complete response and a higher rate of progression compared to ablative regimens. Thus, it appears that substantial cytoreduction pre-allografting is required in order to facilitate the success of a reduced-intensity allograft. Preliminary results suggest the tandem auto/reduced intensity allogeneic strategy can result in complete responses in over 50% of patients with multiple myeloma, similar to what can be achieved with a high-dose conditioning regimen. Reduced-intensity regimens are a promising strategy to ensure reliable engraftment, low mortality and high response rates, as well as the ability to expand this technique to older patients or patients with comorbid conditions. It will be important, however, to have longer follow-up of patients transplanted with non-ablative regimens in order to document the durability of these remissions and to document the rates and severity of chronic GVHD.

ANOTHER LOOK AT ABLATIVE ALLOGRAFTS

The US intergroup trial of early versus late autologous transplant suggested autologous transplant produced equivalent survival to standard chemotherapy when autologous transplant could be given as salvage treatment for patients failing conventional therapy.[37] The trial was started in 1993 and had a third option that allowed patients with matched siblings to undergo allogeneic transplant using an ablative regimen of cyclophosphamide and total body irradiation. That arm of the study was closed after 36 patients were treated, because of an excessively high transplant-related mortality of 53%. At a 7-year follow-up, however, the overall survivals are identical at 39% for both autologous and allogeneic recipients, while the progression-free survivals are 15% for autologous recipients compared to 22% for allogeneic recipients. Additionally, while the risk of relapse continues in the group that received autologous transplant, the overall survival curve for the allogeneic group is flat with follow-up extending to 10 years. Thus at the present time only allogeneic stem-cell transplantation is capable of producing long-term, durable remissions with the potential for cure. This single fact argues that allogeneic transplants should continue to have a role in the management of multiple myeloma, even if only as a continuing investigational field.

A phase-II study – utilizing high-dose busulfan and mephalan followed by allogeneic peripheral-blood stem cells from matched sibling donors in 30 patients with multiple myeloma – has reported a transplant-related mortality of 16% at 100 days, 30% overall, with an 81% complete response rate.[38] Survivals and progression-free survivals at 6 years were 65% and 70%. Thus improvements in patient selection and supportive care have narrowed the differences in transplant-related mortality between ablative (30%) and reduced-intensity (20%) allogeneic stem-cell transplants. This suggests that there may be ways to make ablative regimens more tolerable while still preserving the cytoreductive benefits of an allograft.

WHERE DO WE GO WITH ALLOGRAFTS?

At the present time, allogeneic stem-cell transplant remains the only modality with the potential for long-term disease control in more than a handful of patients. Significant progress has been achieved in reducing transplant mortality. Future work should focus on novel techniques for cytoreduction and enhancing graft-versus-myeloma while reducing or controlling graft-versus-host disease.

One novel technique for improving the ability to eradicate residual host myeloma involves the use of targeted radiation delivered by antibodies or chemically specific uptake. High-energy, short-acting radioisotopes linked to bone-seeking compounds have been utilized in this manner. Holmium-166 (^{166}Ho), a β -emitting radiometal with a half-life of 26 hours, has been linked to a tetraphosphonate chelate (DOTMP) to achieve rapid and specific uptake in bone and bone surfaces. In phase I/II trials, increasing doses of ^{166}Ho -DOTMP were given, along with high-dose melphalan, followed by autologous stem-cell transplant.[39] A complete response rate of 38% was observed, with a median overall survival in excess of 48 months. Samarium-153, another high-energy isotope, was linked to another tetraphosphonate chelate (EDTMP) and studied in 18 patients with multiple myeloma, who received melphalan 200 mg/m² following the isotope.[40] Five patients achieved complete responses. The samarium isotope has also been given to nine patients in a pilot study along with cyclophosphamide as a preparative regimen for allografting in multiple myeloma.[41] Tolerance was very good, with only one patient dying from transplant complications, but responses were disappointing, with only two patients achieving complete response.

One probable reason for the high transplant mortality after allografting for patients with multiple myeloma may be related to the primary immunodeficiency in this disease. Thus

improved sources of stem cells, such as peripheral blood, which result in earlier engraftment and immune reconstitution,[42] should reduce infectious complications.

SUMMARY

Future studies of allogeneic marrow transplantation in multiple myeloma should focus on regimens that are less toxic but able to preserve anti-tumor effects such as radioisotopes linked to bone-seeking chelates[43,44] or dose-adjusted chemotherapy.[45] It should be relatively easy to combine targeted radiotherapy and dose-adjusted chemotherapy to create a more tolerable regimen.

The studies using reduced-intensity regimens appear to effectively reduce the early complications and mortality of allogeneic transplants, but are relatively ineffective at eradicating residual disease unless accompanied by cytoreduction delivered with a prior autograft. Such treatments could be combined with infusions of allogeneic donor lymphocytes or subsets of lymphocytes in the form of 'engineered grafts': for example, CD4 lymphocytes, which may have a graft-versus-myeloma effect without increasing GVHD.[46] It may also be possible to exploit killer-immunoglobulin-like mismatching between donor and recipient, which has been shown to result in improved progression-free survival due to a reduced rate of relapse.[47] Finally, it may be worthwhile to exploit monoclonal antibodies targeting myeloma cells, such as the CD40 antigen[48] or the CS-1 antigen,[49] in order to increase the ability of donor allogeneic cells to eliminate residual host disease.[50]

Currently, it is still not possible to recommend allogeneic transplants outside the context of a clinical trial. While the results from the recent Italian trial are encouraging,[36] the small number of patients actually transplanted should encourage further studies exploring this approach.

