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REVIEW

Current Role of Allogeneic Stem Cell Transplantation in Multiple Myeloma

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ABSTRACT

Major progress in the treatment of multiple myeloma has been made in the last several years. However, myeloma remains incurable and patients with high-risk cytogenetics or advanced stage disease have an even worsen survival. Only allogeneic transplantation may have curative potential in some patients. However, the high non-relapse mortality and incidence of chronic graft-versus-host disease have raised controversy regarding this procedure. In this review, we will address the role of upfront and delayed allogeneic transplant.

Keywords: Multiple myeloma; Allogeneic transplantation; Chronic graft-versus-host disease; CAR-T cell therapy

Key Summary Points

Most patients with multiple myeloma will eventually relapse and die from their disease.

Allogeneic hematopoietic cell transplant is currently the only potentially curative therapy, supporting the existence of a graft-versus-myeloma effect.

Access to an algorithm regarding clinical utilization of allogeneic transplant would benefit clinicians and researchers.

New strategies are necessary to make allogeneic hematopoietic cell transplantation safer while reducing non-relapse mortality and chronic graft-versus-host disease.

In young patients with ultra-high-risk disease, upfront allogeneic transplantation could be a valuable option in the context of clinical trials.

INTRODUCTION

Multiple myeloma (MM) remains incurable for most patients, despite significant improvements

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in treatment. For patients under the age of 70 years with MM, the median overall survival is about 6–7 years [1–3]. Adverse prognostic factors such as high Revised International Staging System (RISS) stage, adverse cytogenetic abnormalities, and plasma cell leukemia result in even shorter survival [4–7]. The vast majority of patients will relapse and succumb to their disease.

Allogeneic hematopoietic cell transplantation (alloHCT) has curative potential in MM, by taking advantage of the dual effect of direct cytotoxicity and graft-versus-multiple myeloma effect (GvMM). The first alloHCT was performed in Seattle by Donnall Thomas on six patients, including one with MM in 1956. Only two patients were engrafted and all died before day +100 [8]. In a series of three patients published in 1986, Gahrton et al. reported one patient with refractory MM achieving complete remission for 3 years after alloHCT, but subsequently relapsed [9]. The first larger studies were published in 1987 and 1991. In 90 patients with MM who received myeloablative alloHCT, overall survival at 76 months was 40%, with 43% achieving complete remission [10].

The high non-relapse mortality (NRM) and incidence of chronic graft-versus-host disease (GVHD) with myeloablative HCT raised significant concerns regarding this procedure. Reduced intensity and nonmyeloablative conditioning regimens were then proposed to reduce NRM but were associated with a higher relapse rate. Currently, alloHCT remains controversial for all these reasons and many centers suggest that it should not be performed at all.

Median total healthcare cost for a reduced-intensity conditioning (RIC) or nonmyeloablative (NMA) allogeneic transplant from day − 10 until day +100 is more than US $161,000. There is also an average of 30 days of hospitalization following the transplant [11]. Triplet or quadruplet drug therapies combinations, used for induction or salvage, can cost US $220,000–590,000 for 1 year of treatment [12, 13]. However, the potential for cure with alloHCT and the lower cost compared with the modern therapies which are not curative should be balanced with the significant morbidity and mortality risk, and there may be selected circumstances where the balance may be more appropriate as discussed later.

In this review, we will address the role of upfront and delayed allogeneic transplant. We will review the different conditioning regimens, type of donors, role of maintenance therapy post-transplantation, and the future perspective of allogeneic transplantation in myeloma. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

UPFRONT ALLOGENEIC TRANSPLANT

Myeloablative Regimens

Traditional myeloablative conditioning regimens include total body irradiation (TBI), cyclophosphamide and busulfan, or melphalan in combination with TBI. A lower relapse rate is associated with myeloablative alloHCT compared to autoHCT [14, 15]. However, the high NRM with myeloablative conditioning substantially decreases overall survival [16]. In a Fred Hutchinson Cancer Center study, 80 patients with MM, with the majority having received more than two prior regimens, received high dose busulfan, cyclophosphamide with or without TBI followed by alloHCT between 1987 and 1994. The NRM at day + 100 was 44% and only 15 patients were surviving disease-free at 7-year post-transplantation [17]. In a larger study by Gahrton et al., 162 patients with newly diagnosed multiple myeloma (NDMM) received alloHCT between 1983 and 1993. Following transplantation, 44% of patients achieved complete remission and the overall survival (OS) at 7 years was 28%. Progression-free survival (PFS) at 6 years was 34% in patients achieving complete remission and NRM at day + 100 after HCT was approximately 41% [18]. Some studies have shown that survival outcome was better in the autoHCT group than with myeloablative HCT as a result of high NRM [19]. The high NRM rates were mainly associated with infections, organ damage, acute GVHD, and chronic GVHD. Refinements in

Table 1 Prospective studies comparing nonmyeloablative autologous/allogeneic transplantation to single auto or tandem auto (auto/auto) in upfront-treated patients with multiple myeloma (MM)

