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Recent Developments in Hematopoietic Stem Cell Transplantation for Multiple Myeloma

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Abstract

Multiple myeloma (MM) is often successfully controlled with conventional chemotherapy; however, complete remissions are uncommon, and cure is rare. High-dose therapy followed by administration of autologous or allogeneic stem cells, used for the treatment of MM in the past 15 years, is promising as a means of increasing remission rates and improving survival. Autologous transplantation has not always demonstrated survival benefits in randomized studies because most of the patients receiving transplants have relapses, whereas patients given conventional therapy can receive salvage transplants when relapse occurs. Efforts to improve the results of autologous transplantation include targeted radiation, tandem transplantation, and posttransplantation immunotherapy. Only allogeneic hematopoietic stem cell transplantation is potentially curative, owing to a graft-versus-myeloma effect. Although patients who receive either allogeneic or autologous stem cell transplants for MM have similar 3- to 5-year survival rates, only allograft recipients appear to enjoy long-term disease-free survival. High transplantation-related mortality associated with allogeneic stem cell transplantation is currently the major limitation to wider use of this potentially curative modality. Strategies designed to improve the therapeutic index of allografts include the use of nonablative conditioning regimens, peripheral blood cells rather than bone marrow, graft engineering, and targeted conditioning therapies, such as bone-seeking radioisotopes. *Int J Hematol.* 2003;77:232-238.

Key words: Multiple myeloma; Stem cell transplantation; Graft-versus-myeloma

1. Introduction

Multiple myeloma (MM) is a clonal B-cell tumor involving plasma cells. The median age of patients at diagnosis is 66 years. The disease is highly sensitive to alkylating agents, corticosteroids, and radiation therapy, but cure has not been achieved with conventional doses and schedules of these agents, and the median survival is only 3 years.

In the 1980s success in the management of refractory hematologic malignant diseases with stem cell transplantation (SCT) led to exploration of this treatment in the care of patients with MM [1-3]. Pioneering studies from the Royal Marsden Hospital demonstrated that high-dose melphalan followed by autologous SCT produced high complete remission rates with the potential of improving survival [4]. SCT from allogeneic donors may be curative for 10% to 20% of patients with refractory hematologic malignant disease and for a larger proportion of patients undergoing transplantation during remission. A "graft-versus-myeloma" (GVM) effect may be associated with allogeneic SCT in the cure of patients with MM [5-7]. In contrast, SCT from autologous or syngeneic donors has little or no GVM effect. This treatment requires either intensive application of chemotherapy with or without radiation for eradication of disease or alternative strategies designed to duplicate or mimic the GVM effect.

2. Autologous SCT

The French intergroup study demonstrated convincingly that autologous SCT, when applied as consolidation therapy after conventional chemotherapy induction, resulted in higher response rates, longer disease-free intervals, and better overall survival than achieved with continued conventional chemotherapy [8]. Seven-year follow-up results of that initial study continue to show a survival advantage for patients in the SCT arm [9]. The Medical Research Council Myeloma VII trial compared combination chemotherapy with combination chemotherapy followed by high-dose melphalan and autologous SCT [10]. This large trial, with 407

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patients randomized, demonstrated 12-month improvement in median survival (P = .04) and similar improvement in event-free survival.

Unfortunately, despite autologous SCT, the majority of patients have relapses and die of recurrent disease. Relapses occur because of failure to eradicate disease in the patient or because of reinfusion of malignant cells contained in the stem cell graft. One randomized study, which evaluated the effect on outcome of removal of myeloma cells from autologous stem cell grafts, showed no improvement in overall or progression-free survival [11]. These results occurred even though the purging technique removed 3 to 4 logs of tumor cells from the grafts. Several explanations may account for these findings. It may be that despite removal of 3 to 4 logs of tumor cells from the stem cell graft, there remained enough residual MM cells to lead to relapse. It is also possible that the majority of malignant plasma cells contained in a peripheral blood stem cell (PBSC) graft are end-stage cells with only a limited capability of dividing and causing relapse. More likely, however, residual host disease is the major contributor to relapse. Although attempts are being made to further deplete stem cell grafts of residual myeloma cells [12], purging, even if 100% effective, will not have much impact on outcome until high-dose conditioning regimens are improved.

