VOLUME 28 · NUMBER 29 · OCTOBER 10 2010

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

International Myeloma Working Group Consensus Statement Regarding the Current Status of Allogeneic Stem-Cell Transplantation for Multiple Myeloma

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Submitted April 16, 2010; accepted June 16, 2010; published online ahead of print at www.jco.org on August 9, 2010.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/10/2829-4521/$20.00

DOI: 10.1200/JCO.2010.29.7929

ABSTRACT

Purpose
To define consensus statement regarding allogeneic stem-cell transplantation (Allo-SCT) as a treatment option for multiple myeloma (MM) on behalf of International Myeloma Working Group.

Patients and Methods
In this review, results from prospective and retrospective studies of Allo-SCT in MM are summarized.

Results
Although the introduction of reduced-intensity conditioning (RIC) has lowered the high treatment-related mortality associated with myeloablative conditioning, convincing evidence is lacking that Allo-RIC improves the survival compared with autologous stem-cell transplantation.

Conclusion
New strategies are necessary to make Allo-SCT safer and more effective for patients with MM. Until this is achieved, Allo-RIC in myeloma should only be recommended in the context of clinical trials.

J Clin Oncol 28:4521-4530. © 2010 by American Society of Clinical Oncology

INTRODUCTION

The survival of patients with multiple myeloma (MM) has improved over the past decade. [1-7] Patients with standard risk factors (absence of t(4;14), t(14;16), 17p−) are projected to live for 7 to 10 years with good quality of life.[8,9] Despite these new developments, however, myeloma remains incurable for the vast majority of patients. Allogeneic stem-cell transplantation (Allo-SCT) is a treatment with a curative potential for myeloma. This is in part due to the graft-versus-myeloma effect (GVM), at best illustrated by the induction of sustained (molecular) remissions after donor lymphocyte infusions (DLIs), and may also be due in part to absence of contaminating myeloma cells in the donor graft.[10-12]

The role of Allo-SCT in myeloma, however, is debated due to the high mortality and morbidity while convincing evidence for a survival benefit is lacking. This review summarizes the data from prospective and retrospective studies of Allo-SCT in myeloma, but also aims to provide suggestions for new safer approaches while preserving the GVM effect.

MYELOABLATIVE CONDITIONING

Early data on myeloablative conditioning can be extracted from the transplant registries: the European Bone Marrow Transplantation (EBMT), International Bone Marrow Transplantation Registry (IBMTR), and the Hutchinson Cancer Center registries.[13-16]

Interpretation of these heterogeneous early data is difficult as the reported patients were not treated in prospective trials; many patients had received several lines of previous chemotherapy, were chemotherapy resistant at the time of transplant, and received a variety of conditioning and graft-versus-host disease (GVHD) prophylaxis regimens. A most consistent finding, however, was high treatment-related mortality (TRM) particularly in patients who were heavily pretreated with chemotherapy-resistant disease. Early TRM in the EBMT report was approximately 45%,[14,15] with deaths due mainly to infection, GVHD, and regimen-related toxicities. Early TRM in the IBMTR report of 265 patients who received transplantation between 1981 and 1991 was 40% and early TRM

reported by the Hutchinson Center was 49% for patients predominantly with chemotherapy-resistant disease.[17]

Actuarial survivals for the EBMT-registered patients was 28% at 7 years,[15] for the Hutchinson Center–registered patients, it was 21% at 5 years, and for the IBMTR, the probabilities of survival at 4 years were 35% for patients with Karnofsky performance scores higher than 70 pretransplantation and approximately 15% for patients with scores lower than 70. Thus, due to the exceedingly high TRM, myeloablative Allo-SCT were largely abandoned worldwide in the 1990s. In patients who survived the procedure and achieved a complete response (CR) after the Allo-SCT, there were apparent plateaus in relapse-free survival (RFS) curves. In the EBMT registry, RFS at 6 years for the patients entering CR was 34%, and for the CR patients reported by the Hutchinson Center, the RFS at 5 years was 39%. The US Intergroup trial (S9321) demonstrated a progression-free survival (PFS) plateau of approximately 22% at 7 years in the 36 patients undergoing Allo-SCT, which was higher compared to the 7-year PFS of patients in the trial who received autologous stem-cell transplantation (Auto-SCT).[18] These long-term remission durations were observed almost exclusively in patients treated within 1 year of diagnosis, after a single line of therapy, and with chemotherapy-sensitive disease.

The EBMT compared 334 patients who received transplants between 1983 and 1993 and 356 patients who received transplants between 1994 and 1998.[19] The most important observation was a marked reduction in TRM from 46% to 30% at 2 years between the two time periods. The median overall survival (OS) for the later transplants was 50 months although without a plateau in PFS and OS curves. Regardless, the transplant-related mortality of 30% was still deemed unacceptably high.

