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Role of Allogeneic Stem Cell Transplantation in Multiple Myeloma

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High-dose chemotherapy with autologous stem cell rescue has been regarded as the standard of care for young newly diagnosed myeloma patients. Moreover, the development of new agents with potent anti-tumor activity has further improved survival. However, relapse is a continuous risk primarily due to the inability of current therapies to eradicate all myeloma cells. Allografting is the only potentially curative treatment at least for a subset of multiple myeloma patients due to its well documented graft-versus-myeloma effects. Given the high transplant mortality of the high-dose myeloablative conditionings used until recently, allografting has for a long time been limited to younger relapsed/refractory patients. These limitations have been reduced significantly by the use of reduced-intensity conditionings. Although results of recent trials are encouraging, the subset of patients who may benefit most from an allograft remains to be determined. An overview of the clinical outcomes obtained with allografting and possible future developments are reported.

Multiple myeloma remains a fatal plasma cell disorder, although progress in the understanding of its pathogenesis has identified mechanisms that have recently become targets of new agents with potent anti-myeloma activity such as thalidomide and its derivatives, and bortezomib.[1, 2, 3, 4 and 5] However, high-dose chemotherapy and autologous stem cell rescue with/without these newer agents is still regarded as standard treatment for newly diagnosed myeloma patients younger than 65 years.[6, 7, 8, 9 and 10] Patients are almost universally at continuous risk of relapse and only a minority live disease-free for longer than 10-15 years.[8 and 9] In at least a subset of patients, allografting from a human leukocyte antigen (HLA)-identical sibling or an unrelated donor appears to be the only potentially curative strategy due to the well-documented graft-versus-myeloma effects.[11] Given the high transplant-related mortality and toxicity related to the intense myeloablative conditioning regimens employed until recently, allografting has frequently been limited to younger patients at relapse or who are refractory to chemotherapy.[12, 13 and 14] Since the early 2000s, these limitations have been dramatically reduced through the introduction of so-called reduced-intensity or nonmyeloablative conditioning regimens.[15] These regimens allowed an increase in the eligible age for allografting up to 65-70 years, even in patients with nonhematological comorbidities, and have shifted the burden of tumor eradication from chemotherapy to donor T cells.[16 and 17] In this article we will review the current evidence of graft-versus-myeloma effects, and the results obtained with conventional myeloablative regimens, and also summarize the results of recent trials with reduced-intensity conditioning regimens.

Allografting and Graft-Versus-Myeloma Effects

The potentially eradicating effect of an allograft relies on the immune attack of donor-derived T cells against myeloma-specific antigens capable of inducing graft-versus-myeloma effects. Direct evidence for the existence of such effects was the transfer of myeloma idiotype-specific immunity from an immunized marrow donor to the patient.[18] Other indirect evidence was initially documented by the achievement of complete remissions following the infusion of donor-derived lymphocytes or discontinuation of immunosuppression in patients who relapsed after an allograft.[19, 20, 21 and 22] However, large studies clearly showed that, although donor lymphocyte infusions could induce high response rates, durable remissions were achieved only in a few patients. Major toxicity of this cell therapy was acute, and chronic graft-versus-host disease (GvHD) was reported in up to 55% and 26% of patients respectively.[22] However, some studies reported that the strongest predictors for response to donor lymphocyte infusions were acute and chronic GvHD,[23, 24 and 25] suggesting that GvHD and the graft-versus-myeloma mechanism/effect may share the same antigenic targets. Overall, chronic GvHD has been associated with longer response duration and overall survival in

several hematological malignancies treated with an allograft. However, in a recent study by the Gruppo Italiano Trapianti di Midollo (GITMO), the development of chronic GvHD did not correlate with the achievement of remission and duration of response.[26] Thus, a graft-versus-myeloma effect may also be distinct from chronic GvHD and associated with subclinical graft-versus-host reactions, especially after a truly nonmyeloablative conditioning regimen. Moreover, further evidence for graft-versus-myeloma effects are the molecular remissions, prelude to possible cure, that are more commonly observed after myeloablative allografting as compared to autografting and that can occur in up to 50% of patients.[27]

Allografting: Past and Present

Myeloablative Conditionings

The most frequently used myeloablative conditionings have included cyclophosphamide with total body irradiation or busulfan, or melphalan and total body irradiation.[12, 13, 14, 28 and 29] The unacceptably high treatment-related mortality of up to 60% has commonly restricted this approach to young, usually in their fifth decade, medically fit patients.[12, 13 and 14] Causes of death were primarily regimen-related events, and GvHD and its treatment-related complications, such as opportunistic infections. The reason for the high transplant-related mortality reported in myeloma compared to other malignancies remains unknown. Theories put forward include detrimental myeloma effects on baseline organ functions and/or a severe immunodeficiency that increases the risks of toxicities and infections.