Recent efforts to improve the ability to eradicate host disease have focused on innovative high-dose therapy regimens or immunotherapy approaches that deal with minimal disease present after SCT. A randomized trial which compared administration of melphalan alone at 200 mg/m^2 versus melphalan 140 mg/m^2 plus 8 Gy total body irradiation (TBI) showed improved survival at 45 months of 45% for the patients undergoing combined treatment versus 66% for patients receiving melphalan alone [13]. The difference was not explained by improved remission rates or longer duration of disease remission but may have been due to greater sensitivity to salvage regimens among patients who received melphalan alone. In another strategy by the French Intergroup, single autologous SCT after administration of melphalan 140 mg/m^2 plus TBI was compared with a double regimen of melphalan 140 mg/m^2 and stem cell infusion followed 2 to 4 months later by administration of melphalan 140 mg/m^2 plus TBI [14]. The tandem-transplantation group had a projected survival at 7 years of 42% versus 21% for the single-transplantation group (P < .01). Despite these promising data, questions remain that prevent the recommendation of tandem transplantation as the standard of care. The TBI-based regimen is no longer considered the best regimen in light of the superiority of melphalan 200 mg/m^2 compared with a TBI-based regimen. Thus more follow-up and studies with melphalan 200 mg/m^2 are needed before firm recommendations can be made about tandem transplantation. The rates of complete response (CR) in the 2 groups were identical. Because CR in previous studies has always been a predictor of survival, other factors, including postrelapse salvage therapies, may be playing a role. The survival of the tandem transplantation group was no better than the survival of the group who received a single transplant in the original randomized study comparing transplantation with conventional therapy, although the results might have been due to differences in patients entered in the 2 trials [8]. Another randomized trial of 1 versus 2 transplantations has not shown a survival benefit, although this result is likely due to limited follow-up [15].

Another 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 used in this manner. Holmium-166 (^{166}Ho), a β-emitting radiometal with a half-life of 26 hours, has been linked to 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene-phosphonic acid (DOTMP), a tetra phosphonate chelate, to achieve rapid and specific uptake in bone and bone surfaces. In a phase I to II trial, increasing doses of ^{166}Ho-DOTMP were given with high-dose melphalan and followed by autologous SCT [16]. A CR rate of 38% was observed with a median overall survival in excess of 24 months. Sammarium-153, another high-energy isotope, was linked to ethylenediaminetetramethylenephosphonic acid (EDTMP), another tetraphosphonate chelate, and studied in 7 patients with MM, 2 of whom received allogeneic marrow [11]. CR occurred in 4 of 7 patients. Further development and studies with targeted radioisotopes are needed.

Because high-dose therapy and autologous SCT cure few patients, the timing of transplantation may be a critical issue, because it may be possible to avoid upfront morbidity and mortality by delaying transplantation until later in the course of the disease. A randomized trial that addressed the timing of transplantation by comparing results for patients undergoing transplantation during initial response with those for a group of patients undergoing transplantation after failure of induction or after relapse showed equivalent overall survival whether autologous SCT was performed either as part of the initial treatment or when patients had relapses after conventional therapy [17]. Patients undergoing transplantation upfront did enjoy a longer initial remission phase and time interval without symptoms.

Post-SCT immunotherapeutic manipulations are attractive theoretical methods for dealing with both residual host disease and reinfused tumor cells. Boosting host immune responses after SCT may eliminate cells that survive high-dose therapies, and patients who are recovering from the effects of transplantation should be more tolerant of these treatments as opposed to further chemotherapy. After SCT the host immune system is recovering, yet studies show that T-cells reactive against residual myeloma can be isolated from peripheral blood. It has been shown in patients recovering from SCT that vaccination with the patient's tumor-specific idiotype (id) protein can be used to generate id-reactive T-cells after autologous SCT [18]. Id also has been used to pulse autologous dendritic cells and generate similar responses [19-21]. In another innovative approach, proteins are used that have limited expression in normal tissues and excess expression in tumors. One such protein, sperm protein 17, has been used to generate autologous, HLA class I–restricted cytotoxic T-lymphocyte responses in patients with MM [22]. It has not yet been shown that these immune responses are clinically important.

3. Current Results with Allogeneic Marrow

More than 1000 transplantations from allogeneic donors have been performed worldwide for patients with MM. The largest series of patients comes from the European Bone Marrow Transplantation (EBMT) Registry, where data on 690 patients with MM have been reported [23]. In the EBMT Registry analysis, investigators examined transplantations performed on 334 patients from 1983 to 1993 and on 356 patients from 1994 to 1998. Of the patients undergoing transplantation during the latter period, 133 (37%) received PBSC rather than marrow. The most important observation was a marked reduction in transplantation-related mortality (TRM) from 46% to 30%. The reduction in mortality was a result of fewer deaths from opportunistic infection and interstitial pneumonia. This outcome was due, in part, to better patient selection with less prior treatment and to improvements in supportive care. The improvement in results did not appear to be a result of the introduction of PBSC (see below). The overall survival after 3 years improved from 35% during 1983-1993 to 56% during 1994-1998.

The International Bone Marrow Transplant Registry (IBMTR) performed an analysis of 265 patients receiving HLA-identical sibling transplants for MM between 1988 and 1993. It is likely there is considerable overlap among patients included in the EBMT Registry and the IBMTR. After 4 years of follow-up, the probabilities of survival were 35% for patients with Karnofsky performance scores >70 pretransplantion and approximately 15% for patients with scores $\leq$70.

