Curr. Treat. Options in Oncol. (2021) 22: 65
DOI 10.1007/s11864-021-00864-x

Leukemia (PH Wiernik, Section Editor)

Allogeneic Stem Cell Transplantation in Patients with High-Risk Multiple Myeloma: Utopia or Continuous Challenge in Aiming for Cure?

Panayotis Kaloyannidis, MD[*]
John Apostolidis, MD

Address
[*]Adults Hematology and Stem Cell Transplantation Department, King Fahad Specialist Hospital, 31444, Dammam, Kingdom of Saudi Arabia
Email: pkaloyannidis@yahoo.gr

Published online: 10 June 2021

This article is part of the Topical Collection on *Leukemia*

Keywords Multiple myeloma · Allogeneic stem cell transplantation · Refractory/relapsed multiple myeloma

Opinion statement

Nowadays, several novel agents have been introduced in the treatment of multiple myeloma, not only resulting in high response rates and prolonged survival but also offering good quality of life. However, the potential of cure, especially for patients with advanced or unfavorable disease features, remains elusive. Allogeneic hematopoietic stem cell transplantation, based mainly on the graft vs. myeloma effect, can offer prolonged disease control and probability of cure but unfortunately at the cost of considerable transplant-related toxicity rates. Therefore, the role of allogeneic hematopoietic stem cell transplantation in the treatment of multiple myeloma has been called into question. Recently, several studies, particularly those with long-term follow-up, demonstrated a trend of survival superiority for allografted patients with high-risk disease. These data fuel again the interest in allogeneic stem cell transplantation for selected patients with high-risk multiple myeloma, especially if the high remission rates which can be achieved with the currently used treatment protocols could be long-life sustained through the additional exploitation of the long-lasting anti-multiple myeloma effect, originating from the allograft.

Introduction

Over the last decade, innovative therapeutic agents such as immunomodulatory drugs (IMIDs), proteasome inhibitors (PIs), and monoclonal antibodies (MoAbs) have resulted in a "scientific revolution" in the treatment of multiple myeloma (MM), improving the disease course and ultimately outcome and patients' quality of life [1]. However, the initial expectations that the current treatment advances could "transform" MM to a chronic illness with non-aggressive course or at least to a well-controlled disease still remain an "unsuccessful story" and the tough reality dictates that the majority of patients, especially those with high-risk disease characteristics, succumb either to disease refractoriness or to complications related to prior multiple lines of treatment [1–3].

Allogeneic stem cell transplantation in MM: cons and pros

It is well documented that the infusion of an allogeneic stem cell graft following myeloablative or reduced intensity conditioning (RIC) regimen offers higher response rates and prolonged disease remission period as compared to other conventional treatments (including autologous stem cell transplantation (autoSCT)) [4–5]. The lower relapse incidence observed following allogeneic stem cell transplantation (alloSCT), especially in the presence of graft versus host disease (GvHD), is an indirect indicator for the existence of a graft versus multiple myeloma (GvMM) effect [6–8]. The direct evidence of a GvMM effect has been demonstrated since the 1990s, when donor lymphocyte infusions (DLIs) given in patients with relapsed or refractory MM (RRMM) resulted in long-lasting complete remissions (CR) [9–11]. Nevertheless, the beneficial GvMM effect is not always translated into better survival rates as compared to the currently available conventional treatments, because alloSCT is often accompanied with considerable, or even unacceptable, transplant-related mortality (TRM) [12, 13]. Consequently, in the era of the constantly emerging effective and less toxic therapies, the arising question is whether a space for allogeneic stem cell transplantation still exists or it should be considered already past?

In a recent publication from the European Society for Bone and Marrow Transplantation (EBMT)/Chronic Malignancies Working Party, Sobh M et al. showed that in the contemporary era of MM treatment there is an increasing trend for alloSCT in MM patients, in particular for tandem (auto/allo) transplants but also single alloSCT in a later disease phase (2nd remission and beyond) [14].

The appropriate patient selection, elimination of conditioning regimen toxicity, better prophylaxis and management of GvHD without adversely affecting the GvMM effect, and the ideal maintenance treatment post alloSCT represent currently research areas, with the intension of improving the alloSCT outcome, thus rendering it as an additional reliable option for patients with MM.