COMPARISON OF AUTOLOGOUS AND MYELOABLATIVE ALLOGENEIC TRANSPLANTS

The EBMT performed a retrospective, case-matched comparison of Auto-SCT and Allo-SCT in 1996.[20] The median survival of 34 months was superior for autologous recipients versus 18 months for the Allo-SCT recipients. This was due to a higher TRM of 41% versus 13%, respectively. There was a trend, however, for better survival in the allogeneic patients surviving at 1 year ($P = .09$).

Two prospective trials have compared autologous with myeloablative Allo-SCT. The US Intergroup trial (S9321) of early versus late Auto-SCT had a third option that allowed patients with matched siblings (younger than age 55) to undergo Allo-SCT using an ablative regimen of melphalan and total-body irradiation (TBI).[18] This arm of the study was closed after 36 patients were treated, due to excessively high TRM of 53%. After 7 years of follow-up, however, the OS rates were identical at 39% for both autologous and allogeneic recipients, while the PFS were 15% for autologous recipients compared with 22% for allogeneic recipients. In addition, while the risk of relapse and death continues in the groups that received autologous SCT, the OS curve for the allogeneic group has reached a plateau with follow-up extending to 10 years.

The Haemato Oncology Foundation for Adults in the Netherlands (HOVON) 24 study was designed to compare Auto-SCT with semi-intensive treatment; however, patients with an HLA-identical sibling donor could proceed to a partially T-cell–depleted myeloablative Allo-SCT after cyclophosphamide/TBI conditioning. [21] Even as part of first-line therapy, TRM of the Allo-SCT patients exceeded 30% while PFS and OS were inferior to the matched group of patients receiving only autologous SCT.

Taken together, these data suggest that myeloablative Allo-SCT is a potentially curative treatment for MM based on the achievement of sustained CRs in a subpopulation of patients.[22] However, due to the high TRM, even when applied as part of first-line therapy, myeloablative transplants are a much less attractive option for patients with MM who may live 5 to 10 years when treated with induction therapy followed by Auto-SCT.

REDUCED INTENSITY CONDITIONING

The promising results of reduced-intensity conditioning (RIC) transplantation in low-grade lymphoproliferative disorders renewed the interest in Allo-SCT as a treatment option for MM. The pioneering studies were performed by the Seattle group who showed that donor engraftment could be achieved with the combination of low-dose TBI (2 Gy) plus fludarabine combined with the immune suppressive drugs cyclosporine and mycophenolate mofetil.[23] They also introduced the strategy of an autologous transplantation followed 2 to 4 months later by a RIC allograft. When the reduced intensity allograft followed shortly after the autograft, graft rejections were not observed even without the use of fludarabine.[24] In 52 patients treated with this tandem modality, a CR was achieved in 48% of patients and PFS and OS at 48 months were 48% and 69%, respectively. The same concept was piloted by Kroger et al[25] using melphalan, fludarabine, and antithymocyte globulin (ATG) with related and unrelated donors. Two large series from Seattle and Italy have recently updated reports on more than 200 patients using the tandem auto/allo strategy. In the Seattle update, 102 patients received this treatment strategy with Allo-SCT from matched-related donors.[26] The overall TRM was 18% at 1 year and the CR rate was 62%. Chronic GVHD developed in 74%. With a median follow-up of 6.3 years the OS was 64% and PFS of 36%. In a very similar approach, an Italian consortium reported on 100 newly diagnosed patients who received vincristine, doxorubicin, and dexamethasone–based induction followed by high-dose melphalan with Auto-SCT, followed by a RIC Allo-SCT from an HLA identical sibling.[27] The CR rate was 53%; the incidence of acute $\geq$ grade 2 and chronic GVHD were 38% and 50%, respectively. With a median follow-up of 5 years, median OS was not reached while EFS was 3 years. In multivariate analysis, disease in remission at Allo-SCT was significantly associated with longer OS and EFS, while immunoglobulin isotype, International Staging System, and a comorbidity index 3 or higher had no impact on outcome. Unfortunately, neither of these studies has shown a plateau in EFS, even in patients with chronic GVHD.

After introduction of the Seattle regimen, a wide variety of conditioning and GVHD prophylaxis regimens were pioneered in MM. Conditioning regimens included fludarabine combined with either melphalan in different dosages (100 to 180 mg/m^2), cyclophosphamide, low-dose busulfan or thiothepa, with or without TBI. Some regimens included ATG or alemtuzumab to facilitate engraftment and reduce GVHD (Table 1[26-35]). In a recent review of the EBMT registry, 26 different conditioning schemes with and without T-cell depletion in 229 patients were identified.[36] Eighty percent of patients received transplants with peripheral blood stem cells. Acute GVHD grades 2 to 4 occurred in 31% of patients and extensive chronic GVHD was reported in 25%. Although the TRM was low at 22%, the 3-year OS and PFS were disappointing at 41% and 21%, respectively. The best outcome after RIC was for those patients who received transplants in