The largest single-center series of patients receiving allografts for MM comes from Seattle, where 136 patients were treated between 1987 and 1999. Results of risk factor analysis have been reported for the initial 80 patients [24]. The median age of patients in these studies was 47 years, all patients being younger than 60 years. In the Seattle experience only 21% of 136 patients had chemotherapy-sensitive disease responsive to initial treatment. The other patients were beyond a first response or had chemotherapy-resistant disease.

Within the first year, mortality due to regimen-related toxicity, graft-versus-host disease (GVHD), hemorrhage, and infection occurred in 60% of patients. *Aspergillus* was a particularly troublesome pathologic organism, accounting for 16 deaths, often in association with GVHD. For all 136 patients the probabilities of survival and relapse-free survival at 8 years were 22% and 14%, respectively. The CR rate was 34%, and for patients who achieved a CR (n = 46), the survival and event-free survival rates at 5 years were 48% and 37%, respectively. Twelve patients were surviving free of disease 7 to 17 years after transplantation.

4. CR as a Surrogate for Survival

Current standards for CR are defined as serum or urine monoclonal proteins undetectable by sensitive assays, usually immunofixation [25,26]. Magnetic resonance imaging (MRI) and computed tomography have been used recently to supplement the information obtained from skeletal surveys [27,28]. The results of these studies indicated a higher degree of sensitivity for active disease and could be used prospectively to follow responses to allogeneic SCT. In addition, MRI may be especially useful for following responses in patients with nonsecretory MM.

Although the requirement for immunofixation to define a CR allows for a more rigorous disease response categorization for MM than for almost any other malignant disease except chronic myeloid leukemia (CML), relapse is still common after allogeneic SCT. This finding has prompted studies with polymerase chain reaction (PCR)-based primers and immunoglobulin H fingerprinting or custom primers from individual patients for the study of marrow and blood from allograft recipients after successful bone marrow transplantation (BMT). The results of these studies indicated that most patients remain PCR positive in the first year after transplantation [28,30]. With continued follow-up, however, results of PCR tests may become negative in subsequent years. In 3 subsequent studies approximately 50% of patients who achieved CR by immunofixation criteria after an allograft had no evidence of disease by PCR [31-33]. Although these studies were conducted with relatively few patients, PCR negativity appears to be associated with prolonged disease-free survival. These studies also included patients who achieved clinical CR after autologous transplantation, and the results indicated that relatively few patients, 7% to 16%, actually achieve molecular remission. Such work is important because it indicates that eradication of minimal residual host disease is crucial to long-term disease-free survival.

5. Graft-versus-Host Disease

The development of GVHD, both acute and chronic, accounted for significant morbidity and mortality in the majority of reports. In the Seattle experience acute or chronic GVHD contributed to the deaths of 18 patients (13%). The Vancouver study found a 68% incidence of grades 2 through 4 acute GVHD among the 19 matched allograft recipients; 2 patients died of GVHD. The incidences of acute GVHD grades 2 through 4 were not different during the 2 time periods of the EBMT Registry analysis (46% versus 44%), although there was a trend toward more grade 3 and 4 GVHD with PBSC (18% versus 11%) [23].

T-cell–depleted grafts are, in theory, an attractive approach to preventing GVHD and its associated morbidity. Unfortunately, most studies of T-cell depletion used for allogeneic SCT in the care of patients with MM have reported continuing problems with GVHD, high mortality from infections, and attenuated GVM effects. A retrospective study with 66 patients from Dana-Farber Cancer Institute indicated that owing to GVHD and infection the risk of mortality was greater than with autologous transplantation. Furthermore, the relapse rate at 2 years was similar to that with autologous transplantation, indicating that T-cell depletion may have interfered with a GVM effect [34]. In another study of T-cell–depleted allografting for MM, performed in the Netherlands, 56 patients were reported to have a survival rate inferior to that of comparable autograft patients. This finding was attributed to high TRM (32%) and lack of a GVM effect [35]. This lack of GVM

may be overcome by preemptive donor lymphocyte infusions (DLI) given soon after transplantation [36].