Conditioning regimens

The initial conditioning regimens were exclusively myeloablative, explaining at least partially the observed high TRM rates (> 50%) [12]. The advances in supportive care dramatically improved the TRM; however, the current 2-year

TRM of approximately 30% still remains a major obstacle to perform alloSCT in MM with myeloablative conditioning regimen [13]. The introduction of the RIC regimens significantly reduced the toxicity and the early post-transplant TRM, thus offering the opportunity to more patients (elderlies or with comorbidities) to benefit from alloSCT. In a retrospective analysis, the EBMT group evaluated the outcome of 229 patients allografted with a RIC regimen. The 4-year overall survival (OS) and progression-free survival (PFS) rates were 40% and 21%, respectively, while the TRM was reported to be 22%. Although a considerable number of patients had been assessed, major weak points of the study were the heterogeneity of the group in terms of disease characteristics and previously given treatments and the fact that 60% of patients underwent in vivo T cell depletion with antithymocyte globulin or anti-CD52 MoAb which adversely affects the GvMM effect (thus increasing the risk of relapse) and transplant-related mortality and morbidity rates [15].

The potency of alloSCT with a RIC regimen is rather based on the graft's T cells alloreactivity against the malignant cells which "escaped" either from previous chemotherapies or from the conditioning regimen. Hence, it is expected that better results could be obtained in patients with low disease burden or with no detectable disease before transplant. Currently, aiming in deeper disease remission before allografting, the tandem approach consisting of an autoSCT followed shortly later by an alloSCT (auto/alloSCT) is explored in selected MM patients. In a randomized study, Giaccone L et al. evaluated 119 newly diagnosed MM (NDMM) patients who underwent 1st autoSCT and subsequently received either 2nd tandem transplantation from a full-matched sibling donor (auto/alloSCT, $n = 60$) or 2nd autologous graft (auto/autoSCT, $n = 59$). After a median follow-up of 7 years, the median OS for the auto/alloSCT group had not been reached, while for the auto/autoSCT group was estimated at 5.3 years ($p = 0.02$). Importantly, when they focused the analysis only on patients who achieved remission after the 1st autoSCT, they found that 53% of those who allografted remained in continuous CR while only 19% of those who received auto/autoSCT achieved long-term remission ($p = 0.02$) [16]. Similarly, another retrospective study showed that auto/alloSCT as compared to auto/autoSCT was superior for both OS (49% vs. 36%, $p = 0.03$) and PFS (22% vs. 12%, $p = 0.025$), but the TRM in the allografted patients was significantly higher as compared to that in the autografted ones (12% vs. 3%) [17]. The above retrospective studies demonstrated that a superior long-term outcome was observed after allografting, reaching a survival plateau of approximately 50% after 4–5 years post-transplant, indicating that alloSCT might offer the potential of cure to those patients who can successfully overcome the "reef" of early TRM (Table 1). Nevertheless, the heterogeneity of the evaluated patients in these two studies (disease phase, unknown cytogenetic profile, different treatment regimens) poses considerable difficulties to draw firm and accurate conclusions, while more importantly, in none of them, novel agents such as PIs and IMIDs had been used as part of the pre-transplant provided therapies. To add more to the difficulty of drawing accurate and reliable conclusions regarding the role of alloSCT in MM, two studies with large series of patients, but with shorter follow-up (3 and 4 years, respectively), failed to demonstrate any superiority of tandem auto/alloSCT over the auto/autoSCT approach. The first study (BMT-CTN-0102) prospectively evaluated 710 patients treated either with auto/alloSCT ($n = 226$) or with auto/autoSCT ($n = 484$). The 3-year survival

Table 1. Auto/allo HSCT vs. auto/auto HSCT: results of studies with large series of patients

Study/author	Type of study	Number of patients	Follow-up	Type of tandem HSCT	OS	DFS	*p* value	TRM
Giaccone I (2011), ref [16]	Retrospective	229	7 y	Auto/allo	NR (med)	39 m (med)	0.02	16%
				Auto/auto	5.3 years	33 m (med)		2%
EBMT (2011), ref [17]	Retrospective	357	8 y	Auto/allo	49%	22%	0.03	12%
				Auto/auto	36%	12%		3%
BMT-CTN-0102 (2011), ref [6]	Prospective	710	3 y	Auto/allo	77%	43%	ns	11%
				Auto/auto	80%	46%		4%
Kawamura K (2016), ref [18]	Retrospective	759	4 y	Auto/allo	59%	NA	ns	NA
				Auto/auto	54%	NA		NA