References	Conditioning	OS	PFS	NRM	Overall cGVHD	Comments
IFM99-03 and IFM99-04 [24]	Bu-Flu-ATG	Median 35 vs. 41 months ($p = 0.27$)	Median 25 vs. 30 months ($p = 0.56$)	10.9%	42.8% (including 16% post-DLI)	Allocation was determined by the presence of HLA-matched sibling donor (IFM99-03 vs. IFM99-04) VAD induction
PETHEMA [25]	Flu-Mel	Median not reached vs. 58 months ($p = 0.9$)	Median not reached vs. 31 months ($p = 0.08$)	16% vs. 5%	66%	Allocation was determined by the presence of HLA-matched sibling donor VAD induction
Torino [26, 27]	TBI 2 Gy	Median 80 vs. 54 months ($p = 0.01$)	Median 35 vs. 29 months ($p = 0.02$)	16 vs. 2% at 2.5 years	32% extensive at 2 years	Allocation was determined by the presence of HLA-matched sibling donor VAD induction
Hovon-50 [62, 81]	TBI 2 Gy	6 years: 55% vs. 55% ($p = 0.68$)	6 years: 28% vs. 22% ($p = 0.19$)	16% vs. 3% at 6 years	64% (9% limited and 55% extensive)	Allocation was determined by the presence of HLA-matched sibling donor VAD induction
EBMT-NMAM2000 [28, 29]	Flu-TBI 2 Gy	3 years: 75% vs. 68% 8 years: 49% vs. 36% ($p = 0.03$)	3 years: 43% vs. 39% 8 years: 22% vs. 12% ($p = 0.027$)	12% vs. 3% at 2 years	54% (31% limited and 23% extensive)	Allocation was determined by the presence of HLA-matched sibling donor VAD induction
BMT CTN [30, 31]	TBI 2 Gy	3 years: 46% vs. 43% ($p = 0.191$) 10 years: 44% vs. 43% ($p = 0.91$)	3 years: 80% vs. 77% ($p = 0.671$) 10 years: 18% vs. 19% ($p = 0.87$)	TRM 11% vs. 4% at 3 years	54% at 2 years	Allocation was determined by the presence of HLA-matched sibling donor. Induction not specified

Table 1 continued

References	Conditioning	OS	PFS	NRM	Overall cGVHD	Comments
Pooled Torino, Pethema, EBMT and BMT-CTN [36]	TBI 2y or Flu-Mel	5 years: 59.8% vs. 62.3% (p = 0.370) 10 years: 36.4% vs. 44.1% (p = 0.110)	5 years: 23.4% vs. 30.1% (p = 0.010) 10 years: 14.4% vs. 18.7% (p = 0.060)	17.4% vs. 6.9% at 5 years 19.7 vs. 8.3% at 10 years	Not available	Meta-analysis/ systematic review
Knop et al. 2019 [37]	Flu-Mel ± ATG if MUD	Median 70.2 vs. 71.8 months (p = 0.856)	Median 34.5 vs. 21.8 months (p = 0.003)	14.3% vs. 4.1% at 2 years	32.8%	Anthracycline-based induction 100% del13q in both groups 59% MUD
Gran et al. 2021 [35]	Treo vs. non-treo RIC vs. non-treo MAC	At 5 years: 62% vs. 57% vs. 47% (p = 0.04)	Relapse incidence at 5 years: 59% vs. 50% vs. 49% (p = 0.079)	17% vs. 21% vs. 23%	Not available	83% unknown cytogenetic Fit patients

ATG antithymocyte globulin, *Bu* busulfan, *cGVHD* chronic graft-versus-host disease, *Cyclo* cyclophosphamide, *Flu* fludarabine, *Mel* melphalan, *MUD* match unrelated donor, *NRM* non-relapse mortality, *OS* overall survival, *PFS* progression-free survival, *TBI* total body irradiation

conditioning regimens have led to improved overall survival in the late 1990s from 30% to 50% at 4 years, without significatively reducing NRM [20, 21]. A more recent long-term follow-up of patients with MM who received a modified myeloablative HCT with TBI, busulfan, cyclophosphamide, and antithymocyte globulin conditioning regimen reported at 12 years an OS of 50% and event-free survival (EFS) of 35%. The NRM of 17% was more acceptable [22].

Introduction of less ablative conditioning regimens called reduced-intensity conditioning (RIC) and nonmyeloablative (NMA) have been used since 1998 [23]. The aim of the RIC and NMA conditioning was to keep the GvMM effect while decreasing systemic toxicity and subsequently NRM. Myeloablative transplant utilization has dramatically fallen since that time and remains reserved for patients with more aggressive disease course.

Reduced Intensity and Nonmyeloablative Regimens

There are several prospective studies regarding reduced-intensity and nonmyeloablative regimens in MM (Table 1). IFM99-03 and IFM99-04 were the first published prospective trials to compare auto-auto (tandem) HCT to auto-allo HCT in patients with high-risk features (deletion 13q or elevated beta2-microglobulin). The conditioning regimen consisted of busulfan, fludarabine, and anti-thymocyte globulin (ATG). The median OS (35 months vs. 41 months, p = 0.27) and PFS (25 months vs. 30 months, p = 0.56) were similar in the auto-allo and tandem autoHCT cohort, respectively. The incidence of extensive chronic GVHD was 35.7%. Indeed, this low chronic GVHD incidence due to the administration of high-dose ATG may also had led to a decrease in the GvMM effect [24].