6. GVM Effect

Because of small patient numbers and heterogeneity of risk factors in registry data, only a few conventional transplantation studies to date have been able to identify a GVM effect. A small retrospective report on 37 patients who received conventional allografts for MM showed that among 15 patients who achieved CR, 11 had chronic GVHD and 4 did not [37]. Individual case reports have documented a GVM effect in association with GVHD when immunosuppression is withdrawn [38]. Small series of patients with MM who developed postallograft relapses and who subsequently received infusion of allogeneic leukocytes from their original stem cell donors (DLI) have clearly demonstrated a GVM effect that was similarly associated with GVHD [5-7,39,40]. Between 50% and 70% of patients receiving DLI for relapsed MM have been reported to achieve CR [7,41,42], although in a more recent survey of 25 patients at 15 centers, CR was obtained by only 7 (28%) of patients who received 1 or more DLI [40]. In a review of DLI for relapsed MM, a GVM effect was noted in 18 of 22 patients who developed GVHD; such an effect occurred in only 2 of 7 patients who did not develop GVHD (P = .02) [43]. The results of this study and of the prior retrospective study with 37 patients suggest that although GVHD may not be essential for GVM, the relationship between the two is very strong. These small studies have paved the way for innovative strategies involving the infusion of selective subsets of allogeneic T-cells, as has been described for CML [44] or in prophylactic DLI after nonablative allogeneic transplantation [44,46]. Such a strategy with CD6 T-cell–depleted allogeneic marrow grafts followed by prophylactic $CD4^+$ donor lymphocytes 6 to 9 months after transplantation has been reported preliminarily for patients with MM [47].

7. Peripheral Blood Stem Cells

Results of allogeneic PBSC transplantation to date suggest that this technique can produce substantially more rapid engraftment than that observed with BMT [48,49]. Furthermore, contrary to widespread expectations, acute GVHD has not been intolerable, even with unmanipulated PBSC containing many more T-cells than are present in a normal BM graft. Although GVHD remains a formidable problem for patients with MM who receive allografts, the earlier recovery of neutrophils and platelets has the potential for reduced infectious complications. This finding should encourage cautious exploration of this new source of stem cells in patients with MM. It has been reported that, with the use of PBSC from healthy donors, a reduction in TRM for patients with MM can be achieved [50]. These results were recently updated to include 30 patients who received unmanipulated PBSC from HLA-matched donors [51]. The TRM was 16% at 100 days with an 81% CR rate. Survival and progression-free survival at 6 years were 60% and 67%. Results of other studies have suggested a favorable effect of PBSC [52], although in the EBMT Registry study, patients undergoing transplantation with PBSC had the same survival and progression-free survival as contemporaneous patients who received BM [23].

8. Nonablative Allogeneic Transplantation

Although high-dose chemoradiotherapy followed by allogeneic SCT is capable of producing remissions and long-term survival for patients with MM, the TRM of 25% to 50%, even among "good-risk" patients, limits the application of this approach. Furthermore, because the majority of patients who develop MM are older than 55 years and need closely HLA-matched family members to serve as donors, fewer than 10% of patients are even eligible for allogeneic SCT. Patients who have undergone unsuccessful prior autologous transplantation are generally poor candidates for full-dose allogeneic SCT because of treatment-related mortality that exceeds 50%. The high-intensity conditioning regimens customarily used before allogeneic transplantation are designed to produce cytoreduction and immunosuppression sufficient to allow establishment of the donor graft. The demonstrated efficacy of DLI in allograft patients who have relapses suggests that the allogeneic GVM effect is a major reason cure can be achieved. This finding has led to exploration of low-intensity conditioning regimens, which are designed more for immunosuppression than for cytoreduction, with the aim of establishing consistent donor engraftment with minimum toxicity and damage to normal host tissues. Furthermore, low-intensity immunosuppression should minimize or eliminate the period of severe pancytopenia that always occurs after high-intensity conditioning. Once donor engraftment is achieved, this technique could in theory allow the GVM effect to operate while high TRM is avoided.

A conditioning regimen developed at the Fred Hutchinson Cancer Research Center was based on results of canine transplantation studies that showed reliable allogeneic donor PBSC engraftment was achieved with a very low dose (200 cGy) of TBI and a combination of 2 potent immunosuppressive drugs, including mycophenolic acid (MMF) and cyclosporine [53]. This strategy was used in the treatment of 14 patients undergoing allogeneic transplantation for MM. These patients generally had very advanced disease, and 50% had received autografts that were unsuccessful. Two patients experienced rejection, a result that led to the addition of fludarabine, which provided additional immunosuppression [54]. Although only 1 of 14 patients died of transplantation-related causes, the response rate was low, a finding suggesting that in MM, additional cytoreduction was needed to improve the ability to achieve responses after an allograft.

A second strategy was adopted for patients with MM who had not received a prior high-dose regimen with a tandem autologous, nonablative allogeneic transplantation approach. Collection of autologous PBSC was followed by administration of melphalan 200 mg/m^2 and reinfusion of PBSC to provide cytoreduction and immunosuppression. Two to 4 months later patients received the nonablative regimen of 200 cGy TBI, MMF, and cyclosporine with allogeneic PBSC. Thirty-two patients 39 to 71 years of age (median age, 55 years) received this tandem transplantation

Table 1.
Early Trials of Reduced-Intensity Allogeneic Transplantation from Related and Unrelated Donors for the Treatment of Multiple Myeloma*