Table 1. Phase II Trials of Reduced Intensity Allogeneic Transplantation From Related and Unrelated Donors With or Without a Planned Prior Autologous Transplant for the Treatment of Multiple Myeloma

Reference	No.		Regimen	No. Planned Prior Autologous Transplant	GVHD Prophylaxis	%					
	Total Patients	From Matched Unrelated Donors				Graft Chim	AGVHD, 2-4	CGVH	TRM	CR	Survival at (year)
Rotta[26]	102	0	Total-body irradiation 12 Gy, ± fludarabine	102	Cyclosporine Tacrolimus Mycophenolic acid	100	42	74	18	62	64 (5)
Bruno[27]	100	0	Total-body irradiation 2 Gy	96	Cyclosporine Mycophenolic acid	97	38	50	11	53	65 (5)
Lee[28]	45*	12	High-dose melphalan 100 (total-body irradiation 2 Gy, fludarabine)	12	Cyclosporine	89	58	13	38	64	36 (3) 86t
Gerull[29]	52	20	Total-body irradiation 2 Gy, fludarabine	0	Cyclosporine Mycophenolic acid	90	37	70	17	27	41 (1,5)
Mohty[30]	41		Busulfan, fludarabine, antithymocyte globulin	0	Cyclosporine Methotrexate (13)	98	36	41	17	24	62 (2)
Kroger[31]	49	49	High-dose melphalan 140, fludarabine, antithymocyte globulin	NR	Cyclosporine Methotrexate	NR	25	35	25	49	26 (5)
Majolino[32]	53	0	Thiotepa, fludarabine, melphanan	NR	Cyclosporine Methotrexate	80	45	64	13	62	45 (3)
Van Dorp[33]	59	16	Total-body irradiation 2 Gy, ± fludarabine, ± antithymocyte globulin	36	Cyclosporine Mycophenolic acid	95	44	54	9	32	82 (2)
Vesole[34]	23	0	Fludarabine Cyclophosphamide	23	Cyclosporine Steroid		17 (> 3)	39	9	33	78 (2)
Einsele[35]	22	15	Total-body irradiation 2 Gy, fludarabine, cyclophosphamide	0	Antithymocyte globulin Cyclosporine Mycophenolic acid	NR	38	32	23	27	26 (2)

Abbreviations: GVHD, graft-versus-host-disease; AGVHD, acute graft-versus-host disease; CGVH, chronic graft-versus-host-disease; TRM, transplant-related mortality rate; CR, complete response rate; NR, not reported.
*Fourteen patients given donor lymphocyte infusion.

first remission with fewer than two previous Auto-SCT. Alemtuzumab for conditioning was an adverse risk factors for TRM, PFS, and OS. Post-transplantation factors for prolonged PFS were achievement of CR and the occurrence of chronic GVHD.

However, due to the heterogeneity of the patient populations, study, and registration designs, no definite conclusions could be drawn which of these regimens was superior in terms of toxicity or efficacy or even whether Allo-RIC was of benefit.

COMPARISONS OF ABLATIVE AND NONABLATIVE ALLOGRAFT

The EBMT has retrospectively compared RIC with standard ablative conditioning for Allo-SCT in MM.[37] Between 1998 and 2002, 196 patients conditioned with ablative regimens were compared with 320 patients undergoing RIC. TRM was significantly lower for the reduced-intensity group ($P = .001$). However, there was no statistical difference in OS between the two groups. Furthermore, PFS was inferior for patients receiving RIC ($P = .009$) due to a doubling of the relapse rate in the RIC group (54% *v* 27%; $P < .001$). The CIBMTR has done a comparable analysis.[38] A total of 1,211 patients undergoing Allo-SCT for MM between 1989 and 2005 were analyzed in three cohorts based on year of Allo-SCT: 1989 to 1994 (n = 346), 1995 to 2000 (n = 285), and 2001 to 2005 (n = 580). There was decreasing use of myeloablative regimens and bone marrow grafts over time (82% *v* 62% *v* 9% for myeloablative regimens and 99%, 62% and 13% for marrow grafts, respectively). Although the TRM at 5 years decreased in the last period (40% and 48% *v* 29%), the OS at 5 years was similar among the groups (30, 32, and 29 months), primarily because of increased risk of relapse in the latter cohort.

PROSPECTIVE STUDIES OF RIC ALLO-SCT AS PART OF FIRST-LINE THERAPY

One way to measure the value of Allo-SCT is to prospectively compare an Auto/Allo-SCT treatment with a tandem Auto-SCT. It is widely accepted that a biologic randomization approach for Allo-SCT based on the availability of an HLA-identical sibling donor is a reliable surrogate. Three studies comparing tandem Auto/Allo-SCT with double Auto-SCT in MM have been published utilizing this biologic randomization concept.