HSCT hematopoietic stem cell transplantation, *y* years, *m* months, *NR* not reached, *med* median, *NA* not available, *ns* non-significant

rates were similar for patients with standard risk (OS: 77 vs. 80%, PFS: 43% vs. 46%) or high-risk disease (OS: 59% vs. 67%, PFS: 40% vs. 33%). However, the TRM, as expected, was higher in the allografted group (11% vs. 4%) [6]. In the second study, 765 patients were retrospectively assessed; the majority (n = 676) underwent tandem autologous transplant while 89 patients received tandem autologous/allogeneic transplant. Similarly to the BMT-CTN-0102 study, no survival advantage was found between the two treatment approaches; the 6-year OS was 58.5% vs. 54.4% for the tandem autografted and auto/allografted patients, respectively [18].

Could the disease risk index be a reliable criterion to select the best candidates for alloSCT?

Alike to other hematological malignant disorders, high-risk MM represents a enormous therapeutic challenge for physicians. Over the last years, the definition of high-risk disease, especially specific cytogenetic abnormalities, have been redefined several times; therefore, it is difficult to carry out direct comparisons and analyses from the existing studies. Currently, (i) baseline abnormal biological markers (serum albumin, beta 2-microglobulin (b2M), LDH), cytogenetic abnormalities (t(4:14), t(14:16), t(14:20), del17p, gain1q, hypoploidy), or high-risk gene expression profiling (GEP^{hi}), (ii) response to initial treatment (disease refractoriness or early relapse), and (iii) plasmacytic leukemia at diagnosis (PCL) represent essential poor prognostic factors for ultimate disease outcome [19–24]. Theoretically, for selected fit and young patients with such high-risk features, alloSCT could be a reasonable treatment approach, offering both the benefits of intensive chemotherapy and GvMM effect.

Newly diagnosed high-risk patients

Few studies have exclusively evaluated the outcome for NDMM patients with high-risk disease characteristics. Particularly in the era of the novel agents, the question whether an alloSCT is really needed has not been answered yet, since

no head-to-head study exists. The BMT CTC 0702 trial evaluated patients who received treatment with the currently used novel agents plus autoSCT and assessed the outcome of three different treatment approaches, allocating patients to receive either (a) tandem auto/autoSCT plus maintenance or (b) single autoSCT plus maintenance or (c) single autoSCT plus consolidation and maintenance. Analysis in the whole cohort of patients revealed similar OS and PFS rates in the 3 studied groups; however, the sub-analysis showed higher treatment failure (progression or death) and mortality rates for patients with poor prognosis characteristics [25•]. In another randomized phase II trial, the presence of GEP^{hi}, t(14; 16), t(14; 20), del(17p), amplification 1q21, primary plasma cell leukemia (pPCL) and elevated serum LDH were defined as high-risk features; all patients received a combination of novel agents (bortezomib-lenalidomide-dexamethasone with or without elotuzumab), and after a median follow-up of 53 months, the PFS did not exceed 3 years [26•]. So, it is obvious that for selected patients with high-risk characteristics there is an unmet need for more effective and with acceptable toxicity treatment modalities.

Schilling G. et al. published the results of 101 NDMM patients with high-risk disease (elevated b2M, t(4:14), t(14:16)) who underwent alloSCT and the outcome was compared to that of patients who had standard-risk disease features and received conventional treatment. The survival rates were similar between both groups and only the presence of del(17p) negatively affected the remission rates and PFS [27]. Similarly, in a French retrospective analysis, the outcome of 143 patients with poor prognosis cytogenetic abnormalities allografted early after induction remission treatment was compared with that of a group of non-allografted patients who had standard risk disease. Again, the OS, PFS, and relapse rates did not differ between the two groups [28]. Nishihori T. et al. reported promising results in 22 high-risk patients who underwent early alloSCT after a RIC regimen as 1st consolidation treatment, after achievement of CR or very good partial remission (VGPR). The 2-year OS and PFS for the allografted patients reached 77% and 75%, respectively, and compared favorably to a historical control group of patients with similar characteristics who were consolidated with autoSCT. The TRM for the allografted and autografted groups of patients was 16% vs. 2.5%, respectively [29]. In the above studies, despite their inherent limitations (retrospective origin, heterogeneity, non-use of the recent novel agents, different conditioning regimens), the common denominator was that high-risk patients consolidated with alloSCT enjoyed similar survival rates with those who had standard-risk disease, indicating that allografting may mitigate the poor prognosis associated with high-risk disease features.