The largest single-center experience on myeloablative allografting comes from the Seattle group.[13 and 28] One hundred thirty-six heavily pretreated or disease-refractory patients younger than 60 years of age received an allograft between 1987 and 1999 from either a related (84%) or an unrelated donor (16%). The authors reported a day-100 transplant-related mortality of 48%. Overall, the 5-year survival was 22% with disease-free survival of 14%. Importantly, in 34% of patients who achieved post-transplant complete remission, overall and disease-free survivals at 5 years were 48% and 37%, respectively. Moreover, a subgroup analysis showed that early transplant-related mortality was approximately 20% for patients with chemo-sensitive disease who were transplanted within 1 year from diagnosis.

Barlogie et al reported on the multicenter prospective randomized US Intergroup Trial S9321.[30] The three-arm study included a myeloablative allograft for newly diagnosed patients younger than 55 years with an HLA-identical sibling donor. However, this arm was soon closed due to a 53% transplant-related mortality rate. Importantly, at the time of publication, 22% of the patients enrolled were reported alive and progression-free at 7 years. Moreover, both overall and event-free survival curves showed a plateau with follow-up extending to 10 years, likely consistent with a cured subgroup of patients.

The largest retrospective multi-center analysis by the European Bone Marrow Transplant (EBMT) registry showed a remarkable improvement in survival in the late 1990s due to a reduction in transplant-related mortality through improved supportive care and more careful patient selection.[31] In this study, 690 patients, with a median age at transplant of 44 years, who underwent a myeloablative allograft were divided into two cohorts: patients who received a bone marrow allograft between 1983-1993 and those grafted between 1994-1998. In the latter cohort, some patients also received granulocyte colony-stimulating factor (G-CSF) mobilized peripheral blood hematopoietic cells (PBHCs). Transplant-related mortality at 6 and 24 months was lower in the cohort transplanted between 1994-1998 than in the cohort transplanted between 1983-1993 (21% *v* 38% and 30% *v* 46%, respectively). The reduced toxicity led to increases in overall and progression-free survivals at 3 years from 35% to 55% and from 7 to 19 months for patients transplanted between 1994-1998. Moreover, no differences in clinical outcomes were observed between patients who received marrow and those who received PBHCs.

Comparing results from different studies does not help to establish the real role of myeloablative allografting. In fact, most trials are retrospective and their inclusion criteria and pretransplant characteristics vary greatly. Despite these selection biases, it is widely assumed that better clinical outcomes are associated with patients with chemosensitive myeloma at transplant. In most studies, about 50% of these patients achieved complete remission at a median of 3 months from transplant. However, late relapses may occur, and in most series, only 10%-25% of patients eventually become long-term disease-free survivors and are possibly cured.

Reduced-Intensity Conditionings

Despite the high transplant-related mortality, the association of myeloablative allografting with long-term disease-free survival in some patients indicated that graft-versus-myeloma effects may have been curative for multiple myeloma. These findings prompted clinicians in the late 1990s to explore highly immunosuppressive, though less myelosuppressive and less intense, conditionings that could establish stable donor engraftment while reducing transplant-related organ toxicity. These more recent conditionings were defined as reduced-intensity or truly nonmyeloablative. The most widely used conditioning was originally developed at the Fred Hutchinson Cancer Research Center in Seattle and was based on preclinical animal studies that showed that donor cell engraftment could be steadily achieved after a truly nonmyeloablative regimen consisting of low-dose total body irradiation (200 cGy) followed by intense post-transplant immunosuppression with cyclosporine and mycophenolate mofetil.[32] This strategy was soon translated from the bench to the bedside.[33] After the first initial clinical experiences, a novel treatment modality was designed for untreated, newly diagnosed myeloma patients. This trial involved an autologous transplant followed 2 to 4 months later by a low-dose total-body irradiation–based nonmyeloablative allograft.[17] The rationale for this so-called "tandem autologous-allogeneic" approach was to separate in time the high-dose cytoreduction with melphalan at standard 200 mg/m^2 and the graft-versus-myeloma effect with the potential of drastically reducing treatment-related toxicity. The very first multicenter prospective experience of the "Seattle Consortium" included 54 stage II-III newly diagnosed patients, median age 52 years, half of them with refractory or relapsed disease.[17] Fifty-two of 54 patients completed the protocol. Complete remission was reported in 57%, and overall transplant-related mortality was reduced to 22%. After a median follow-up of 60 months, overall and progression-free survivals were 69% and 38%, respectively.