The French Study

In the French study, patients with an HLA-identical sibling donor and high-risk MM defined by beta-2 microglobulin (β-2 M) higher than 3 mg/L and deletion of chromosome 13 (13q−; by fluorescent in situ hybridization [FISH]) were candidates for Auto-SCT followed by RIC Allo-SCT with a conditioning regimen consisting of busulfan, fludarabine, and ATG.[39] Patients without a sibling donor

were treated with double Auto-SCT using melphalan 220 mg/m^2 for the second autologous transplant with or without anti-interleukin 6 monoclonal antibody therapy. Utilizing an intent-to-treat analysis, with a median follow-up of 56 months, no difference in EFS was observed.[40] Nevertheless, there was a trend for a superior OS in the double Auto-SCT trial (median 48 *v* 34 months, $P = .07$). Also, when the analysis was restricted to the patients who completed the planned tandem transplants, a trend toward improved OS was observed with the tandem Auto-SCT (median OS, 57 *v* 41 months, $P = .08$), due to a longer survival after relapse in the tandem auto-SCT arm. This study was criticized for the inclusion of high-dose ATG 12.5 mg/kg in the conditioning regimen that might have negatively influenced the desired GVM effect as measured by a relatively low CR rate of 23%.[41]

The Spanish PETHEMA Study

The Spanish PETHEMA found a trend for better PFS ($P = .08$), but did not observe a difference in EFS and OS between 85 patients receiving tandem Auto-SCT compared with 25 patients treated with Auto/Allo-SCT, although higher CR rates after the Allo-SCT, were achieved (40% *v* 11%; $P = .001$).[42] Complicating the interpretation of this study is the treatment schema which included only patients not in CR or near CR after the first Auto-SCT proceeded to the second transplant and the number or patients who actually completed both planned transplants was small. However, the authors noted a plateau in PFS for the 36% of patients in CR after the Allo-SCT.

The Italian Study Group

More positive results were published by Bruno et al.[43] In that study, 82 patients with an HLA-identical sibling donor assigned to be treated with Auto/Allo-SCT (conditioning low-dose TBI only) achieved higher CR and significantly longer PFS and OS as compared to the 80 patients assigned to the tandem Auto-SCT arm. After the second transplant, CR rates were 55% versus 26% ($P = .004$), median PFS durations were 36 versus 29 months ($P = .02$), and OS durations were 80 versus 54 months ($P = .01$), respectively. The TRM was only 11%. Critics of the study cited that only 58 and 46 patients in the Auto/Allo-SCT and double Auto-SCT, respectively, completed their assigned treatments and the relatively poor outcome of the patients assigned to the tandem Auto-SCT.[44] OS of the Auto-SCT patients in the Bruno et al study was only a median of 48 months compared to the more than 60 months in all the recently published prospective phase III auto-transplant studies[2-6] especially in the arms that included thalidomide.

HOVON, EBMT, and Blood and Marrow Transplant Clinical Trials Network

A more definite conclusion about the role of Allo-SCT in MM may come from three other prospective donor versus no donor studies with larger groups of patients that were performed in the United States, the Dutch HOVON,[45] and the EBMT.[46] The large US multicenter trial from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN) comparing tandem Auto-SCT with Auto/Allo-SCT completed the targeted accrual in March 2007 with more than 150 patients biologically randomly assigned to the Auto/Allo-SCT group. The results from this study are anticipated to be released in 2010.

In the HOVON 54 study, patients with an HLA-identical sibling donor included in the HOVON 50 study (phase III study for the evaluation of thalidomide combined with HDM) could proceed to RIC Allo-SCT between 2 and 6 months after Auto-SCT, while the other patients were assigned to thalidomide or interferon maintenance after the first Auto-SCT. On the basis of an intention-to-treat analysis, no difference in PFS and OS were found during an interim analysis that included 126 patients with a donor and 141 patients without a donor. In the EBMT study, PFS at 60 months was 35% for Auto/Allo-SCT compared with 18% for tandem Auto-SCT and OS 65% and 57%, respectively. This trend for improvement was seen in patients with both deletion 13 and nondeletion 13. In both the HOVON as in the EBMT study, the OS of the Auto-SCT group was better compared with the Bruno et al study, which might explain why the outcome of the Bruno et al study was more positive. The final analyses of the HOVON and of the EBMT study are expected in 2010.

German DSMMM

German DSMMM has performed a prospective study comparing double Auto-SCT (HDM200) with Auto/Allo-SCT (fludarabine/melphalan).[47] Inclusion was restricted to newly diagnosed patients with of deletion 13q14 as determined by FISH. Allocation to either treatment arm was by availability of an HLA-matched (one mismatch allowed) sibling or matched unrelated donor (MUD). ATG was added to the conditioning in case of a MUD donor. Preliminary analysis showed a higher CR rate in FISH 13q− subjects undergoing Allo-SCT when compared to tandem Auto-SCT (59% *v* 32%; $P = .003$). However, the projected OS at 3 years was 70% for double Auto-SCT versus 60% for the Auto/Allo-SCT patients ($P = .22$). TRM at 2 years from Allo-SCT was only 12.7% even though 60% received MUD Allo-SCT. Table 2 summarizes the prospective comparative studies of RIC Allo-SCT. Taken together from these prospective studies, it should be concluded that convincing evidence is lacking that Allo-RIC induces durable remissions of better quality as compared to Auto-SCT. This may become even more clear now that novel agents are given as post-transplantation therapy as demonstrated by the higher and sustained molecular remission rate after Auto-SCT than previously reported when a regimen of bortezomib, thalidomide, and dexamethasone is given as consolidation therapy.[48]