Unlike the aforementioned studies, a retrospective analysis from the MD Anderson Cancer Center with 149 patients reported no survival advantage in allografted MM patients with high-risk cytogenetic features (t(4:14), t(14:16), del17p and del 13q). However, it should be seriously taken into consideration that the vast majority of allografted patients (85%) had high tumor burden before transplant and were heavily pretreated [30]. Recently, a meta-analysis evaluated the results of 61 clinical trials with 8698 patients. The OS and PFS were similar between patients with high-risk disease who received an allograft in comparison with patients with standard-risk disease who underwent autoSCT [31••].

Only few prospective trials have compared the outcome of high-risk patients who received auto/alloSCT versus those who received conventional chemotherapy with or without autoSCT (Table 2). In a French study, patients characterized to have high-risk disease based on elevated b2M levels and/or presence of del13 were assigned to consolidation with either auto/alloSCT or auto/autoSCT early after induction remission therapy, consisting of vincristine, adriamycin, and dexamethasone (VAD). Though the long-term PFS was comparable between the two groups (35% vs. 32%), there was a tendency for better OS for those who underwent auto/autoSCT (47% vs. 35%, $p = 0.07$). However, in this study, as high-risk factors were considered only the elevated b2M and del13 (which currently is not considered a high-risk cytogenetic abnormality), the follow-up period was quite short (median of 2 years), and even more importantly, novel agents were not included in the induction remission therapy [32]. As already mentioned previously, the BMT-CNT-0102 failed to demonstrate superiority of auto/alloSCT over auto/autoSCT in high-risk patients [6]. The HOVON-50 study prospectively evaluated high-risk MM patients who were induced with VAD or thalidomide-AD followed by autoSCT. Subsequently, patients who had a full-matched sibling donor ($n = 114$) received a 2nd tandem alloSCT while those lacking a donor continued with conventional treatment. The 6-year PFS and OS rates were similar for both groups. The TRM was 16% for the allografted patients and 3% for those who received conventional treatment ($p < 0.001$) [33].

Another prospective study, published by Kröger et al., evaluated the outcome of 73 patients with disease stage ≥ II and cytogenetic abnormalities of 13q14, del17p, or t(4:14) and treated with auto/alloSCT after induction remission therapy. At the time of transplant, 15% were in molecular CR and 60% in partial remission, while 20% had disease progression. The 5-year PFS differed

Table 2. Allo HSCT vs. auto HSCT in high-risk newly diagnosed patients: results of prospective studies with large series of patients

Study/author	Number of patients	Follow-up	Risk factors	Type of HSCT	OS	DFS	*p* value	TRM
IFM99 03/04 (2006), ref [30]	166	2.5 y	b2M, del13	Allo	35%	31%		10%
				auto	47%	31%	ns	5%
BMT-CTN-0102 (2011), ref [6]	85	3.5 y	b2M, del13	Allo	67%	40%		21%
				auto	59%	38%	ns	11%
HOVON-50 (2012), ref [33]	170	6 y	b2M, del13, R-ISS: III	Allo	59–62%	35–41%		16%
				auto	42%	13%	ns	4%
EBMT (2011), ref [17]	92	5 y	b2M, del13	Allo	69%	31%	0.003	16%
				auto	55%	11%		4%

HSCT hematopoietic stem cell transplantation, *y* years, *m* months, *b2M* beta-2 microglobulin, *del13* deletion 13, *R-ISS* Revised International Scoring System

substantially according to the remission status. It was estimated at 41% for CR, 57% for molecular CR, and 85% for sustained molecular CR [34].

Patients with relapsed disease

Despite the fact that, in NDMM patients the novel treatment protocols with or without autoSCT offer significant improvement in survival rates, in a considerable number of patients, disease progression or recurrence usually occurs within 2–4 years after disease diagnosis [35].