The PETHEMA trial reported by the Spanish group included 25 patients who received auto-allo HCT in comparison with 85 tandem autoHCT after VAD-based induction. There was a trend for longer median OS (not reached vs. 58 months) and median PFS (not reached vs. 31 months) for the alloHCT group, but NRM was higher (16% vs. 5%). However, this study lacked statistical power to demonstrate differences between both groups [25].

In the Italian trial, a VAD induction and autograft HCT was followed by either NMA alloHCT or a second autoHCT. The median OS (80 months vs. 54 months, $p = 0.01$) and median PFS (35 months vs. 29 months, $p = 0.02$) were significatively longer in the alloHCT cohort. However, an NRM of 16% was reported [26, 27].

The European Bone Marrow Transplant centers (EBMT) prospectively followed 249 patients who received alloHCT and 249 who received second autoHCT patients after VAD induction and a first autoHCT. Patients in the tandem autoHCT arm received thalidomide maintenance after transplant. Patients in alloHCT arm were younger (54 years vs. 57 years, $p < 0.001$). Overall survival (49% vs. 36%, $p = 0.03$) and PFS (22% vs. 12%, $p = 0.027$) showed benefit for alloHCT at 8 years [28, 29].

The BMT CTN study enrolled 436 patients in the auto-auto HCT arm and 189 patients in the auto-allo HCT arm. The 10-year OS (44% vs. 43%, $p = 0.91$) and PFS (18 vs. 19%, $p = 0.87$) were similar between both arms with standard risk disease [30, 31]. True randomized trials comparing alloHCT outcomes have not been done in MM. Indeed, the allocation in these five prospective studies (IFM, PETHEMA, Torino, EBMT, and BMT CTN) was based on the presence of an HLA-matched sibling donor. If no compatible HLA-matched was found, patients were enrolled in the tandem autoHCT arm ("biological randomization"). However, it is unclear if any systematic bias is introduced by the biological randomization.

In the latest retrospective study performed by the EBMT, all patients with myeloma who received post-transplant cyclophosphamide for an alloHCT were reviewed. This included patients who had matched related donors, matched unrelated donors (MUD), haploidentical donors, and mismatched related or unrelated donors. The incidence of overall chronic GVHD was 27%, limited 21%, and extensive 6% without difference among the type of donor. Two-year OS, PFS, and NRM were 51%, 26%, and 19%, respectively. In Cox multivariate analysis, use of matched related donor was associated with improved overall survival (HR = 0.6, $p = 0.029$). The PFS was improved by RIC conditioning (HR = 1.42, $p = 0.041$) and there was a trend toward better PFS with use of MUD (HR = 0.69, $p = 0.08$) [32].

Alternative Conditioning Regimens

Few studies compared the outcomes with different conditioning regimens. In an EBMT retrospective study, patients who received treosulfan conditioning (Treo) were compared with non-Treo myeloablative conditioning (MAC) and non-Treo RIC. The Treo regimen was based on previous studies which showed stable engraftment and low NRM [33, 34]. In the upfront single alloHCT or auto-allo HCT subgroup, there were 136 patients receiving Treo, 587 non-Treo RIC, and 375 non-Treo MAC. The 5-year NRM was 10% with Treo, 17% with non-Treo RIC, and 19% with non-treo MAC. The 5-year OS was 65%, 57%, and 47% respectively for Treo, RIC, and MAC ($p = 0.04$). The 5-year overall survival was also better for Treo auto-allo HCT patients than for patients with single alloHCT (59% vs. 46%, $p<0.01$). The cumulative incidence of relapse showed no statistical difference between the three different regimens (59% for Treo vs. 50% for RIC vs. 49% for MAC, $p = 0.07$) [35].

Meta-Analysis/Pooled Data Analysis

A pooled analysis that included prospective trials with upfront auto-allo HCT and tandem autoHCT with allocation based on the presence or not of HLA-matched sibling donor was published in 2020. This study included four clinical trials discussed previously: Blood and Marrow Transplant Clinical Trials Network (BMT-CTN), EBMT, Torino, and PETHEMA. The IFM and

Table 2 Studies with nonmyeloablative autologous/allogeneic transplantation in salvage for patients with multiple myeloma (MM)