ALLO-SCT IN HIGH-RISK MYELOMA

Before the incorporation of novel therapies into pre- and postautologous transplantation regimens, the outcome of patients with poor prognostic features defined by cytogenetics (t4;14; t14;16; 17p−) were universally dismal.[8,9] Whereas thalidomide does not appear to be able to improve outcomes in these high-risk patients,[5] there is increasing evidence that bortezomib-based regimens are capable of overcoming at least some of the adverse prognostic outcomes (eg, t(4;14)).[49,50]

It was hoped that the use of Allo-SCT, through a donor-mediated GVM effect would also be capable of eradicating any residual clonal MM cells with these poor prognostic constitution. The older literature reporting conventional myeloablative allogeneic transplantation did not discern between risk groups determined by cytogenetics.[19,36] In these studies, the high-risk patients

Table 2. Comparison Trials of Tandem Autologous Transplant With Autologous + Reduced Intensity Allografting

Regimen	No.	TRM (%)	Response (%)		DFS		OS	
			CR	VGPR	%	Follow-Up Year	%	Follow-Up Year
Garban[36a]								
Auto Mel 200/220	219	5	33	18	0	5	44	5
Auto Mel 200	65[b]	11	33	29	0	5	33	5
Allo Bu, Flu, ATG								
Bruno[40]								
Auto Mel 200	80[c]	4	26	NR	20	4	53	4
Auto Mel 200	82[d]	10	55	NR	42[e]	4	75[e]	4
Allo 2 Gy TBI, *P*		< .001	.004		.01		.02	
Rosignol[37f]								
Auto Bu Mel-Mel, CBV	88	5	11	6	Med 26 months		Med 57 months	
Auto Bu Mel-Mel	26	16	33	NR	Med 19 months		Med not reached	
Allo Flu Mel 140								
Lokhorst[42]								
Auto Mel 200/IFN or Thal maintenance	141	NR	42	NR	Med 30 months		Med 60 months	
Auto Mel 200	126	14	45	NR	Med 30 months		Med 50 months	
Allo 2 Gy TBI								
Bjorkstrand[43]								
Auto Mel 200	251	5	38	NR	18	4	57	5
Auto Mel 200	107	13	43	NR	35	4	65	5
Allo 2 Gy TBI								
Knop[44g]								
Auto Mel 200	73	NR	32	NR	NR		70	3
Auto Mel 200	126	16	59	NR	NR		60	3
Allo Flu Mel 140 ± ATG[h]								

Abbreviations: TRM, transplant-related mortality; DFS, disease-free survival; OS, overall survival; CR, complete remission; VGPR, very good partial remission; Auto, autologous stem-cell transplantation; Mel, melphalan; Allo, allogeneic stem-cell transplantation; Bu, busulphan; Flu, fludarabin; ATG, antithymoglobulin; NR, not reported; TBI, total-body irradiation; CBV, cyclophosphamide, carmustine, and etoposide; Med, median; IFN, interferon; Thal, thalidomide; FISH, fluorescent in situ hybridization.

[a]High-risk patients with elevated B-2 M and deletion 13 by FISH.
[b]Nineteen of 65 patients did not receive the reduced intensity allograft.
[c]Forty-six of 80 patients completed the tandem autograft.
[d]Fifty-eight of 82 patients received the reduced intensity allograft.
[e]Statistically significant.
[f]ATG was added to the conditioning regimen in case of unrelated donor.
[g]High-risk patients with deletion 13 by FISH.
[h]Only patients not in CR after autograft 1 proceeded to second autograft or RIC allograft.

