

## Reduced intensity allogeneic stem cell transplantation in multiple myeloma

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### 1. ABSTRACT

Allogeneic stem cell transplantation (SCT) is an attractive form of immunotherapy for multiple myeloma (MM) due to well documented graft versus myeloma activity. High transplant related mortality with allogeneic SCT is currently the major limitation to wider use of this potentially curative modality. Mortality can be significantly reduced through the use of lower intensity conditioning regimens which allow engraftment of allogeneic stem cells. This comes at a cost, however, of higher rates of disease progression and relapse. Because allografting is currently the only modality with potential for cure, further studies designed to improve the therapeutic index of allografts are warranted. These include the use of intermediate intensity, yet still non-myeloablative conditioning regimens, autologous transplant performed just prior to allografting, peripheral blood cells, graft engineering to improve the graft versus myeloma activity while reducing GVHD, post transplant maintenance and targeted conditioning therapies such as bone seeking radioisotopes.

### 2. INTRODUCTION

Multiple myeloma is a clonal B cell malignancy with a median survival of 3-4 years. Although, the treatment of multiple myeloma has dramatically improved in the last 10 years due to the introduction of high-dose therapy followed by autologous stem cell support and the introduction of new drugs with unique mechanisms of action, long-term survival after treatment with stem cell transplantation or the newly developed drugs is rare and virtually all patients recur. (1, 2).

Stem cell transplantation from allogeneic donors can be curative for 10-20% of patients with chemotherapy resistant, refractory hematologic malignancies and up to 80% of 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 multiple myeloma this effect has been well documented (3-5). In contrast, stem cell transplantation from autologous or syngeneic donors provide little or no immunologic effect against the myeloma cell. Thus autologous or syngeneic

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stem cell transplants are mainly a form of supportive care and require intensive chemotherapy +/- radiation to accomplish eradication of disease or alternate strategies designed to duplicate or mimic the graft versus myeloma effect. Long-term follow-up of recipients of autologous stem cells 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. (6)

Although treatment with high-dose chemoradiotherapy followed by allogeneic SCT is capable of producing remissions and long-term survival for patients with multiple myeloma, the transplant-related mortality (TRM) 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 SCT due to treatment related mortality that exceeds 50%. Furthermore, since more than 80% of patients who develop multiple myeloma are greater than age 55 years and need closely HLA-matched family member or unrelated individuals to serve as stem cell donors, less than 10% of patients are even able to receive an allogeneic stem cell transplant.

### 3. 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). Due to 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 (CR), 11 had chronic GVHD while 4 did not. (7) Individual case reports have documented a graft versus myeloma effect in association with GVHD when immunosuppression was withdrawn. (8) 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, 9, 10). As high as 50-70% of patients receiving donor lymphocyte infusions for relapsed multiple myeloma in early studies were reported to achieve CRs (5, 11, 12). A more recent survey of 25 patients at 15 centers reported CRs in only 7 (28%) patients who received 1 or more infusions of donor lymphocytes. (10) In a review of donor lymphocyte infusions for relapsed multiple myeloma, a graft versus myeloma effect was noted in 18 of 22 patients who developed GVHD compared to only 2 of 7 patients who did not develop GVHD ( $p=0.02$ ). (13) 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,  $p=0.02$ ). (14, 15) Furthermore, when one compares overall 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 other diseases such as chronic myeloid leukemia, chronic lymphocytic leukemia, mantle cell or follicular lymphoma. (16-18) This suggests that reduced intensity allografting for multiple myeloma may not be successful unless patients can first be treated to a state of minimal disease. Subsequent studies have confirmed this prediction.

### 4. NON-ABLATIVE ALLOGENEIC TRANSPLANTS

Historically, 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, and the long-term disease control associated with Allogeneic transplants suggests that the 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 with 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. This technique could in theory, 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 2 potent immunosuppressive drugs including mycophenolic acid and cyclosporine. (19) This strategy was applied to 18 patients undergoing allogeneic transplant for multiple myeloma. Seven patients had refractory disease and 6 had failed a prior autograft. Two patients of the first 4 rejected the donor graft leading to the addition of fludarabine, which provided additional immunosuppression designed to ensure donor engraftment. (20) There were no further occurrences of rejection following the addition of fludarabine to the regimen. Although only 1 of 18 died of transplant related toxicities, CRs occurred in only 2 patients and only 3 others achieved partial responses. None of the responses were durable. These results confirmed that in multiple myeloma, the graft versus myeloma effects are relatively modest and that additional cytoreduction would be needed to improve the responses after a reduced intensity allograft.