References	Conditioning	OS	PFS	NRM	Overall cGVHD	Comments
de Lavallade et al. 2008 [82]	RIC MUD Flu-Bu-ATG or Flu-TBI	50% donor group vs. 49% no-donor group at 3 years	46% donor group vs. 48% no-donor group at 3 years	33% at 3 years	74%	Donor vs. non-donor analysis Absence cytogenetic data Heavily pre-treated patients
Patriarca et al. 2012 [83]	RIC/NMA conditioning Flu-TT-TBI, Flu-Cy, Flu-Treo	54% donor group vs. 53% no-donor at 2 years	42% donor group vs. 18% no-donor at 2 years	22% vs. 1% at 2 years	39%	48% ATG 40% cytogenetic high risk Donor vs. non-donor analysis
Auner et al. 2013 [84]	RIC various conditioning	Median 24.7 months 30% at 5 years	Median 9.6 months	28.4% at 3 years	48%	
Freytes et al. 2014 [85]	RIC/NMA various conditioning vs. Mel autoHCT	20% vs. 46% at 3 years 9% vs. 29% at 5 years	6% vs. 12% at 3 years 2% vs. 4% at 5 years	14% vs. 4% at 3 years	Not available	Relapsed after a first autoHCT. Heavily pre-treated patients Absence cytogenetic data AlloHCT vs. second autoHCT analysis
Pawarode et al. 2016 [86]	Flu-Bu4 MAC regimen	29% at 3 years	15% at 3 years	29% at 3 years	68% at 3 years	Refractory or high-risk patients 46% score Karnofsky $\leq$ 80%
Sohb et al. 2017 [87]	RIC with various conditioning 45% Flu-Bu-ATG 30% Flu-TBI CB: Flu-Cy-TBI	At 3 years MUD: 47% MMUD: 45% CB: 38%	At 3 years MUD: 25% MMUD: 31% CB: 19%	At 3 years MUD: 22% MMUD: 33% CB: 27%	MUD: 41% MMUD: 47% CB: 31%	79% no cytogenetic data 45% ATG MUD vs. MMUD vs. CB analysis
Schneidawind et al. 2017 [38]	37% myeloablative, 44% RIC, 19% NMA	50% at 3 years 39% at 40 months	15% at 3 years	20% at 3 years	47% (19% limited and 28% extensive)	19% cytogenetic high risk

Table 2 continued

References	Conditioning	OS	PFS	NRM	Overall cGVHD	Comments
Castagna et al. 2017 [50]	Haplo with RIC (53%): Flu-Mel-TT or NMA (47%): Flu-Cy-TBI All patients: PT-Cy	63% at 18 months	33% at 18 months	10% at 18 months	20% at 18 months	Heavily pre-treated HLA mismatch donor ($\leq$ 7/10) 50% $\geq$ 3 lines of therapy 100% previous BTZ and 90% previous lenalidomide No cytogenetic data
Shingaki et al. 2017 [88]	Flu-Mel-TBI MAC regimen	62.5% at 3 years	33% at 3 years	0%	50% moderate-severe	Relapsed and/or refractory patients heavily pre-treated. $N = 8$
Kawamura et al. 2018 [89]	Various conditioning	47.2% at 3 years	18.8% at 3 years	23.4% at 3 years	44.1% at 2 years	27% high-risk cytogenetic 74% RIC, 24% myeloablative
Patriarca et al. 2018 [39]	Flu-based RIC plus TBI 2 Gy or Mel or other alkylants ± ATG	31% at 7 years in donor group vs. 9% no-donor group ($p < 0.001$)	18% at 7 years donor group vs. 0% no-donor group ($p < 0.001$)	27% at 5 years	65%	33% ATG 41% high-risk cytogenetic Salvage based on IMiDs or BTZ
Greil et al. 2019 [40]	Flu-based RIC conditioning	43.6% at 5 years 26.1% at 10 years	23.5% at 5 years 20.1% at 10 years	12.4% at 5 years	36%	58% relapsed patients, heavily treated
Sahebi et al. 2019 [51]	Haplo 81% PT-CY	48% at 2 years	17% at 2 years	26% at 2 years	46% at 2 years	75% RIC/NMA conditioning regimen. No cytogenetic data or previous therapy
Byant et al. 2020 [41]	T-depleted/CD34 selected Flu-Bu-Mel-ATG2	50% at 3 years	30% at 3 years	23% at 3 years	11% at 2 years	Relapsed MM with high-risk cytogenetics

Table 2 continued

References	Conditioning	OS	PFS	NRM	Overall cGVHD	Comments
Val Elssen et al. 2021 [90]	Flu-Cy-TBI KIR-ligand mismatched Haplo donor PT-Cy	52% at 2 years	Median 90 days	18% at 12 months	36%	Heavily pre-treat patient Poor risk patients (high-risk cytogenetics or relapse within a year after autoHCT or relapse after $\geq$ 3 lines of therapy)

ATG antithymocyte globulin, *Bu* busulfan, *BTZ* bortezomib, *CB* umbilical cord blood, *cGVHD* chronic graft-versus-host disease, *Cyclo* cyclophosphamide, *Flu* fludarabine, *IMiDs* immunomodulatory drugs, *MAC* myeloablative conditioning, *Mel* melphalan, *MUD* match unrelated donor, *MMUD* mismatch unrelated donor, *NMA* nonmyeloablative, *NRM* non-relapse mortality, *OS* overall survival, *PFS* PFS, *RIC* reduced-intensity regimen, *TBI* total body irradiation, *Treo* treosulfan, *TT* thio

Hovon-50 studies were not included in the analysis. Patients in the auto-allo HCT cohort had better OS (HR 0.84, $p = 0.02$) and PFS (HR 0.85, $p = 0.004$) than the tandem autoHCT cohort. The cumulative incidence of relapse was lower in auto-allo at 10 years (61.6% vs. 77.2%, $p < 0.001$). Rate of NRM at 10 years was higher in the auto-allo HCT cohort (19.7% vs. 8.3%, $p < 0.001$). The 5-year post relapse survival rates were 51.1% and 37.0% in the auto-allo and autoHCT cohort, respectively. Even though these patients were not exposed to newer drugs, this study clearly demonstrated a long-term benefit, likely driven by the GvMM effect [36].