were defined by disease status at transplantation, number of prior therapies, time to transplantation, and sex match. Chromosome 13 deletions by FISH were previously considered a poor prognostic factor.[51-55] However, since it is detected in more than 50% of patients, it no longer considered as predictive of a negative outcome except when it is associated with t(4;14).[56,57] Regardless, Kroger et al[58] retrospectively reported their outcomes in 31 patients with del13q14 in comparison with 37 patients without this deletion treated identically. Response rates and TRM were comparable between the groups. However, at 2 years they observed a significantly shorter EFS (18% *v* 42%), OS (18% *v* 67%) in patients with del(13) due to significantly higher relapse rates in the del(13) patients (77% *v* 44%). As mentioned earlier, in the Intergroupe Française Myeloma, study patients with high-risk disease, defined as β-2 M higher than 3 mg/L and chromosome 13 deletion (by FISH), did not benefit from Auto/Allo-SCT as compared with the patients who were treated with double Auto-SCT. Schilling et al[59] reported their retrospective observations in 101 patients undergoing reduced-intensity transplantations with a variety of cytogenetics abnormalities: 61% with del(13q14), 19% with t(4;14)(p16.3;q32), 16% with del(17p13), and 5% with t(14;16)(q32;q23). There were no differences in response rates nor in transplantation-related mortality with the exception that patients with 17p13 deletions had a lower CR rate (7% *v* 56%). In multivariate analyses, age (hazard ratio [HR], 2.8; $P = .01$) and del(17p13) (HR, 2.05; $P = .03$) retained their negative prognostic value. Bruno et al reported their outcomes in 100 patients undergoing Auto/Allo-SCT. For del13, 13 of 39 studied had del13 by FISH. There was no significant difference in OS whereas EFS was better in patients without del(13) (4.3 *v* 2.2 years, $P = .01$).[26] Rotta et al[27] reported the Seattle Consortium experience in 102 patients completing Auto/Allo-SCT that β-2 M higher than 3.5 mg/L was a poor risk factor for relapse, PFS, and OS (HRs, 2.3, 1.98, and 2.87, respectively). Cytogenetic abnormalities, none of which included the high-risk features discussed above, were not predictive of outcome. Given the small number of patients in these various studies, it is uncertain whether reduced-intensity allogeneic transplants can overcome poor risk indicators. However, it is conceivable that in exceptional cases a full Allo-SCT may be considered like in patients with high lactate dehydogenase myeloma younger than 50 years who are aware of their unfavorable prognosis and accept the risks of myeloablative conditioning given the US Intergroup trial (S9321) showing a plateau.

UNDERSTANDING THE MECHANISMS OF GRAFT VERSUS MYELOMA IS OF VITAL IMPORTANCE FOR IMPROVING THE SAFETY AND EFFICACY OF ALLO-SCT

The GVM effect is at best illustrated by the remissions induced by DLI in patients with relapsed or persistent disease after Allo-SCT. Response to DLI and chronic GVHD are highly associated indicating that the targets for GVHD and GVM are similar or identical (ie, minor histocompatibility antigens [mHa]) expressed on patients normal and MM cells.[12,60,61] Susceptibility of malignant plasma cells to the mHa HA-1(H) specific lysis in vitro suggests a role for the mHa HA-1 in the GVM effect.[62]

Clinical support for this concept has been provided by the demonstration that, in a patient with MM who received HLA-matched, mHag-mismatched DLI, achievement of CR was accompanied by the emergence and expansion of HA-1, HA-2, and LB-ADIR-1F–specific cytotoxic T cells in the circulation.[63] However, responses to DLI may occur without GVHD, indicating that tumor-associated antigens may be involved as well, as illustrated by strong antibody responses against cancer testis antigens and MUC-1.[64,65] The relation between GVM and GVHD after Allo-SCT is less clear. Although positively demonstrated in several, mostly retrospective studies,[35,36,60,66] among them one indicating the mHa HY as the target antigen in HLA-identical female-to-male sibling transplants,[67-69] more recent data from the large prospective studies indicate that GVHD is not associated with better outcome from Allo-RIC.[26,27,36,43,46] This intriguing observation should stimulate more in-depth studies to unravel the mechanisms of GVM, which could result in safer strategies with better management of acute and chronic GVHD. New strategies might include targeted T-cell therapy with hematopoietic restricted mHa that can now be easily identified by a recently developed method via genome-wide zygosity-genotype correlation,[70-73] which are seen preferentially in patients with MM who had received Allo-SCT and not in patients with MM treated otherwise.

POTENTIAL ROLE OF NOVEL ANTIMYELOMA AGENTS TO IMPROVE THE GVM EFFECT

Due to their immune modulating capacities, the novel antimyeloma agents might be of therapeutic interest for post–Allo-SCT therapy. This is illustrated by the improved response to DLI by thalidomide apparently without enhancing GVHD.[74] Impressive results were obtained with lenalidomide as salvage therapy in a group of patients with progressive symptomatic disease after Allo-RIC.[75,76] Bortezomib has also been shown to be remarkably effective in patients with relapsed disease after Allo-SCT, without apparent excessive stimulation of GVHD.[77-79]

In a murine BMT model, bortezomib downregulated cytokine production, induced T-cell apoptosis, and prevented GVHD, while the graft-versus-tumor effects were preserved. Nonetheless, delayed bortezomib administration in this mouse model accelerated GVHD.[80,81] Blanco et al[82,83] showed that bortezomib induces selective depletion of alloreactive T lymphocytes, decreases the production of T helper 1 cytokines while treatment of CD4+ T cells preserves regulatory T cells, and allows the emergence of a suppressor T-cell subset.