In order to accomplish cytoreduction, an autologous stem cell transplant was performed first followed by a reduced intensity allograft in patients with multiple myeloma who had not received a prior high dose

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**Table 1.** Phase 2 trials of reduced intensity allogeneic transplantation from related and unrelated donors for the treatment of multiple myeloma

Reference	No	Regimen	Proph GVHD	AGVHD%, 2-4	CGVH%	TRM %	CR%	%Survival at (yr)
33	15 (2)	Flu, Bu, ATG	Mtx, CSA	7	60	7	13	39 (4)
32	41	Bu, Flu, ATG	CSA Mtx (13)	36	41	17	24	62 (2)
31	20 (8)	TBI, Flu, alemtuzumab <sup>1</sup>	CSA Mmf	25 <sup>1</sup>	nr	15	10	71 (2)
25	22 (15)	TBI2Gy, Flu, Cyclo	ATG, CSA Mmf	38	32	23	27	26 (2)
24	22 (9)	Flu, HDM	FK506 Mtx	46	27	41	32	30 (2)
23	19 (6)	TBI2Gy, Flu	CSA Mmf	37	nr	32	nr	50 (2)
51	52 (20)	TBI2Gy, Flu	CSA Mmf	37	70	17	27	41 (1.5)
52	10 (0)	TBI3Gy, FLU	CSA Mmf	60	40	0	30	100 (1)
53	22 (22)	TBI2Gy, Flu	CSA Mmf	50	59	18	20	73 (1)

Notes: No=total number of patients (number from matched unrelated donors), Regimen HDM=high dose melphalan, TBI=total body irradiation, Flu=fludarabine, Cyclo=cyclophosphamide, ProphGVHD graft-versus-host disease prophylaxis, 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=CR rate, nr=not reported, <sup>1</sup>14 patients given DLI

**Table 2.** Phase 2 trials of reduced intensity allogeneic transplantation with and without prior autologous transplant from related donors for the treatment of multiple myeloma

Reference	No	Regimen	# Tandem Auto	Proph GVHD	AGVHD%, 2-4	CGVH%	TRM %	CR %	%Survival at (yr)
21	54 (0)	TBI2Gy, Flu	52	CSA Mmf	45	60	22	57	69 (5)
36	20 (0)	Flu, TBI	20	Mtx CSA	nr	nr	0	50	40 (4)
22	45 (12)	HDM100 (TBI2Gy, Flu)	12	CSA	58	13	38	64	36 (3)
28	17 (8)	HDM100, Flu, ATG	17	CSA, Mtx	38	7	18	73	74 (2)
29	21 (21)	HDM100-140, Flu, ATG	9	CSA, Mtx	38	12	24	40	74 (2)
30	20 (0)	TBI2Gy, Flu (10) Cy, Flu (10)	20	CSA Mmf	25	30	20	35	58 (2)

Notes: No.=total number of patients (number from matched unrelated donors), Regimen HDM=high dose melphalan, TBI=total body irradiation, Flu=fludarabine, Cyclo=cyclophosphamide, # Tandem Auto-planned prior autologous transplant, ProphGVHD graft-versus-host disease prophylaxis, 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=CR rate, nr=not reported

regimen. Patients first have autologous peripheral blood stem cells collected, followed by melphalan 200 mg/m<sup>2</sup> and reinfusion of autologous stem cells to provide cyto-reduction and some immunosuppression. In this way the high dose therapy is separated in time from the introduction of the allograft. Two to 4 months' later, after 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 ages 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, 1 patient progressed after the autograft and 52 proceeded to Allogeneic stem cell transplant. All 52 except 1 achieved full donor chimerism with a single patient requiring donor lymphocyte infusions on day 84 for partial chimerism. The overall TRM was 22% and the complete remission rate was 57%. Four patients developed severe acute GVHD (grades 3-4) and chronic GVHD developed in 60%. (21) With a median follow-up of 60 months after allograft, the survival at 60 months was 69%, and the progression-free survival 38%.

There are over 425 patients who have received allogeneic stem cell transplants after reduced intensity regimens for multiple myeloma with results reported in full manuscript or abstract form in 15 phase 2 studies (Tables 1 and 2). Approximately 130 of these patients had the

reduced intensity allograft performed as part of a tandem strategy following an ablative autologous transplant. (Table 2) The types of regimens used varied widely and include melphalan 100-140 mg/m<sup>2</sup> often with added fludarabine, TBI 200 cGy, with fludarabine, or sometimes with added cyclophosphamide or low to intermediate 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. G-CSF mobilized PBSC have been used for the majority of studies due to fewer graft failure/rejections and putatively greater graft versus myeloma effects when compared to bone marrow. Unrelated donors were utilized in 123 transplants. Acute GVHD grades 2-4 occurred in 7-58% of patients. Chronic GVHD was reported in 7-70% of patients. Overall TRM has ranged from a low of 0% to a high of 41%. Survival has ranged from 70-100% at 1 year, 26-74% at 2 years, 36% at 3 years, 39-40% at 4 years and one trial with 69% at 5 years. CR rates have ranged from a low of 10% to as high as 73%.