Reference	No.	Regimen	Tandem Auto	ProGVH	Graft Chimerism Rate	AGVHD	CGVHD	TRM	CR	Survival Rate, No. of Years
Badros et al [56]	31 (6)	HDM100 (TBI, Flu)	12	CSA	89%	58%	13%	29%	39%	31%, 2
Kröger [57]	17 (8)	HDM100, Flu, ATG	17	CSA, Mtx	100%	38%	7%	18%	73%	74%, 2
Kröger [58]	(21)	HDM100-140, Flu, ATG	9	CSA, Mtx	100%	38%	12%	24%	40%	74%, 2
Maloney et al [55]	32	TBI, Flu	32	CSA MMF	100%	45%	55%	16%	53%	81%, 2
Hoepfner et al [59]	19 (6)	TBI, Flu	0	CSA MMF	NR	37%	NR	32%	NR	50%, 3
Einsele et al [60]	22 (15)	TBI, Flu, Cyclo	0	ATG, CSA MMF	NR	38%	32%	23%	27%	46%, 2

*No. indicates total number of patients (number from matched unrelated donors); Tandem Auto, number of planned prior autologous transplantations; ProGVH, graft-versus-host disease prophylaxis; AGVHD, acute graft-versus-host-disease; CGVHD, chronic GVHD; TRM, transplantation-related mortality rate; CR, complete response rate; HDM, high-dose melphalan; TBI, total body irradiation; Flu, fludarabine, CSA, cyclosporine; ATG, antithymocyte globulin; Mtx, methotrexate; MMF, mycophenolic acid; NR, not reported; Cyclo, cyclophosphamide.

strategy. All patients had stage II or III disease, and 43% had refractory or relapsed disease. One patient died of cytomegalovirus pneumonia after autografting, and 31 received a nonablative transplant. All 31 patients achieved full donor chimerism, although 1 received DLI on day 84 for partial chimerism. With a follow-up of 20 months after autografting, the survival was 81%, day 100 TRM was 6%, and the CR rate was 53%. Only 3 patients developed severe GVHD, and the overall TRM was 16% [55].

Nonablative or reduced-intensity regimens prior to allogeneic SCT for MM have been reported from other centers and are summarized in Table 1. One promising report described the use of melphalan 100 mg/m^2 to prepare 31 patients prior to allografting. These patients had either undergone 2 or 3 unsuccessful autologous transplantations or received an allograft as part of a tandem autologous-allogeneic transplantation strategy (n = 13). The patients had a median age of 56 years, and all donors were HLA matched; 25 donors were related. TBI and fludarabine were added to the regimens of patients receiving transplants from unrelated donors. The day 100 TRM was 10%; overall TRM was 29%; and 73% of the patients achieved CR or near CR. There was a significantly better survival among patients who underwent transplantation as part of the planned tandem strategy versus 2 failed autografts for the other patients (86% versus 31%, $P = .01$) [56]. At least 2 other studies of nonablative allografts from family or unrelated donors have confirmed that results are poor when prior autologous transplantation is unsuccessful [59] or the patient has chemotherapy-resistant disease [60]. Other regimen variations with fludarabine and melphalan with or without antithymocyte globulin have been used with both family members and unrelated donors [57,58].

Nonablative allogeneic transplantation regimens can result in reliable donor engraftment with relatively low TRM compared with results of high-dose regimens. It appears, however, that substantial cytoreduction before allografting is necessary because of a limited GVM effect. Preliminary results suggest the tandem autologous/mini-allogeneic strategy can result in CR in at least 50% of patients with MM, results similar to those that 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. For documentation of the durability of these remissions and of the rates and severity of chronic GVHD, it will be important to have longer follow-up of patients undergoing transplantation with nonablative regimens.

9. Future Directions

High-dose therapy with autologous SCT has improved the response rate and survival among patients with MM. Long-term disease-free survival or cure is still an elusive goal for the majority of autograft patients. Strategies that may increase the cure rate include targeted radiation, tandem transplantation or posttransplantation vaccines, and immune stimulation.

One probable reason for the high TRM after allografting in the treatment of patients with MM may be related to the primary immunodeficiency in this disease. Thus improved sources of stem cells such as PBSC, use of which results in earlier engraftment and immune reconstitution [61], should reduce the rate of infectious complications.

Future studies of allogeneic marrow transplantation for MM should focus on regimens, such as radioisotopes linked to bone-seeking chelates, that are less toxic but are able to preserve antitumor effects [11,16]. Studies with low-intensity, nonablative regimens appear to show effective reduction of early complications and mortality for allogeneic transplantation while retaining GVM effects sufficient to induce remission. Such treatments could be combined with infusions of allogeneic donor lymphocytes or subsets of lymphocytes in the form of "engineered grafts," such as CD4 lymphocytes, which may have a GVM effect without increasing the rate of GVHD [44]. The tandem autologous, reduced-intensity allogeneic transplantation regimen looks very promising in terms of low mortality and high response rates. Longer follow-up is needed to determine whether these remissions are durable. Randomized trials will likely be required to determine the relative benefits of these treatments compared with those of autologous transplantation.