In patients with MM, both stimulation and improvement of GVHD has been reported.[84-86] In a recent study, bortezomib combined with tacrolimus and methotrexate proved to be a very effective regimen to prevent GVHD after Allo-RIC with mismatched unrelated donors.[87]

PROSPECTIVE EVALUATION OF LENALIDOMIDE AS MAINTENANCE AFTER ALLO-SCT

In the HOVON 76 phase II study, the effect of lenalidomide maintenance after tandem Auto/Allo is being evaluated.[88] After Auto/Allo-SCT, lenalidomide maintenance 10 mg/d for 21 days with 7 days rest (28 day cycle) is started between 1 and 6 months after the Allo-SCT if there are no signs of GVHD. As of October 2009, 36 patients were registered with a median age of 54 years. Preliminary results found that 41% of patients were withdrawn from the study after two cycles and 54% of patients were withdrawn after four cycles of lenalidomide. The major cause was rapid development of acute sometimes fulminate GVHD grade $\geq$ 2 to 4 after start of lenalidomide. The CIBMTR is also conducting a phase II trial of lenalidomide after Allo-SCT for patients with high-risk disease.

SYNGENEIC TRANSPLANTATION IN MYELOMA

Two large registry analyses have compared the results of syngeneic transplantation with Auto-SCT or Allo-SCT. Gahrton et al[89] reported on 25 syngeneic recipients reported to the EBMT and Bashay et al[90] reported on 43 subjects reported to the CIBMTR. The outcomes of syngeneic transplant recipients were superior in terms of lower incidence of relapse/progression, PFS and, for the EMBT patients, longer OS compared to Auto-SCT. A possible explanation for this observation would be the presence of a syngeneic GVM (as demonstrated in animal models, but has not been successfully reproduced in humans)[91,92] or due to absence of contaminating myeloma cells in the donor graft. This latter explanation is not supported by purging results of Auto-SCT.[93-96] These results also support the use of syngeneic stem-cell transplantation as consolidation therapy of an initial remission in patients who have identical twin donors.

CONCLUSION AND FUTURE

The prognosis of MM has improved substantially in the last decade and the majority of younger patients may enjoy remissions of excellent quality for a median of 3 years. It is hotly debated whether patients should be subjected to the morbidity and mortality of Allo-SCT as part of first-line therapy even when a (late) survival benefit is further proven by the outcome of the expected donor versus no donor comparisons. However, as the prospective studies of RIC Allo-SCT did not include the novel antimyeloma agents in the Allo-SCT arm, it would be of interest to challenge again Auto-SCT with Allo-RIC but now with the novel antimyeloma agents incorporated in both arms. Another option would be to explore Allo-RIC in high-risk patients only. High risk defined by the genetic markers including t(4;14); t(14;16); 17p−, or not achieving at least very good partial response after Auto-SCT. There is increasing evidence that bortezomib-based regimens are capable of overcoming at least some of the adverse prognostic outcomes, however and benefit of Allo-SCT in high-risk patients is not evident. Alternatively, Allo-SCT could be reserved for patients with a

chemotherapy-sensitive first relapse after Auto-SCT. Recently two prospective studies showed the feasibility and acceptable TRM of this approach using both sibling and unrelated donors. Nonrelapse mortality at 1 year was only 10% for those transplants with completely matched (10/10 alleles) donors. However, in both studies PFS with 13 months and 17 months and OS of 32 and 38 months, respectively, were limited. Due to improved supportive care, early detection/treatment of viral infections and careful donor selection using high-resolution HLA typing toxicity including TRM associated with unrelated transplants is comparable to related transplants.[31,66,97,98] Under the umbrella of European Myeloma Network, two studies have been developed for patients with a first relapse in which the focus is on effective GVHD prevention, early consolidation with novel antimyeloma agents and pre-emptive DLI. Both sibling and unrelated donors will be used and bortezomib is also part of the GVHD preventive regimen.

Other strategies that can be explored are natural killer cell therapies, adoptive T-cell therapy, and vaccination studies.[99-107] However, the clinical results of such approaches in MM are few and not yet fully evaluable. Even when proven effective these strategies can be difficult to apply on a wide scale due the high costs, the specific need of Good Clinical Practice facilities, and the laborious procedures. All authors of this article agree that an allograft should only be recommended in the context of clinical trials.

In Table 3, prospective trials of Allo-SCT that are being performed or planned by the different study groups are summarized.

The conclusions and recommendations of the International Myeloma Working Group are as follows. Myeloablative Allo-SCT may cure a minority of patients, but is associated with a high TRM even when applied in the first-line setting, but since smaller phase II studies suggested an improvement in TRM, myeloablative conditioning could be evaluated in well-designed prospective clinical trials. Nonmyeloablative Allo-SCT in first-line therapy is associated with a lower TRM, but a greater risk of relapse and convincing evidence is still lacking that Allo-RIC improves survival as compared to autologous SCT. Even though different in design, the outcomes of expected donor versus no donor comparisons of BMT CTN, Dutch HOVON, the EBMT, and German DSMM may allow more definite conclusions about the value of first-line Allo-RIC. Even when a late survival benefit is shown by the expected donor versus no donor comparisons, it may still be questionable if in the era of (Auto-SCT combined with) novel agents Allo-RIC should be routinely offered to patients in first-line therapy, especially as there are no convincing data indicating that high-risk myeloma may benefit from Allo-RIC.