Role in High-Risk Patients

In the updated results from the BMT-CTN study, a subgroup analysis was done on patients with deletion 13q or beta-2-microglobulin level greater than 4 mg/L. The 10-year OS was similar in both arm (37% for the auto-allo arm vs. 29% for auto-auto arm, $p = 0.45$). The 10-year PFS (21% vs. 4%, $p = 0.03$) was better for the high-risk auto-allo arm than for the tandem autoHCT arm [31]. In the EBMT-NMAM 2000 study, for patients with deletion 13q, 5-year OS (69% vs. 55%, $p = 0.003$) and PFS (31% vs. 10%, $p = 0.002$) were better for the auto-allo group than for the tandem autoHCT group. The 5-year relapse risk was also lower in the auto-allo group (55% vs. 86%, $p = 0.004$) [29]. In the pooled analysis, patients with high-risk disease (beta-2 microglobulin level greater than 4 mg/L or presence of deletion 13q) have a better 10-year PFS in the auto-allo HCT than with tandem autoHCT (22% vs. 9%, $p = 0.008$). The 10-year OS was similar (39 vs. 29%, $p = 0.120$) [36]. In a randomized phase 3 trial, the German Myeloma Study Group (DSMM) compared tandem autoHCT versus auto-allo HCT in patients with NDMM with deletion 13q. This study enrolled 126 auto-allo HCT patients and 73 tandem autoHCT. After randomization, approximately 15% of the study population was excluded from the modified intention-to-treat analysis. Median overall survival was not significatively different between both arms. However, median PFS was respectively better in the alloHCT arm than in the tandem autoHCT arm (34.5 months vs. 21.8 months, $p = 0.003$). In patients with deletion 13q and deletion 17p in this same study, median OS (61.5 months vs. 23.4 months, $p = 0.0002$) and PFS (37.5 months vs. 6.5 months, $p = 0.032$) were respectively significantly better in the alloHCT arm than in the tandem autoHCT arm [37]. However, the definition of high-risk disease has significantly changed over the last decade and deletion 13q is now considered as a standard cytogenetic risk abnormality. Thus, these studies may not be a

true reflection of alloHCT outcome in high-risk patients.

USE OF ALLOGENEIC TRANSPLANTATION AS SALVAGE AFTER RELAPSE

Allogeneic HCT after relapse is more widely used than as an upfront therapy. Studies have used various conditioning regimens with related donors, unrelated donors, and more recently haploidentical donors with post-transplant cyclophosphamide (Table 2).

In a study by the German Myeloma study group, 41 patients received myeloablative (37%), reduced intensity (44%), or non-myeloablative (19%) conditioning. The OS, PFS, and NRM at 3 years were 50%, 15%, and 20%, respectively. In addition, treatment with immunomodulatory drugs (IMiDs) or proteasome inhibitors on relapse after allogeneic stem cell transplant were associated with a significantly improved 3-year OS, when compared to patients that did not receive these drugs (68% vs. 14%, $p = 0.004$) [38].

In a larger retrospective multicenter study, Patriarca et al. compared 79 patients who received alloHCT after relapse to 90 patients without donors that were instead treated with bortezomib and/or IMiDs. The alloHCT patients had a better OS (31% vs. 9%, $p < 0.001$) and PFS (18% vs. 0%, $p < 0.001$) at 7 years. The 5-year NRM incidence was 27%. Forty-one percent of patients in this study had high-risk cytogenetics including t(4;14), deletion 17p, and deletion 13q [39]. In another retrospective study where 52% of patients received alloHCT in salvage with fludarabine-based RIC, 10-year OS and PFS were 26.1% and 20.1%. In subgroup analysis, patients with progressive disease according to International Myeloma Working Group (IMWG) criteria had worse 10-year OS (28.4% vs. 22.5%, $p = 0.003$) and PFS (24.0% vs. 10.0%, $p = 0.001$) than patients with inactive disease [40].

In a recent retrospective study published by Bryant et al., 73 patients underwent $CD34^{+}$ selected alloHCT, including 40% with high-risk cytogenetics. The 3-year OS, PFS, and NRM were 50%, 30% and 23%. The rates of grade II–IV acute GVHD were 18% at day +180 and overall chronic GVHD was 11% at 2 years. In multivariate analysis, age 55 years or older (HR 3.5, $p = 0.001$) and presence of acute or chronic GVHD by 6 months post-allo HCT were associated with reduced OS (HR 2.8, $p = 0.02$). In addition, multivariate analysis, age 55 years or older (HR 2.2, $p = 0.006$) and partial response/minimal response disease status at alloHCT (HR 2.6, $p = 0.001$) were associated with worse PFS [41].

CAR-T CELL THERAPY IN PATIENTS WITH RELAPSED AND REFRACTORY MYELOMA

CAR-T cell therapy are T cells modified to express a chimeric receptor with an antigen receptor containing a single chain variable fragment and an intracellular T cell receptor signaling domain. The B cell maturation antigen (BCMA), a protein selectively expressed in B cells, is currently the main target in MM [42].