The Arkansas group utilized melphalan 100 mg/m<sup>2</sup> to prepare 45 patients prior to RIC allografting. These patients had either failed 2 or 3 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. TBI and fludarabine were added to the regimens of patients receiving transplants from unrelated donors. The day 100 transplant related mortality was 15%, overall TRM was 38% and 64% achieved CR or near CR. Overall survival at 3 years was poor, only 36%, but was significantly better among the 12 patients transplanted as part of the planned tandem strategy compared to others, 86% v. 31%,  $p=0.01$ . (22) 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. (23-25) Two German studies and a study from MD Anderson confirmed 2 year survivals of 26-50% for patients who had failed 1 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 TRM (HR 2.80;  $p=0.02$ ), relapse (HR 4.14;  $p<0.001$ ), and death (HR 2.69;  $p=0.005$ ). (14) 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. (26) 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. (27) Thus it remains to be determined whether or not a reduced intensity allograft or a second autograft is the best choice once patients have already failed a prior autograft. Conversely, CR rates and early survivals were very good when a planned tandem, reduced intensity allograft approach was utilized as part of the initial treatment. (21, 22, 28-30)

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. (31) Fourteen of 20 were given donor lymphocyte infusions post transplant for residual or progressive disease. Although TRM and survival at 2 years were acceptable at 15% and 71%, respectively, the CR rate of 10% was disappointing. The low response rate may have been due to the addition of alemtuzumab, which may have interfered with the graft versus myeloma effect. In another study anti-thymocyte globulin at doses of 2.5 to 12.5 mg/kg were added to a busulfan-fludarabine regimen. The incidences of TRM and GVHD were relatively low at 17% and 27%, respectively, but the CR rate was also low at 24%. (32) Yet another study utilized a busulfan and fludarabine regimen with ATG at doses of 4.5 mg/kg. (33) Only 1/15 patients developed acute GVHD but again the CR rates were low at 13%, with only 20% alive, progression free at 4 years. Thus all the studies employing antibodies such as alemtuzumab or anti-thymocyte globulin to prevent GVHD are associated with relatively low CR rates and low disease free survivals.

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. (34) The

regimens varied widely but almost all utilized fludarabine with a large majority receiving either low dose total body irradiation, melphalan or cyclophosphamide. Approximately 50% of the reduced intensity regimens also contained anti-thymocyte globulin or alemtuzumab. Eighty percent of patients were transplanted with peripheral blood stem cells. Acute GVHD grades 2-4 occurred in 31% of patients and extensive chronic GVHD was reported in 25%. Although the transplant related mortality was relatively low at 22% the 3 year overall survivals and progression-free survivals were disappointing at 41% and 22%. Disease status and duration of disease at transplant, and the use of alemtuzumab for conditioning were found in multivariate analysis to be adverse risk factors for TRM, 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 a 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. (35) Between 1998-2002 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 24% v. 37% at 2 years,  $p=0.002$ . In a multivariate analysis there were, however, no statistical differences in overall survivals or progression free survivals between the 2 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,  $p=0.0001$ .

## 5. RANDOMIZED TRIALS

No prospective randomized trials have been published comparing ablative with non-ablative conditioning regimens for the transplant of patients with multiple myeloma. A retrospective comparison of tandem autologous transplant ( $n=35$ ) versus an autologous, non-ablative allograft from HLA identical siblings ( $n=20$ ) was reported at ASH. (36) The conditioning regimen was TBI and fludarabine with GVHD prophylaxis consisting of Mtx and cyclosporine. TRM was 0% in both groups but the allogeneic group had a complete remission rate of 50% compared to 14% for tandem autologous group. Disease free survivals at 4 years were superior for the allogeneic group at 45% compared to 14% for the tandem autologous group. Overall survivals at 4 years were also superior. Allogeneic 40% v. 28% tandem autologous.

There are a number of prospective studies reported or underway 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,

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**Table 3.** Prospective studies comparing tandem autologous transplant with autologous + reduced intensity allografting

Reference	Regimens	GVHD proph	Number	TRM	Response CR/VGPR	DFS (f/u yr)	OS (f/u yr)
37 <sup>1</sup>	Auto mel 200/220		219 (166) <sup>2</sup>	5%	33%/18%	0% 5yr	44% 5yr
	Auto mel200 Allo bu.flu.ATG	CSA Mtx	65 (46) <sup>3</sup>	11%	33%/29%	0% 5yr	33% 5yr
39	Auto mel 200/200		82 (46) <sup>4</sup>	2%	26%/ nr	20% 4yr	55% 4 yr
	Auto mel200 Allo 2Gy TBI	Mmf CSA	80 (58) <sup>5</sup>	10%	55%/ nr	45% 4yr <sup>6</sup>	80% 4 yr <sup>6</sup>

<sup>1</sup> high risk patients with elevated beta-2M and deletion 13 by FISH, <sup>2</sup> 53 patients did not receive the 2nd autograft, <sup>3</sup> 19 patients did not receive the RIC allogeneic transplant, <sup>4</sup> 36 patients did not receive the 2nd autograft, <sup>5</sup> 22 patients did not receive the allogeneic transplant, <sup>6</sup> statistically significant, analysis by intention to treat, nr = not reported

they were offered a non-ablative transplant as the second transplant. (Table 3) While not truly randomized, they provide some comparative data on the relative risks and benefits of the 2 techniques.