The outcome for patients who have early disease relapse/progression (less than 12 months after treatment initiation) or experience more than 2 relapses/progressions is extremely dismal with a median survival not exceeding 20–40 months [22, 23, 36, 37]. Whether this poor-risk group of patients might benefit from alloSCT remains debatable. In a retrospective analysis from the Cancer of International and Bone and Marrow Transplantation Research (CIBMTR), patients who experienced early relapse post autografting and were subsequently salvaged with alloSCT had disappointing 3-year OS and PFS rates of 20% and 6%, respectively, which were significantly inferior to those of patients who had been treated with a 2nd autoSCT (OS: 46%, PFS:12%). However, it has to be underlined that in this particular study the majority of allografted patients experienced relapse early, within 12 months post-autoSCT, whereas in patients treated with a 2nd autoSCT, the disease recurred after 2 years and beyond following the first autograft, and more importantly, 35% of patients who received 2nd autograft were in CR or PR, while less than 10% were in remission in the group of allografted patients [38]. In another retrospective study with a small series of relapsed patients post-autoSCT, the 3-year PFS was 46% for those who had a suitable sibling donor versus 6% for those who lacked a donor ($p = 0.01$), though there was no significant difference in 3-year OS (50% vs. 49%) [39]. Patriarca et al. reported results from a retrospective study with long-term follow-up, in which patients who failed 1st autoSCT were salvaged either with alloSCT or with conventional treatment approaches. In a preliminary analysis with a 2-year follow-up, OS survival rates were similar between the two groups, although the PFS was found to be superior for the allografted patients. However, it was extremely interesting that, in the updated analysis, after a median follow-up of 110 months, both OS and PFS were significantly better in the alloSCT group (5-year PFS 31% vs. 3% and 5-year OS: 40% vs. 19%, p =0.007) [40, 41••].

Although several studies showed that alloSCT could be considered a feasible and effective treatment approach for strictly selected patients with high-risk features, TRM is steadily higher in the allograft setting. Given the lack of well-designed prospective trials with long-term follow-up, the issue of whether and when alloSCT should be offered in NDMM patients with high-risk features or in patients with RRMM disease continues to be an unresolved dilemma.

Patients diagnosed with plasma cell leukemia

Even in the modern era of various and effective treatment options for plasma cell dyscrasias, the prognosis of primary plasma cell leukemia (pPCL) still remains poor, and in the majority of clinical trials, the median survival is reported to be less than 3 years [42, 43]. Only few studies and with a small series of patients have assessed the safety and efficacy of the currently available treatment options in pPCL. EBMT and CIBMTR jointly conducted a

retrospective study with 73 patients diagnosed with pPCL and reported superior outcomes for allografted patients in comparison to those treated with conventional treatment (median OS: 38 vs. 27 months and median PFS: 9 vs.7 months) [44]. A Japanese retrospective study evaluated 26 patients with pPCL who completed induction remission treatment and subsequently underwent either alloSCT or autoSCT or continued with conventional maintenance treatment. Allografting resulted in better outcome, offering a median OS of 61 months, as compared to autoSCT (median OS 40 months) or conventional maintenance treatment (median OS 28 months) [45]. In two separate retrospective studies, CIBMTR and EBMT registries evaluated a total of 643 pPCL patients treated either with alloSCT (n = 135) or with autoSCT (n = 508). Both studies failed to demonstrate any survival benefit for allografted over autografted patients [46–47]. More recently, Lawless et al. published the results of a 15-year retrospective analysis with 751 pPCL patients who underwent tandem allo/auto or auto/autoSCT. Though without statistical significance, a trend for better survival rates was noticed in the auto/alloSCT patients' group [48]. Encouraging results for patients with pPCL have been reported with current treatment protocols using novel agents. In the SWOG1211 study, though not designed exclusively for patients with pPCL, the combination of bortezomib-lenalidomide-dexamethasone plus elotuzumab offered significantly higher PFS rates as compared to historical controls [26•].

The aggressiveness and the poor outcome in pPCL patients necessitate the timely search for a suitable donor aiming in early alloSCT for selected candidates with chemosensitive disease. As per the most recent consensus statement on treatment recommendations by the International Myeloma Working Group (IMWG), for younger individuals (less than 50 years old), a myeloablative conditioning regimen is considered the preferable choice [49].

AlloSCT in MM from alternative donors

Given that only 25–30% of patients have a suitable full HLA–matched sibling donor, the exploitation of alternative graft sources, at least theoretically, could be a reasonable approach for selected MM patients who fulfill the criteria to undergo alloSCT.