Idecabtagene vicleucel (ide-cel) is the first US Food and Drug Administration (FDA)-approved autologous BCMA-directed CAR-T cell. In a total of 128 patients refractory to previous line of therapy, the overall response rate was 73% for the whole cohort. Patients included in the KARMMA trial had received a median 6 previous therapy and 65% of patients had a standard-risk cytogenetic. The median PFS and median OS were 8.8 and 19.4 months across all treated patients. More than 84% of the patients developed a cytokine release syndrome (CRS), mostly grade 1 or 2 [43].

Ciltacabtagene autoleucel (cita-cel) is another autologous BCMA-directed CAR-T cell. In the CARTITUTDE-1 trial of 97 refractory patients mostly characterized by standard-risk cytogenetic profile (76%), the overall response rate was 97.9% with 80.4% achieving stringent complete response or better. The 18-month PFS was 66% and the 18-month OS was 80.9%. Cytokine release syndrome occurred in 95% of patients, mostly grade 1 or 2 [44].

Additionally, BCMA targeting CAR-T cells with human scFv (orvacabtagene autoleucel

[45] and CT053 [46]) and allogeneic BCMA-targeting CAR-T cell with human scFv [47] (ALLO-715 product) are showing promising results. In the abstracts presented at 2020 American Society of Clinical Oncology meeting and 2021 American Society of Hematology meeting, 38–64% of patients in these trials are achieving very good partial response or better. BCMA-targeting CAR-T therapy has demonstrated remarkable efficacity, although long-term follow-up data are needed. The BCMA CAR-T cell therapy is well positioned to take the place of allogeneic transplantation in patients with relapsing and refractory myeloma in the future.

One case report demonstrated that an anti-BCMA CAR-T followed by haploidentical HCT in a patient with triple refractory extramedullary myeloma is feasible [48]. However, no other literature or ongoing clinical trials were found regarding CAR-T cell therapy as a bridge before alloHCT in patients with relapse/refractory MM.

Alternative Donors

In the past years, allogeneic transplantation from haploidentical donors has been proven safe and feasible with nonmyeloablative conditioning regimen followed by post-transplantation cyclophosphamide (PT-Cy) [49]. In a retrospective multicenter study, 30 patients receiving bortezomib or IMiDs followed by haploidentical HCT with PT-Cy between 2011 and 2017 were evaluated. No cytogenetic data were available. More than half of the patients had received at least three lines of therapy before HCT. The 18-month OS, PFS, and NRM were 63%, 33%, and 10%. The rate of grade II–IV acute GVHD was 29% at day + 100 and overall chronic GVHD was 20% at 18 months [50]. Additionally, PT-Cy is also a very interesting option, especially in patients who do not have a suitable donor.

A retrospective study from the registries of the EBMT and CIBMTR showed 2-year OS, PFS, and NRM of 48%, 17%, and 26%, respectively, in patients with haploidentical HCT. The population was heterogenous with 20% receiving myeloablative conditioning regimen and 80% PT-Cy, in addition to the presence of older patients (up to 73 years) [51].

There are few studies on outcomes of umbilical blood cord (CB) transplantation with MM. The retrospective EBMT study in 95 patients who received single or double CB with reduced-intensity conditioning, showed a 3-year OS and PFS of 40% and 24% respectively. The NRM at 3 years was 29% [52]. One study is currently in progress to assess outcomes with UM171 expanded cord blood transplant in MM (NCT03441958). Finally, TCRαβ and CD19-depleted peripheral blood stem cells from a haploidentical familial donor after reduced-intensity conditioning may also be promising in MM [53].

Is There a Role for Maintenance Post Allogeneic Transplantation?

In a prospective trial, Green et al. evaluated patients who received auto-allo HCT followed by bortezomib (BTZ) maintenance for 9 months. In the 24 patients with upfront alloHCT, the 4-year OS and PFS were 61% and 75%. The 2-year NRM for patients with upfront alloHCT and those who failed therapy were 8% and 14%, respectively [54].

In a similar study, a Canadian myeloma group prospectively followed up 39 patients with NMA upfront auto-allo HCT with BTZ maintenance q2 weeks for 1 year compared to a historical cohort. After BTZ-based induction, both cohorts received autologous HCT followed by nonmyeloablative conditioning with or without BTZ maintenance. BTZ was started at day + 120 after alloHCT. OS, PFS, and NRM at 5 years were respectively 80%, 41%, and 12% in the alloHCT cohort. At 2 years, the incidence of overall and moderate/severe chronic GVHD were 57% and 46%, respectively. Achievement of negative minimal residual disease status (MRD) by flow cytometry prior to alloHCT (HR = 0.27, $p = 0.037$) and at 4 months after alloHCT (HR 0.08, $p = 0.018$) was also associated with better PFS in multivariate analysis in patients who received BTZ maintenance [55]. An active clinical trial is currently randomizing patients with high-risk myeloma to ixazomib

maintenance or placebo after alloHCT (NCT02440464). In a retrospective study, daratumumab given as consolidation or at a median of 30 months post-alloHCT seems to be safe. There was no significant impact on acute and chronic GVHD and no clear increase in the incidence of infection [56].