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References

1. Buckner CD, Fefer A, Bensinger WI, et al. Marrow transplantation for malignant plasma cell disorders: summary of the Seattle Experience. *Eur J Haematol.* 1989;43(suppl 51):186-190.
2. Gahrton G, Svensson H, Björkstrand B, et al. Syngeneic transplantation in multiple myeloma: a case-matched comparison with autologous and allogeneic transplantation. *Bone Marrow Transplant.* 1999;24:741-745.
3. Bensinger WI, Demirer T, Buckner CD, et al. Syngeneic marrow transplantation in patients with multiple myeloma. *Bone Marrow Transplant.* 1996;18:527-531.
4. McElwain TJ, Powles RL. High-dose intravenous melphalan for plasma cell leukaemia and myeloma. *Lancet.* 1983;1:822-824.
5. Tricot G, Vesole DH, Jagannath S, Hilton J, Munshi N, Barlogie B. Graft-versus-myeloma effect: proof of principle. *Blood.* 1996;87: 1196-1198.
6. Verdonck LF, Lokhorst HM, Dekker AW, Nieuwenhuis HK, Petersen EJ. Graft-versus-myeloma effect in two cases. *Lancet.* 1996;347:800-801.
7. Aschan J, Lonnqvist B, Ringden O, Kumlien G, Gahrton G. Graft-versus-myeloma effect [letter]. *Lancet.* 1996;348:346.
8. Attal M, Harousseau J-L, Stoppa A-M, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. *N Engl J Med.* 1996;335:91-97.
9. Attal M, Harousseau JL, Stoppa AM, et al. High dose therapy in multiple myeloma: an updated analysis of the IFM 90 protocol [abstract]. *Blood.* 1998;92(suppl 1):418a. Abstract 1858.
10. Morgan GJ, Davies FE, Hawkins K, et al. The MRC myeloma VII trial of standard versus intensive treatment in patients <65 years of age with multiple myeloma [abstract]. *Blood.* 2002;100:178a. Abstract 668.
11. Macfarlane DJ, Durrant S, Bartlett ML, Allison R, Morton AJ. 153Sm EDTMP for bone marrow ablation prior to stem cell transplantation for haematological malignancies. *Nucl Med Commun.* 2002;23:1099-1106.
12. Rasmussen T, Bjorkstrand B, Andersen H, Gaarsdal E, Johnsen HE. Efficacy and safety of CD34-selected and CD19-depleted autografting in multiple myeloma patients: a pilot study. *Exp Hematol.* 2002;30:82-88.
13. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m^2 melphalan and 8 Gy total body irradiation plus 140 mg/m^2 melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. *Blood.* 2002;99:731-735.
14. Attal M, Harousseau J-L, Facon T, et al. Double autologous transplantation improves survival of multiple myeloma patients: final analysis of a prospective randomized study of the "Intergroupe Francophone du Myélome" (IFM 94) [abstract]. *Blood.* 2002;100: 5a. Abstract 7.
15. Cavo M, Tosi P, Zamagni E, et al. The "Bologna 96" clinical trial of single vs. double autotransplants for previously untreated multiple myeloma patients [abstract]. *Blood.* 2002;100:179a. Abstract 669.
16. Giralt S, Bensinger W, Goodman M, et al. Long-term follow-up of 83 patients with multiple myeloma (MM) treated on a phase I-II study of skeletal targeted radiotherapy (STR) using ^{166}Ho-DOTMP plus melphalan with or without total body irradiation (TBI) and autologous hematopoietic stem cell transplant (AHSCT) [abstract]. *Blood.* 2002;179a. Abstract 670.
17. Fermand J-P, Ravaud P, Chevret S, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. *Blood.* 1998;92:3131-3136.
18. Massaia M, Borrione P, Battaglio S, et al. Idiotype vaccination in human myeloma: generation of tumor-specific immune responses after high-dose chemotherapy. *Blood.* 1999;94:673-683.