A retrospective study from the EBMT analyzed the outcome of 570 patients with relapsed MM who received grafts from alternative donors (matched unrelated (MUD): 419, mismatched unrelated (MMUD): 93, cord blood units (CBU): 58). Only 12 of the 570 patients had high-risk cytogenetic features at diagnosis. The 5-year OS was 33%, 39%, and 25%; the 5-year PFS was 14%, 27%, and 4%; and the TRM was 22%, 33%, and 27% for transplants performed from MUD, MMUD, and CBUs, respectively [50]. In a German retrospective study, 64 patients received a graft from MUD or MMUD for refractory MM disease. After a median follow-up of 6 years, the 10-year OS and PFS were 29% and 24%, respectively, while the TRM was within acceptable rates of 12%, similar to the TRM rates observed for transplants from MUD/MMUD donors for other hematological malignancies. An interesting finding of this study was that patients who underwent early alloSCT had better outcome in comparison to the heavily pretreated patients, achieving a 5-year OS rate of 50% vs. 5% [51]. In a prospective trial with 49 relapsed MM patients who underwent MUD or

MMUD transplant, the estimated incidence of acute and chronic GvHD after a median follow-up of 4 years were 25% and 25%, respectively, whereas long-term OS and PFS were 26% and 20%, respectively. Of notice, patients who remained relapse-free after the first 3 months post-transplant had significantly superior survival rates (OS: 56% vs. 16% and PFS: 41% vs. 7%, $p = 0.02$). The 1-year TRM was estimated to be 10% for those who had MUD transplant compared to 53% for those who had MMUD transplant ($p = 0.001$) [52].

Cord blood units represent a readily available graft sources that bear well-known advantages and disadvantages of their usage. In a retrospective study, Kröger et al. analyzed 95 patients who received CBU allografts. The 3-year OS and PFS were 40% and 25%, respectively, while the TRM reached 29% [53].

Nowadays, it is well proved that alloSCT with T cell replete (TCR) grafts from haploidentical donors using post-transplant cyclophosphamide (PTCy) in combination with calcineurin inhibitors plus mycophenolate mofetil as GvHD prophylaxis represents a feasible, effective, and with acceptable toxicity approach, in particular for patients with high-risk leukemias or lymphomas. However, the experience of transplantations from haploidentical donors in the field of MM is extremely limited. In a retrospective cooperative study from EBMT and CIBMTR, Sahebi F et al. evaluated 96 patients who received a TCR graft from a haploidentical donor along with PTCy as GvHD prophylaxis; 70% had already undergone autoSCT, while in 30% of patients more than two autoSCT had been previously performed. In this heavily pretreated population, engraftment was successful and the 2-year OS and PFS rates were 48% and 17%, respectively. TRM was strongly related to the source of the graft and estimated at 11% for those who received a marrow graft and 35% for those who received mobilized stem cells from peripheral blood [54].

The limited data from the few existing clinical studies demonstrate that, for selected high-risk patients (fit enough, in CR or with extremely low tumor burden), alloSCT from alternative donors might be a treatment option; however, such transplants in MM patients should be performed only in the context of clinical trials in highly experienced transplant centers (Table 3).

Table 3. Allo HSCT in multiple myeloma from alternative donors: results of studies with large series of patients

Study/author	Follow-up	Donors	OS	DFS	TRM
EBMT (2017), ref [50]	5 y	MUD: 419	33%	14%	22%
		MMUD: 93	39%	27%	33%
		CBU: 58	25%	4%	27%
Creil C (2019), ref [51]	6 y	MUD/MMUD: 62	29%	26%	12%
EBMT (2010), ref [52]	3 y	MUD/MMUD: 49	26%	20%	20% (MUD: 10%, MMUD: 53%)
EBMT (2016), ref [53]	3 y	CBU:95	40%	25%	29%
EBMT/CIBMTR (2019), ref [54]	2 y	Haploidentical	48%	17%	BM-graft:11%
					PB-graft: 35%

HSCT hematopoietic stem cell transplantation, *y* years, *m* months, *MUD* matched unrelated donor, *MMUD* mismatched unrelated donor, *CBU* cord blood unit, *BM* bone marrow, *PB* peripheral blood

Can we make the alloSCT procedure even better?

The currently used conditioning regimens in the alloSCT setting for MM patients are exclusively of reduced intensity; thus, it is anticipated that the risk of relapse is higher especially for patients with high-risk or detectable disease before transplant. The strengthening of (a) the anti-MM potency of the conditioning regimens and (b) the GvMM effect without negatively influencing the TRM are highly desirable targets in the alloSCT field.