Long-term outcomes of 102 patents treated with this tandem approach after a follow-up of 6.3 years were recently described by the same investigators.[34] However, unlike the previous study, patients were not uniformly in first-line treatment. Overall, 42% of patients developed grade II-IV acute GvHD and 74% experienced chronic GvHD. Transplant-related mortality at 5 years post-allografting was 18%, primarily due to GvHD and/or infections. Overall response rate was 94%, with 65% and 29% of patients achieving complete and partial remissions, respectively. Median time to progression was 5 years. Median overall survival was not reached and progression-free survival was 3 years. Estimated 5-year overall and progression-free survivals were 64% and 36%.

The Gruppo Italiano Trapianti di Midollo recently reported their experience with the same tandem approach.[26] One hundred newly diagnosed patients younger than 65 years were enrolled in a prospective multicenter study. A major strength of the study was the strict enrollment of untreated myeloma patients who underwent the same vincristine, doxorubicin, and dexamethasone (VAD)-based induction chemotherapy before the autologous cytoreductive transplant. This strategy meant that all patients were treated uniformly and any statistical bias was greatly reduced. Primary endpoints were overall and event-free survivals from diagnosis. After a median follow-up of 5 years, overall survival was not reached and event-free survival was 37 months. Incidences of acute and chronic GvHD were 38% and 50%, respectively. Complete remission was achieved in 53% of patients. Complete or very good partial remission prior to allografting was significantly associated with achievement of post-transplant remission and longer event-free survival. Interestingly, both the

Seattle study and that from the Italian group concluded that graft-versus-myeloma effects were not associated with clinical GvHD.

In recent years, a number of other reduced-intensity regimens have been developed and employed in clinical trials, including melphalan 100-140 mg/m^2 with or without fludarabine, 200 cGy total body irradiation with/without fludarabine, and intermediate-dose busulfan. Furthermore, anti-thymocyte globulin or the anti-CD52 antibody alemtuzumab have been employed in some trials to reduce GvHD.[35, 36, 37, 38, 39, 40, 41 and 42] Overall, despite the high number of conditionings, a planned autograft followed by a nonmyeloablative or reduced-intensity allograft with G-CSF–mobilized PBHCs appears to be the most widely used transplant approach.[17]

The EBMT group reported a comparison between 321 transplants after reduced-intensity conditionings and 196 transplants after myeloablative conditionings performed in 103 EBMT Units between 1998 and 2002.[43] The two cohorts of patients were significantly different. Patients in the reduced-intensity group were older, median age 51 versus 45 years, more commonly with progressive disease, 28% versus 21%, and more heavily pretreated including one or more autologous transplants, 76% versus 11%. Although transplant-related mortality was significantly lower in the reduced-intensity group, 24% versus 37% at 2 years, no statistical differences in overall and progression-free survivals were observed between the two cohorts primarily due to significantly higher relapse in the reduced-intensity cohort. The conclusions of this retrospective study should be considered with a degree of caution as many statistical biases are evident between the two cohorts.