19. Lim SH, Bailey-Wood R. Idiotypic protein-pulsed dendritic cell vaccination in multiple myeloma. *Int J Cancer.* 1999;83:215-222.
20. Cull G, Durrant L, Stainer C, Haynes A, Russell N. Generation of anti-idiotype immune responses following vaccination with idiotype-protein pulsed dendritic cells in myeloma. *Br J Haematol.* 1999;107:648-655.
21. Titzer S, Christensen O, Manzke O, et al. Vaccination of multiple myeloma patients with idiotype-pulsed dendritic cells: immunological and clinical aspects. *Br J Haematol.* 2000;108:805-816.
22. Chiriva-Internati M, Wang Z, Salati E, Bumm K, Barlogie B, Lim SH. Sperm protein 17 (Sp17) is a suitable target for immunotherapy of multiple myeloma. *Blood.* 2002;100:961-965.
23. Gahrton G, Svensson H, Cavo M, et al. Progress in allogeneic bone marrow and peripheral blood stem cell transplantation for multiple myeloma: a comparison between transplants performed 1983-93 and 1994-98 at European Group for Blood and Marrow Transplantation centres. *Br J Haematol.* 2001;113:209-216.
24. Bensinger WI, Buckner CD, Anasetti C, et al. Allogeneic marrow transplantation for multiple myeloma: an analysis of risk factors on outcome. *Blood.* 1996;88:2787-2793.
25. Roberts RT. Usefulness of immunofixation electrophoresis in the clinical laboratory. *Clin Lab Med.* 1986;6:601-605.
26. Bladé J, Samson D, Reece D, et al. Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. *Br J Haematol.* 1998;102: 1115-1123.
27. Ludwig H, Fruhwald F, Tscholakoff D, Rasoul S, Neuhold A, Fritz E. Magnetic resonance imaging of the spine in multiple myeloma. *Lancet.* 1987;2:364-366.
28. Laroche M, Assoun J, Sixou L, Attal M. Comparison of MRI and computed tomography in the various stages of plasma disorders: correlations with biological and histological findings. Myeloma-Midi-Pyrenees Group. *Clin Exp Rheumatol.* 1996;14:171-176.
29. Billadeau D, Blackstadt M, Greipp P, et al. Analysis of B-lymphoid malignancies using allele-specific polymerase chain reaction: a technique for sequential quantitation of residual disease. *Blood.* 1991;78:3021-3029.
30. Bird JM, Russell NH, Samson D. Minimal residual disease after bone marrow transplantation for multiple myeloma: evidence for cure in long-term survivors. *Bone Marrow Transplant.* 1993;12: 651-654.
31. Martinelli G, Terragna C, Zamagni E, et al. Molecular remission after allogeneic or autologous transplantation of hematopoietic stem cells for multiple myeloma. *J Clin Oncol.* 2000;18:2273-2281.
32. Cavo M, Terragna C, Martinelli G, et al. Molecular monitoring of minimal residual disease in patients in long-term complete remission after allogeneic stem cell transplantation for multiple myeloma. *Blood.* 2000;96:355-357.
33. Corradini P, Voena C, Tarella C, et al. Molecular and clinical remissions in multiple myeloma: role of autologous and allogeneic transplantation of hematopoietic cells. *J Clin Oncol.* 1999;17: 208-215.
34. Alyea EP, Weller E, Schlossman RL, et al. Comparison of autologous and allogeneic stem cell transplantation in patients with multiple myeloma (MM): impact of graft versus myeloma (GVM) on relapse [abstract]. *Blood.* 2001;98:482a. Abstract 2014.
35. Lokhorst HM, Segeren CM, Holt B, et al. T-cell depleted allogeneic stem cell transplantation as part of first line treatment of multiple myeloma is inferior to intensive treatment alone: results from a prospective donor versus no donor comparison of patients treated in the HOVON 24 study [abstract]. *Blood.* 2001;98:481a. Abstract 2008.