Intensification of the conditioning regimen

Preclinical models have shown that PIs, apart from a proven strong anti-myeloma, also exert an inhibitory effect on the alloreactive T cells. These functions render them as appealing agents for conditioning regimen intensification offering also a potential mitigation of the GvHD incidence without adversely affecting the beneficial GvMM effect. However, it seems there are some restrictions regarding the timing of PI administration as part of the conditioning regimen. In a mouse model, administration of PI beyond day 5 of graft infusion was correlated with an increased incidence of severe gut GvHD and with high mortality [55]. In a phase I–II clinical study with 22 patients who experienced relapse after autoSCT, bortezomib was given as part of the conditioning regimen for an allograft. Approximately 70% of patients had been previously exposed to at least 3 lines of treatment. The incidence of clinically significant acute GvHD was 44%, while the 3-year OS, PFS, and TRM were 41%, 44%, and 25% respectively, which can be considered rewarding given the disease refractoriness and patients were heavily pretreated [56]. Similar results have been published from the Moffitt Cancer Center group, incorporating bortezomib into the conditioning regimen for patients who underwent early allotransplant as consolidation treatment for high-risk MM [29]. Currently, ongoing prospective trials are evaluating the role of the novel anti-MM agents as part of the conditioning regimens.

Maintenance treatment post-allogeneic stem cell transplantation

Proteasome inhibitors have been already incorporated in maintenance treatment protocols post autografting; therefore, it is a reasonable and also attractive approach as a post allografting maintenance treatment [57]. In a prospective study, 18 patients received after a median of 9 months post-alloSCT a minimum of 2 cycles of bortezomib at the dose of 1.3 mg/m^2 on days 1, 4, 8, and 11 of a 21-day cycle for 2–4 cycles. The overall response reached an encouraging rate of 80% [58]. In another multicenter retrospective study, bortezomib was given in the aforementioned dose and schedule with or without steroids, for a median of 6 cycles. Alike to the previous study, the response rate was 73% while the 1.5-year OS was 65% [59].

Immunomodulating agents (thalidomide or lenalidomide) have also been widely used as maintenance treatment for selected autografted patients. Nevertheless, scant data are existing regarding their role in the allografting setting. Lenalidomide enhances the cytotoxic NK cell activity, while it delays the T-

regulatory cell recovery, thus resulting in a better anti-myeloma effect, but at the potential cost of a higher GvHD incidence [60]. The prospective HOVON-76 study evaluated 35 patients who received lenalidomide at the dose of 10 mg daily, for 21 consecutive days in 28-day cycles. Although in 37% of patients a promising PFS rate was observed, the toxicity was remarkable, since almost half of the patients were unable to complete more than 2 cycles of the maintenance treatment due to severe manifestations of GvHD [61]. Another prospective non-randomized study conducted by the CIBMTR assessed 30 patients who received lenalidomide in the abovementioned dose, as maintenance treatment, 60–170 days post-alloSCT. Similar to the HOVON-76 study, 63% of patients discontinued the treatment due to either severe GvHD or relapsed disease. However, for those who completed the treatment, the estimated 1.5-year OS and PFS were 78% and 63%, respectively, while the TRM was 11% [62]. To reduce the toxicity rates, Wolschke et al., in a phase I–II trial, utilized a lower dose of lenalidomide (5 mg daily) for 21 consecutive days in a 28-day cycle, initiating the maintenance treatment 3 months post-graft infusion. This approach demonstrated better tolerability, without adversely affecting the survival outcomes (2-year OS: 80%, 2-year PFS: 60%) [60]. A potential take home message from these published studies is that lenalidomide could be a reliable maintenance treatment strategy post-alloSCT, in doses of 5–10 mg daily every 28 days and with preferable onset of treatment beyond 3 months post-stem cell infusion.