Alsani et al. designed a lenalidomide dose escalating protocol starting 96 days (range 66–171 days) after alloHCT. Overall response improvement of 33% was observed with lenalidomide, but 47% of patients developed acute GVHD [57]. HOVON-76 trial had similar results with an incidence of grade II-IV acute GVHD % and chronic GVHD of 37% and 53% respectively. In this study, lenalidomide was started 3 months after alloHCT [58]. Thus, some concerns have been expressed about increased incidence of acute GVHD with lenalidomide maintenance. However, a multicenter Italian study showed that lenalidomide and dexamethasone as part of salvage therapy, started at a median of 860 days after alloHCT, showed a much lower rate of acute GVHD. In this study, the incidence of grade II–IV acute GVHD at day +100 and chronic GVHD at 5 years were 13% and 35%, respectively. The 5-year OS, PFS, and NRM were 60%, 39%, and 12%, respectively [59]. Kroger et al. reported 33 patients with lenalidomide maintenance, started after a median of 168 days after alloHCT with myeloablative conditioning. The 3-year PFS was 52%, while 34% of patient developed grade II-IV acute GVHD [60]. In conclusion, lenalidomide maintenance seems safe but must be started at least 3–6 months after transplantation [61]. However, there is a lack of prospective clinical trial and firm guidelines cannot be given.

GRAFT-VERSUS-HOST DISEASE PROPHYLAXIS

The standard graft-versus-host prophylaxis used in Hovon-50 [62], Italian study [26], BMT CTN [30], and NMAM2000 [28] is cyclosporine in combination with mycophenolate mofetil. In contrast, PETHEMA investigators were using cyclosporine with methotrexate [25] and other groups tacrolimus with mycophenolate mofetil or methotrexate [14, 63]. On average, an extensive or moderate-severe chronic GVHD incidence of 40–70% has been reported in these trials. In a first phase I study, the Spanish group showed that adding bortezomib in the conditioning regimen and in the combination of tacrolimus and sirolimus GVHD prophylaxis was safe and effective at reducing the risk of GVHD [64]. In a more recent phase II trial, these investigators used combination of tacrolimus and methotrexate as GVHD prophylaxis. The conditioning regimen included bortezomib and was followed by bortezomib and lenalidomide maintenance. This combination of new drugs seems to decrease the relapse rate after transplantation. However, a synergistic effect of the combination of bortezomib with methotrexate instead of sirolimus seems to have increased the incidence of acute GVHD [65].

INFECTION AND ALLOGENEIC TRANSPLANTATION

Infectious diseases remain one of the most frequently encountered complications in patients with MM after alloHCT and are associated with an early mortality. The most frequent pathogens observed are *Staphylococcus aureus*, *Streptococcus pneumonia*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Aspergillus* species, *Candida* species, and *Pneumocystis jirovecii*. In addition, herpes simplex virus, varicella zoster virus, CMV, and EBV are other frequent pathogens [66]. Letermovir prophylaxis for CMV-seropositive transplant recipients is effective in preventing clinically significant CMV infection [67]. Antifungal prophylaxis targeting either *Candida* species alone or *Candida* species plus molds is generally recommended in all patients [68]. Acyclovir or valacyclovir prophylaxis is recommended in patients seropositive for varicella zoster virus or herpes simplex virus. Prophylaxis against *P. jirovecii* is also recommended after engraftment and continued for as long as immunosuppressive therapy is given. Trimethoprim-sulfamethoxazole is the preferred regimen for PCP prophylaxis when available, which is also effective against

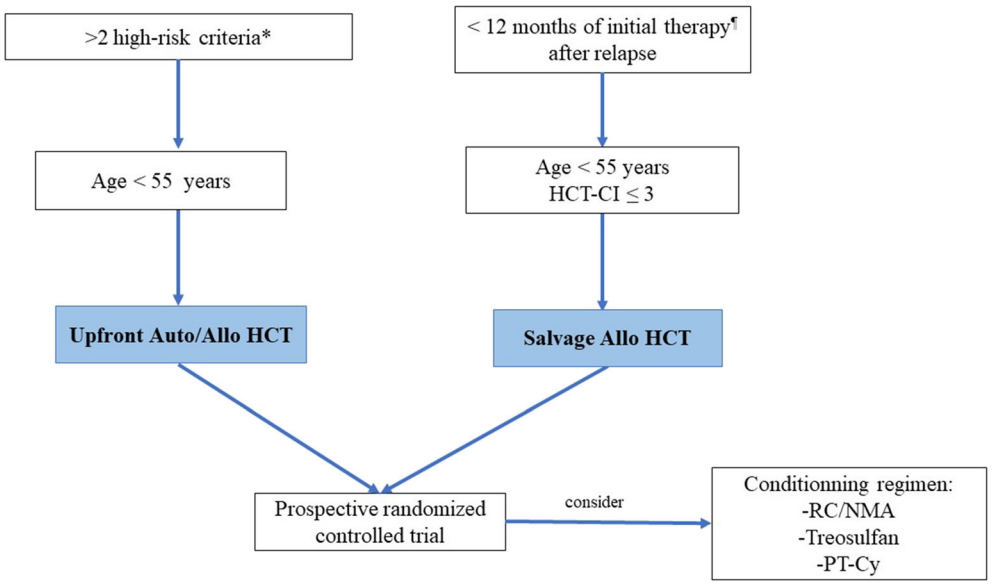

Fig. 1 Suggested algorithm for clinical utilization of allogeneic transplant, preferably in the context of a clinical trial. *High risk criteria: ISS 3, elevated LDH at diagnosis, extramedullary disease, high risk cytogenetic abnormalities (17p deletion, t(14;16), t(4;14), 1q amplification) or high number of circulating plasma cells (CPCs). ¶Less than 12 months of initial therapy including auto HCT. *HCT-CI* hematopoietic cell transplantation comorbidity index, *NMA* nonmyeloablative conditioning, *PT-Cy* posttransplant cyclophosphamide, *RIC* reduced-intensity conditioning