Practice points

allogeneic stem-cell transplantation remains the only treatment shown to be capable of long-term disease control of multiple myeloma, but should be performed only in clinical trials

reduced-intensity allogeneic transplants have reduced but not eliminated the risk of transplant mortality, but at a cost of increased relapse

currently, the most promising approach to reduce relapse is to perform an autologous transplant followed by a reduced-intensity allograft

Research agenda

future studies should focus on targeted preparative regimens for more effective, less toxic cytoreduction, and graft manipulation to enhance the immunologic anti-tumor effect of the donor cells

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Table 1

Phase-II trials of reduced-intensity allogeneic transplantation from related and unrelated donors for the treatment of multiple myeloma.

Reference	n	Regimen	# Tandem auto	GVHD prophylaxis	% Graft chimerism	AGVHD %, 2-4	CGVH %	TRM %	CR %	% Survival at (years)
Maloney et al[20]	54 (0)	TBI2Gy, Flu	54	CSA Mmf	100	45	60	22	57	69 (5)
Lee et al[21]	45 ^a (12)	HDM100 (TBI2Gy,Flu)	12	CSA	89	58	13	38	64	36 (3)
Kroger et al[27]	17 (8)	HDM100, Flu, ATG	17	CSA, Mtx	100	38	7	18	73	74 (2)
Kroger et al[28]	21 (21)	HDM100-140, Flu, ATG	9	CSA, Mtx	100	38	12	24	40	74 (2)
Gerull et al[51]	52 (20)	TBI2Gy, Flu	0	CSA Mmf	90	37	70	17	27	41 (1.5)
Mohy et al[31]	41	Bu,Flu,ATG	0	CSA Mtx(13)	98	36	41	17	24	62 (2)
Peggs et al[30]	20 (8)	TBI, Flu, alemtuzumab	0	CSA Mmf	nr	25*	nr	15	10	71 (2)
Einsele et al { 23720}	22 (15)	TBI2Gy, Flu, Cyclo	0	ATG, CSA Mmf	nr	38	32	23	27	26 (2)
Giralt et al[23]	22 (9)	Flu,HDM	0	FK506 Mtx	100	46	27	41	32	30 (2)
Hoepfner et al[22]	19 (6)	TBI2Gy, Flu	0	CSA Mmf	nr	37	nr	32	nr	50 (2)
Galimberti et al[29]	20 (0)	TBI2Gy,Flu (10) Cy, Flu (10)	20	CSA Mmf	nr	25	30	20	35	58 (2)
Ma et al[52]	10 (0)	TBI3Gy,FLU	0	CSA Mmf	80	60	40	0	30	100 (1)
Perez-Simon et al[53]	29 (nr)	Me1,Flu	10	CSA Mtx		41	51	21	28	60 (2)
Sorasio et al[54]	22 (22)	TBI2Gy, Flu	nr	CSA Mmf	91	50	59	18	20	73(1)

n, total number of patients (number from matched unrelated donors); HDM, high-dose melphalan; TBI, total body irradiation; Flu, fludarabine; Cyclo, cyclophosphamide; # Tandem auto, planned prior autologous transplant; GVHD, graft-versus-host disease; CSA, cyclosporine; ATG, anti-thymocyte globulin; Mtx, methotrexate; Mmf, mycophenolic acid; FK506, tacrolimus; AGVHD, acute graft-versus-host-disease; CGVH, chronic GVHD, TRM, transplant-related mortality rate; CR, complete response rate; nr, not reported.

^a 14 patients given donor leukocyte infusion (DLI).

Table 2

Comparison trials of tandem autologous transplant with autologous (Auto) + reduced-intensity allografting (Allo).

Reference	Regimens	Number	TRM	Response CR/VGPR	DFS (follow-up, years)	OS (follow-up, years)
Garban et al[34] ^a	Auto mel 200/220	219	5%	33%/18%	0% 5 years	44% 5 years
	Auto mel200 Allo bu.flu.ATG	65 ^b	11%	33%/29%	0% 5 years	33% 5 years
Bruno et al[36]	Auto mel 200/200	80 ^c	4%	26%/nr	20% 4 years	53% 4 years
	Auto mel200 Allo 2 Gy TBI	82 ^d	10%	55%/nr	42% 4 years ^e	75% 4 years ^e

TRM, transplant-related mortality; CR, complete response; VGPR, very good partial response; DFS, disease-free survival; OS, overall survival; mel, melphalan; bu, busulfan; flu, fludarabine; ATG, anti-thymocyte globulin; nr, not reported; TBI, total body irradiation.

^aHigh-risk patients with elevated $\beta 2$ -microglobulin and deletion 13 by fluorescence in-situ hybridization (FISH).

^b19/65 patients did not receive the reduced-intensity allograft

^c46/80 patients completed the tandem autograft.

^d58/82 patients received the reduced-intensity allograft.

^eStatistically significant.