More recently, studies comparing allografting after reduced-intensity conditionings and autografting have been published. An Italian study reported on 245 consecutive untreated myeloma patients, up to the age of 65 years, diagnosed between 1998-2004 where 162 of 199 with at least one sibling were HLA-typed with their potential sibling donors.[44] This trial was based on the concept of Mendelian or genetic randomization, which relies on the biological process through which offspring randomly inherit genetic traits half from each parent so that one in four siblings is expected to have a potential HLA-identical sibling donor. The new feature was the treatment assignment in function of the presence or absence of an HLA-identical sibling donor. The comparison by the intention-to-treat principle between patients with and without HLA-identical siblings was used as a surrogate for an unbiased randomization. All patients received induction with VAD-based regimens followed by an autograft with melphalan. Eighty patients with an HLA-identical sibling were offered total body irradiation–based nonmyeloablative conditioning followed by an allograft with G-CSF–mobilized PBHCs, whereas 82 patients without an HLA-identical sibling were assigned to receive a second autograft after high-dose (140-200 mg/m^2) or intermediate-dose (100 mg/m^2) melphalan. At a median follow-up of 45 months, overall and event-free survivals were significantly longer in patients with donors: 80 versus 54 months and 35 versus 29 months, respectively. By multivariate analysis, having an HLA-identical sibling was an independent variable significantly associated with longer overall and event-free survivals. Overall, 58 and 46 patients completed the tandem autologous-allogeneic and the tandem autologous programs, with complete remission rates of 55% versus 26%, respectively. Transplant-related mortality was 10% and 2%, respectively. Median overall survival was not reached in the tandem autologous-allogeneic cohort and was 58 months in the tandem autologous cohort. Event-free survivals were 43 and 33 months, respectively. This study was recently updated[45] after a median follow-up of 6 years. Overall survival was not reached for the 80 patients with an HLA-identical sibling and was 52 months for those without (P = .004); event free survival remained significantly longer in patients with HLA-identical siblings: 35 versus 29 months (P = .009). Moreover, the median overall survival was not reached in the 58 patients who completed the tandem autologous-allogeneic program and was 64 months in the 46 patients who completed the high-dose melphalan double autologous program (P = .04). Event-free survivals were 37 and 33 months (P = .06).

Another French study compared two trials that enrolled high-risk myeloma patients in the light of elevated serum β_2-microglobulin and del(13).[46] All patients underwent an autograft after melphalan at 200 mg/m^2. Sixty-five patients with HLA-identical sibling donors were then treated with an

allograft after a conditioning consisting of busulfan, fludarabine, and high-dose anti-thymocyte globulin, 12.5 mg/kg. These patients were compared with 219 high-risk patients who were treated with a second autograft after melphalan at 220 mg/m^2. Transplant-related mortality and response rates were not significantly different. At a median follow-up of 2 years, overall and event-free survivals were 35% and 25%, and 41% and 30% for the double autologous and the autologous-allogeneic cohorts. These findings may indicate that patients with disease features such as del(13) and high β_2-microglobulin may not benefit from a reduced-intensity allograft. Although the incidence of chronic GvHD was 7%, the high dose of anti-thymocyte globulin may have prevented potentially curative *graft-versus-myeloma* effects. This study was also recently updated. [47] As of July 1, 2008, by intent-to-treat analysis on all 284 patients, at a median follow-up of 56 months, event-free survival did not significantly differ between tandem autologous and a single autograft followed by a reduced-intensity allograft (median, 22 *v* 19 months; $P = .58$). There was a trend for a superior overall survival in the tandem autologous trial (median, 48 *v* 34 months; $P = .07$). Similar results were observed when the two cohorts of patients who completed the programs were compared. Indeed, newer biological parameters such as genetic abnormalities have been widely used for categorizing patients. Chromosome 13 deletion, detected by standard cytogenetics or fluorescence in situ hybridization (FISH), has been the genetic abnormality most frequently associated with worse prognosis in a number of studies. [48, 49, 50 and 51] However, a recent more comprehensive analysis clearly showed that chromosome 13 deletion alone did not affect overall survival after transplant unless it was associated with other abnormalities such as translocation 4;14 and chromosome 17 deletion. [52] In the light of these findings, the impact of genetic abnormalities after an allograft should be evaluated with more comprehensive analyses that include all the chromosomal abnormalities associated with multiple myeloma rather than single abnormalities.
A third genetically randomized study was recently reported by the Spanish group.[53] One hundred ten patients who failed to reach at least near-complete remission after a first autograft were scheduled to receive either a second autograft (n = 85) or an allograft (n = 25) after a reduced-intensity conditioning with melphalan and fludarabine. There was a higher complete remission rate (40% *v* 11%, $P = .001$), and a trend towards a longer progression-free survival (median, 31 months *v* not reached; $P = .08$) in the reduced-intensity group. However, patients who underwent an allograft showed a trend towards a higher transplant-related mortality (16% *v* 5%, $P = .07$) and no statistical difference in overall and event-free survivals.
Finally, two large prospective randomized studies, the BMT-CTN-0102 trial in the United States and the Dutch-Belgian Hemato-Oncology Cooperative Group (HOVON) trial in Europe, have recently been presented. However, their final analyses are not yet available.