Future studies of Allo-SCT in myeloma should aim at improving the graft-versus-tumor effect while reducing the morbidity and mortality of Allo-SCT. Novel anti-MM agents in the post-Allo setting may favor the GVM effect. However, exact mechanisms of action as well as the optimal timing and dosage of these agents after transplantation have yet to be determined. New strategies should be explored prospectively in selected groups of patients. Due to careful high resolution HLA typing and improved supportive care, the outcome and toxicity

Table 3. Currently Performed and Planned Prospective Trials With Reduced Intensity Allografting in Myeloma

Study Group	Coordinator(s)	Target No.	Patients	Design	Regimen	Proph GVHD	Post Allo Therapy	Time Period
DSMM XII	Einsele/Berdel/ Bunjes/Finke/ Bornhäuser	160	Newly diagnosed (stratification by prognostic factors)	Phase II	Fludarabin, treosulfan	Mycophenolic acid, cyclopsporin	Lenalidomide	2009-2010
Gimema	Bruno	53	Newly diagnosed (stratification by prognostic factors)	Phase II (match-control analysis included)	Auto/low-dose total-body irradiation	Mycophenolic acid, cyclopsporin	Lenalidomide (start at month 6 after transplantation)	2009-2013
HOVON	Lokhorst	104	Chemotherapy-sensitive first relapse	Randomized phase II	Melphalan/ fludarabin CD3/ CD19 depletion	Short-time cyclopsporin	Lenalidomide *v* lenalidomide/ bortezomib/pre-emptive DLI	2010-2013
Intergroupe Française Myeloma	Yacoub-Agha	30	Newly diagnosed 17 P deletion	Phase II	Tandem Allo/Auto	Cyclopsporin, mycophenolic acid	Lenalidomide/pre-emptive DLI	2010-2012
Pethema/EUMN	Perez-Simon/ SanMiguel	90	Chemotherapy-sensitive first relapse	Phase I/II	Melphalan/ fludarabin /Bortezomib	Rapamycin/ bortezomib *v* tacrolimus/ methotrexate/ bortezomib	Lenalidomid/ bortezomib	2010-2013
Seattle	Mielcarek	40	High-risk first-line or failed autologous	Phase II	Tandem Allo-Auto fludarabin/total-body irradiation	Cyclopsporin, mycophenolic acid	Bortezomib maintenance for 9 months	2009-2011
Hamburg/Münster	Kröger/Kropff	200	Newly diagnosed fewer than 8 cycles induction	Auto-allo with thalidomide/ DLI *v* auto-auto/ thalidomide	Melphalan 140/ fludarabin/ antithymoglobulin	Cyclopsporin/ mycophenolic acid/ antithymoglobulin	Thalidomide 100 for 2 years (in Allo also DLI)	2009-2012
Hamburg/ Heidelberg	Kröger/Hegenbart/ Dreger	180	Relapse after autograft	Allo *v* RD	Busulphan (14 mg/kg/Cy/ antithymoglobulin	Cyclopsporin/ mycophenolic acid/ antithymoglobulin	Lenalidomide 5 mg	2011-2015

Abbreviations: GHVD, graft versus host disease; Allo, allogeneic stem-cell transplantation; Auto, autologous stem-cell transplantation; DLI, donor lymphocyte infusions; EUMN, European Myeloma Network; RD, lenalidomide and dexamethasone; Cy, cyclophosphamide.

of transplants with related and unrelated donors are comparable. Allo-RIC in myeloma should only be recommended in the context of clinical trials. This recommendation is in agreement with the National Comprehensive Cancer Network guidelines on treatment of myeloma (http://www.nccn.com/multiple-myeloma/).

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: None **Consultant or Advisory Role:** Jesus San Miguel, Celgene (C), Millennium Pharmaceuticals (C), Johnson & Johnson (C); Gosta Gahrton, Fujimoto Pharmaceutical Co (C), Karolinska Institutet/Avaris AB (C); William Bensinger, Millenium Pharmaceuticals (C), Onyx Pharmaceuticals (C) **Stock Ownership:** None **Honoraria:** Jesus San Miguel, Celgene, Millennium Pharmaceuticals, Johnson & Johnson; Cristina Gasparetto, Celgene, Millennium Pharmaceuticals; William Bensinger, Celgene **Research Funding:** Cristina Gasparetto, Celgene, Cephalon; William Bensinger, Millennium Pharmaceuticals, Celgene, Onyx Pharmaceuticals, Facet Biotech **Expert Testimony:** None **Other Remuneration:** None

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