Donor lymphocyte infusions (DLIs)

Preemptive or prophylactic DLIs enhance the graft vs. malignancy effect, resulting in a lower incidence of disease recurrence or progression. The reported response and survival rates for allografted patients who received DLIs for high-risk MM disease were encouraging; though not surprisingly, the incidence of induced GvHD, especially for those patients who received higher doses of DLIs, was considerable [10, 63, 64]. The co-administration of DLIs along with PIs or IMIDs is an appealing treatment approach, given the documented inhibitory effect of the latter on the alloreactive T cells. In an interesting phase I/II study, Kröger et al. treated 18 patients with advanced/refractory disease with thalidomide 100mg/day followed by DLIs. After a relative short median follow-up of 12 months, no patient experienced acute GvHD (aGvHD) ≥ grade 2 while the incidence of limited chronic GVHD (cGvHD) was 38%, with none of the patients experiencing extensive cGvHD. The 2-year OS and PFS were at least promising, 100% and 84%, respectively [65]. The same group published also the clinical results for MM patients who failed to achieve complete remission post allografting and were treated with a combination of DLIs plus either PI (bortezomib, $n = 8$) or IMIDs (thalidomide or lenalidomide, $n = 17$). Achievement of CR was observed in 60% of patients and the incidence of clinically significant aGvHD and cGvHD was acceptable (grade II–IV aGvHD: 33%, grade III–IV aGvHD: 7%, extensive cGvHD: 17%). For patients who achieved CR after DLIs plus PIs or IMIDs, the 5-year OS and PFS were 90% and 60%, respectively. Though the number of patients and the short-term follow-up are prohibitive in reaching any firm conclusions, it seems that the reported results should be considered at least promising given the poor disease characteristics [10].

Novel T cell–based therapies

Currently, T cell immunotherapy represents the most "active" research area for cancer treatment. Chimeric antigen receptor (CAR) T cell therapy represents the spearhead of clinical research in the field of cellular therapies. Several clinical trials with CAR T cells in heavily pretreated and refractory MM patients are ongoing or have been completed. The preliminary results have shown remarkable responses, may be the highest ever reported as compared to other therapies in a similar setting (including auto or alloSCT); however, the response durations are not long lasting and the median event-free survival does not exceed 6–16 months in the majority of the reported results [66•]. Bispecific T cell engaging agents (BiTEs) have also been explored in the treatment of refractory MM patients and preliminary results of clinical trials have shown deep responses, but due to the limited data and the short-term follow-up, long-term efficacy in heavily pretreated patients remains unknown [67•].

Another interesting treatment approach to augment the GvMM effect without worsening the GvHD incidence is the generation and administration of cytotoxic T cells with specificity against common antigens on the MM cells. Tyler et al. evaluated 10 patients with high expression of the WT-1 antigen in the myeloma clones and allografted them with T cell–depleted grafts followed by DLIs. Interestingly, patients found to have high circulating numbers of specific cytotoxic T cell clones against WT-1 antigens achieved better response and survival rates without unacceptable GvHD manifestations [68]. Nowadays, it is feasible to generate clinically relevant numbers of specific T cells against WT-1 antigens as well as against other antigens known to be expressed from MM clones [69].

Summary

Allogeneic stem cell transplantation has a documented advantage over other approved treatments in reducing the incidence of relapse; however, the TRM, which still accompanies the procedure, impedes its widespread use as a treatment option for patients with high-risk MM who otherwise are fit enough for intensive treatment approaches. Despite the toxicity-related disadvantages, even in the era of novel treatment agents in MM, the definite role of alloSCT has not been elucidated yet, largely due to the lack of well-designed prospective clinical trials. Given that the majority of the adverse and severe/lethal toxicity events occur during the early transplant period (up to 12 months) and since the plateauing in OS and PFS curves appears 3–5 years post allografting, it is obvious that studies with long-term follow-up (> 4–5 years) are warranted to draw firm conclusions.

The current non–transplant-based treatment options (next-generation PIs, IMIDs, monoclonal antibodies, checkpoint inhibitors, CAR T cells, and BiTEs) can offer extremely promising response rates including high rates of CR achievement for NDMM patients with high-risk features or for patients with RRMM, but unfortunately, in most of the cases, disease relapse remains an inevitable process. Undoubtedly, significant improvements have been achieved in the field of alloSCT which have resulted in significant minimization of the treatment-related toxicity coupled with the well-proven existing beneficial and durable GvMM effect. The combination of novel treatment modalities with

alloSCT has emerged as an extremely appealing approach, aiming not only in prolonged disease-free period but even in cure of the young and fit MM patients with high-risk disease. Under this point of view, new therapeutic horizons are opened and the role of alloSCT in the MM treatment algorithm needs be redefined in the near future.

Declarations

Conflict of Interest

Panayotis Kaloyannidis declares that he has no conflict of interest. John Apostolidis declares that he has no conflict of interest.

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- •• Of major importance

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