36. Schaap N, Schattenberg A, Bär B, Preijers F, van de Wiel van Kemenade E, De Witte T. Induction of graft-versus-leukemia to prevent relapse after partially lymphocyte-depleted allogeneic bone marrow transplantation by pre-emptive donor leukocyte infusions. *Leukemia.* 2001;15:1339-1346.
37. Le Blanc R, Montminy-Métivier S, Bélanger R, et al. Allogeneic transplantation for multiple myeloma: further evidence for a GVHD-associated graft-versus-myeloma effect. *Bone Marrow Transplant.* 2001;28:841-848.
38. Libura J, Hoffmann T, Passweg J, et al. Graft-versus-myeloma after withdrawal of immunosuppression following allogeneic peripheral stem cell transplantation. *Bone Marrow Transplant.* 1999;24: 925-927.
39. Bertz H, Burger JA, Kunzmann R, Mertelsmann R, Finke J. Adoptive immunotherapy for relapsed multiple myeloma after allogeneic bone marrow transplantation (BMT): evidence for a graft-versus-myeloma effect. *Leukemia.* 1997;11:281-283.
40. Salama M, Nevill T, Marcellus D, et al. Donor leukocyte infusions for multiple myeloma. *Bone Marrow Transplant.* 2000;26: 1179-1184.
41. Collins RH Jr, Shpilberg O, Drobyski WR, et al. Donor leukocyte infusions in 140 patients with relapsed malignancy after allogeneic bone marrow transplantation. *J Clin Oncol.* 1997;15:433-444.
42. Alyea E, Ritz J. Induction of graft versus myeloma by donor lymphocyte infusions following allogeneic bone marrow transplant. In: Anderson KC, ed. Syllabus of the VI International Workshop on Multiple Myeloma 1997; June 14-18, 1997; Boston, Mass, USA.
43. Mehta J, Singhal S. Graft-versus-myeloma [review]. *Bone Marrow Transplant.* 1998;22:835-843.
44. Champlin R, Giralt S, Gajewski J, Hester J, Körbling M, Deisseroth A. CD8 depleted donor lymphocytes for CML relapsing post BMT. *Exp Hematol.* 1995;23:939.
45. Molina A, Sahebi F, Maloney DG, et al. Non-myeloablative peripheral blood stem cell (PBSC) allografts following cytoreductive autotransplants for treatment of multiple myeloma (MM) [abstract]. *Blood.* 2000;96:480a. Abstract 2063
46. Badros A, Barlogie B, Cottler-Fox M, et al. Improved outcome of allogeneic transplants in high risk multiple myeloma (MM) patients (pts) following non-myeloablative conditioning [abstract]. *Blood.* 2001;98:414a. Abstract 1738.
47. Alyea E, Weller E, Schlossman R, et al. T-cell–depleted allogeneic bone marrow transplantation followed by donor lymphocyte infusion in patients with multiple myeloma: induction of graft-versus-myeloma effect. *Blood.* 2001;98:934-939.
48. Bensinger WI, Buckner CD, Shannon-Dorcy K, et al. Transplantation of allogeneic CD34+ peripheral blood stem cells in patients with advanced hematologic malignancy. *Blood.* 1996;88:4132-4138.
49. Bensinger WI, Clift R, Martin P, et al. Allogeneic peripheral blood stem cell transplantation in patients with advanced hematologic malignancies: a retrospective comparison with marrow transplantation. *Blood.* 1996;88:2794-2800.
50. Majolino I, Corradini P, Scimè R, et al. Allogeneic transplantation of unmanipulated peripheral blood stem cells in patients with multiple myeloma. *Bone Marrow Transplant.* 1998;22: 449-455.
51. Majolino I, Corradini P, Santoro A, et al. In multiple myeloma (MM) allogeneic PBSC transplantation results in high rate of remission and low rate of recurrence [abstract]. *Blood.* 2001;98: 419a. Abstract 1757.
52. Russell N, Bessell E, Stainer C, Haynes A, Das-Gupta E, Byrne J. Allogeneic haemopoietic stem cell transplantation for multiple myeloma or plasma cell leukaemia using fractionated total body radiation and high-dose melphalan conditioning. *Acta Oncol.* 2000; 39:837-841.
53. Storb R, Yu C, Sandmaier B, et al. Mixed hematopoietic chimerism after hematopoietic stem cell allografts. *Transplant Proc.* 1999;31: 677-678.
54. McSweeney PA, Niederwieser D, Shizuru JA, et al. Hematopoietic cell transplantation in older patients with hematologic malignancies: replacing high-dose cytotoxic therapy with graft-versus-tumor effects. *Blood.* 2001;97:3390-3400.
55. Maloney DG, Sahebi F, Stockerl-Goldstein KE, et al. Combining an allogeneic graft-vs-myeloma effect with high-dose autologous stem cell rescue in the treatment of multiple myeloma [abstract]. *Blood.* 2001;98:434a-435a. Abstract 1822.
56. Badros A, Barlogie B, Siegel E, et al. Improved outcome of allogeneic transplantation in high-risk multiple myeloma patients after nonmyeloablative conditioning. *J Clin Oncol.* 2002;20:1295-1303.
57. Kröger N, Schwerdtfeger R, Kiehl M, et al. Autologous stem cell transplantation followed by a dose-reduced allograft induces high complete remission rate in multiple myeloma. *Blood.* 2002;100: 755-760.
58. Kröger N, Sayer HG, Schwerdtfeger R, et al. Unrelated stem cell transplantation in multiple myeloma after a reduced-intensity conditioning with pretransplantation antithymocyte globulin is highly effective with low transplantation-related mortality. *Blood.* 2002; 100:3919-3924.
59. Hoepfner S, Probst SM, Breitkreutz I, et al. Non-myeloablative allogeneic transplantation as part of salvage therapy for relapse of multiple myeloma after autologous transplantation [abstract]. *Blood.* 2002;100:859a. Abstract 3387.
60. Einsele H, Schäfer HJ, Bader P, et al. Allografts after reduced intensity conditioning can induce long-term remission in patients with chemosensitive relapsed multiple myeloma (MM) [abstract]. *Blood.* 2002;100:635a. Abstract 2499.
61. Bensinger WI, Martin PJ, Storer B, et al. Transplantation of bone marrow as compared with peripheral-blood cells from HLA-identical relatives in patients with hematologic cancers. *N Engl J Med.* 2001;344:175-181.