A French trial using 2 parallel protocols compared outcomes in 284 patients with multiple myeloma who were high risk by virtue of elevated beta-2-microglobulin and deletion of chromosome 13 by fluorescence in-situ hybridization. (37) 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/m<sup>2</sup>. TRM was 5% for the tandem auto group compared to 11% for the auto-allo group. The CR and very good PR 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% v. 41%, and 25% v. 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 CR rate (33% of evaluable patients). This study agrees with another report analyzing the outcome of RIC allografting in patients with or without del13. (38) 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. It remains to be determined whether or not any allograft procedure can overcome this adverse risk factor.

A more recent prospective study registered 162 patients with stage II or II multiple myeloma that had available donors that could be HLA typed. All patients received induction with vincristine, adriamycin, and dexamethasone for 2-3 cycles, one cycle of cyclophosphamide and granulocyte colony stimulating factor followed by autologous peripheral blood stem cell collection, high dose melphalan and autologous stem cell transplant. (39) 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. Thus randomization was based solely on the availability of an HLA identical donor. Only 58 and 46 patients in the auto-allo and auto-auto groups respectively completed their assigned treatments. The CR rate was 26% with the tandem auto and 55% with the auto-allo group (p=0.004). The TRM was 2% and 10% for the tandem auto and auto-allo groups, respectively, p=ns. 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 v. auto-allo groups, respectively, p=0.01. The progression free survivals were 29 months v. 35 months for the auto-auto and auto-allo groups respectively, p=0.02. An important strength of this trial is the treatment assignment based solely on donor availability and analysis on intention to treat. These results suggest a possible advantage for the auto-allo approach, although longer follow-up is needed.

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. In multiple myeloma, the immunologic effect of the allograft is, however, relatively modest resulting in a reduced rate of CR 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 CRs in over 50% of patients with multiple myeloma; similar to what can be achieved with a high dose conditioning regimen. Reduced intensity regimens are another 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 co-morbid 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.

## 6. FUTURE RESEARCH

There may be methods for building on the basic platform of non-ablative transplants in order to improve cytoreduction just prior to the allograft or by enhancing immunologic effects once engraftment has been achieved. One technique for increasing 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 ( $^{166}\text{Ho}$ ) a beta emitting radiometal with a half-life of 26 hours has been linked to DOTMP, a tetra phosphonate chelate to achieve rapid and specific uptake in bone and bone surfaces. In phase I-2 trials, increasing doses of  $^{166}\text{Ho}$ -DOTMP were given, along with high dose melphalan, followed by autologous SCT. (40) A CR rate of 38% was observed with a median overall survival in excess of 48 months. Samarium-153, another high energy isotope was linked to EDTMP, another tetraphosphonate chelate and studied in 18 patients with multiple myeloma, who received melphalan 200 mg/m<sup>2</sup> following the isotope. (41) CR resulted in 5 patients with a very good PR in another 7. The samarium isotope has also been given to 9 patients in a pilot study along with cyclophosphamide as a preparative regimen for allografting in multiple myeloma. (42) Tolerance was very good with only 1 patient dying from TRM. Responses were disappointing with only 2 CRs. Further development and studies with targeted radioisotopes are needed.

Patients with multiple myeloma experience a higher transplant mortality after allografting due to more advanced age and underlying immunodeficiency. Thus improved sources of stem cells such as PBSC which result in earlier engraftment and immune reconstitution (43) should reduce infectious complications.

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 (44) (45) or dose adjusted chemotherapy (46). It should be relatively easy to combine targeted radiotherapy and dose adjusted chemotherapy to create a more tolerable regimen. The studies using RIC 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 GVM effect without increasing GVHD (47). Another technique would be to enhance the antigen presenting function of target myeloma cells by transduction with costimulator molecules such as B7-1. (48) It may also be possible to exploit killer-immunoglobulin-like mismatching between donor and recipient, which has been shown to result in improved PFS due to a reduced rate of relapse. (49) Finally, it may be worthwhile to exploit monoclonal antibodies targeting myeloma cells such as the CD40 antigen, in order to increase the ability of donor allogeneic cells to eliminate residual host disease. (50)

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