GvHD and T-Cell Depletion

Overall, GvHD and its complications account for most transplant-related mortality. However, the incidence of GvHD may be reduced in the future when its pathogenesis becomes clearer. For example, a conditioning of marrow-sparing total lymphoid irradiation and anti-thymocyte globulin was shown to decrease GvHD incidence to 3% without affecting graft-versus-leukemia effects.[54]
T-cell depletion has been rather extensively used to eliminate GvHD even though this approach has invariably been associated with a higher risk of relapse of the underlying malignancies.[55] Although limited in myeloma patients, partial T-cell depletion to allow donor engraftment and reduce the risk of GvHD has been employed by Alyea et al. Patients were infused with CD6-depleted donor bone marrow grafts after a myeloablative conditioning. Selected CD4$^+$-donor lymphocytes were scheduled later to enhance graft-versus-myeloma effects.[56] The incidence of grade II-III GvHD was 21%, and transplant-related mortality was dramatically reduced to 10%. Only one patient achieved a complete remission at 6 months without the addition of donor lymphocytes. Fourteen of 24 patients received donor lymphocyte infusions and disease response was observed in 10 patients.

However, seven of 10 developed acute or chronic GvHD. Two-year overall and progression-free survivals were 55% and 42%, respectively.
The use of the monoclonal anti-CD52 antibody alemtuzumab has also been rather extensively explored to reduce the incidence of GvHD, either by the so-called treatment “in the bag” or by systemic intravenous infusion before the conditioning.[57] Alemtuzumab reduced GvHD, but at the same time its use remarkably affected response rates and response duration. These findings further confirm the pivotal role of donor T cells in providing graft-versus-myeloma activity. Lokhorst et al on behalf of the HOVON group reported on 53 patients with an HLA-identical sibling who underwent a partially T-cell–depleted allograft as first-line treatment.[58] The overall response rate was 89% with 19% complete remissions. At a median follow-up of 38 months, 20 patients were alive and 33 dead, 14 from progressive disease and 18 from transplant-related mortality. Overall and progression-free survivals after allografting were 17 and 25 months. Unfortunately, only three patients were in continuous clinical remission. These findings did not support the use of T-cell–depleted myeloablative allografting in myeloma.
Overall, although GvHD was associated with disease response in most clinical trials employing myeloablative conditionings, it is encouraging that, by contrast, recent studies employing T-repleted transplants after nonmyeloablative conditionings have not correlated disease response and its duration with the development of acute or chronic GvHD.[26 and 34]

Allografting: Future Perspectives

Whether an allograft should be part of a first-line treatment plan or of salvage therapy for refractory/relapsed patients is still hotly debated.[59] Although allografting with reduced-intensity/nonmyeloablative conditioning has evolved into a less toxic procedure, new methods to augment graft-versus-myeloma effects to allow long-term disease control and possibly decrease toxicity are currently sought. For this purpose, new drugs such as thalidomide, lenalidomide, and bortezomib should not be viewed as mutually exclusive with an allograft. They may be employed to achieve profound cytoreduction before allograft and enhance graft-versus-myeloma effects as maintenance therapy afterwards.[60, 61, 62 and 63]
In summary, current clinical observations suggest that allografting may be an effective treatment at least in a subset of multiple myeloma patients. The possible combination of graft-versus-myeloma effects with “new drugs” should be clinically explored in well-designed phase III clinical trials. Control groups should include patients treated with new agents with potent anti-myeloma activity with/without autografting. Moreover, stratification of patients by prognostic factors, especially chromosomal abnormalities, is indispensable to determine the patient subgroup that may most benefit from an allograft and to explain discrepancies seen in recently published studies. Moreover, in the future, other advanced technologies such as gene-expression profiling may be able to predict the biological behavior of the disease and determine how these factors influence graft-versus-myeloma effects.[64, 65 and 66]

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