Toxoplasma gondii. Patients with pretransplant screening tests positive for *Strongyloides stercoralis* or unexplained eosinophilia with travel history suggesting exposition to *S. stercoralis* should receive empiric treatment prior to HCT [68]. Post-transplantation, HCT recipients should be vaccinated against pneumococcus, *Haemophilus influenzae*, tetanus, and others according to European Society for Blood and Marrow Transplantation (EBMT), American Society of Blood and Marrow Transplantation (ASBMT), and Center For International Blood and Marrow Transplant Research (CIBMTR) guidelines [69].

COMORBIDITIES AND ALLOGENEIC TRANSPLANTATION

The hematopoietic cell transplantation specific comorbidity index (HCT-CI) can predict NRM, OS, and to a lesser extent PFS in patients having reduced-intensity/nonmyeloablative conditioning regimens [70–72]. Moreover, Karnofsky performance status is also associated with OS and NRM in recipients of alloHCT [70]. Veeraputhiran et al. showed that higher HCT-CI score predicted all-cause mortality in patients receiving nonmyeloablative allogeneic stem cell transplantation [73]. According to Maziarz et al., pre-existing invasive fungal infection is not a contraindication for allogeneic HCT in patients with hematologic malignancies [74]. However, caution should be exercised given that few data are available with patients with MM. Frailty [75], pretransplantation hepatic [76], lung [77], or renal [78] dysfunction had been identified as determinants for OS.

FUTURE PERSPECTIVE

Allogeneic transplantation for MM has the potential to cure patients and may allow long-term survival in carefully selected patients. Future studies need to be done to minimize conditioning regimen toxicity and reduce

incidence of GVHD while preserving GvMM effects. As recommended by the International Myeloma Working Group, alloHCT must be restricted to patients participating in clinical trials, preferably in prospective randomized trials [79, 80].

Upfront nonmyeloablative and reduced-intensity conditioning are associated with a plateau in the survival curves around 5–7 years. It is very uncommon to see late relapse after more than 10 years, highlighting the relevance of a GvMM effect [36].

Nonmyeloablative or reduced-intensity conditioning should be the conditioning of choice based on the lower NRM and GVHD incidence. New conditioning regimens like treosulfan could be considered given their lower NRM. In contrast, myeloablative conditioning regimens should only be used in exceptional circumstances considering their high rate of NRM. Allogeneic HCT should be done preferably after autologous HCT to obtain deeper response and reduce future risk of relapse. Achieving a negative MRD before alloHCT seems to improve long-term outcomes, but more studies are warranted. Maintenance after transplant should be considered with the aim to lower relapse rates, but not to increase the incidence of GVHD. Bortezomib, lenalidomide, and possibly monoclonal antibodies look promising. However, maintenance must be delayed 3–6 months after transplantation to reduce the incidence of acute GVHD.

To the best of our knowledge, there are no studies comparing upfront versus delayed allogeneic transplant. When contemplated in the context of relapse, it should be done earlier in the course of the disease. It may be particularly relevant for patients with high-risk disease, including high-risk cytogenetic, plasma cell leukemia, extramedullary disease, and/or high RISS score while having a low HCT-CI.

In 2015, the IMWG together with the ASBMT, EBMT, and the BMT-CTN proposed guidelines for allogeneic transplant as salvage treatment in myeloma. The experts' consensus states that allogeneic HCT should be considered as an appropriate therapy in early relapse (less than 24 months) the in context of prospective randomized trials. In addition, they suggested that alloHCT should always be performed in clinical trials and recommended to evaluate the role of maintenance treatment after autoHCT.

Many clinical trial results for alloHCT in first line and for relapsed patients were biased by the retrospective nature of the analyses, absence of randomization, and heterogeneity of the patient cohorts. Patients with different cytogenetic risks, different induction therapy, and with incomplete previous treatment data were often included in clinical trials. Many studies enrolled patients who had not received new drugs like bortezomib, IMiDs, and/or monoclonal antibodies. Thus, optimal use of upfront versus delayed allogeneic stem cell transplantation, conditioning regimens, and maintenance need to be extensively explored through well-designated randomized trials (Fig. 1). The use of novel therapy, CAR-T cell therapy, and monoclonal antibodies also need to be explored in this setting.

CONCLUSION

Allogeneic transplantation in MM is a potential curative option in high-risk patients with myeloma. More studies are requested to decrease acute and chronic GVHD, NRM, and understand the role of novel drugs in the context of allogeneic transplantation.

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