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Allogeneic Hematopoietic Cell Transplantation in Multiple Myeloma

Pervin Topcuoglu, Sinem Civriz Bozdog and
Taner Demirer

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1. Introduction

The improvement in the survival of multiple myeloma patients has been attributed to autologous stem cell transplantation (ASCT) after induction with novel agents [1,2]. Nevertheless, ASCT has not been considered to have a curative potential, maintenance treatment seems to be one of the solutions to decrease the high relapse rates after ASCT [3]. Therefore, allogeneic stem cell transplantation (Allo-SCT) is a potentially curative approach; the role of allo-SCT is still an ongoing debate due to high transplant-related mortality and lack of large prospective randomized studies in the newly diagnosed patients. A retrospective case-matched analysis was performed comparing myeloma patients treated with Allo-SCT with an equal number of patients who received ASCT by European Group for Blood and Bone Marrow Transplant (EBMT) [4]. Overall survival (OS) for the whole patient group was significantly better for the ASCT group compared with those for allo-SCT (Median survival: 34 months vs 18 months, $p=0.001$). Therefore, we should answer the question of which patients with multiple myeloma have to be directed to allo-SCT modality.

Prognosis of myeloma patients have been found strongly associated with their cytogenetic features and gene expression profiling [5,6]. Increasing data on the poor prognosis of the 'high risk myeloma patients' changed the trends towards to the allo-transplantation in the earlier period. The Société Française de Greffe de Moelle et de Thérapie Cellulaire evaluated the role of allo-SCT for cytogenetically high-risk myeloma patients in a retrospective multicenter analysis [7]. They showed that allo-SCT could potentially be of benefit to the patients carrying cytogenetic abnormalities such as deletion (del) of (13q), t(4;14), t(14;16) and del(17p) compared to those without the same abnormalities.

In this chapter, we discussed the role of allo-HCT in MM patients, and also we tried to clarify the issues as the intensity of conditioning regimen, the timing of the transplantation, and post-transplantation approaches in relapse or refractory patients.

2. The intensity of conditioning regimen

The early data on myeloablative conditioning (MAC) regimen can be obtained from the transplant registries [8-12]. Cyclophosphamide (Cy) with total body irradiation (Cy-TBI) and busulfan with Cy were the mostly used conditioning regimens. Transplant-related mortality (TRM) rates ranged from 30% to 50%. Actuarial survival for the EBMT-registered patients was 28% at 7 years [9], 15% for the Hutchinson Center-registered patients [10]. IBMTR data showed that the probabilities of survival at 4 years was 35% for patients with Karnofsky performance scores higher than 70 at pretransplantation and approximately 15% for patients with scores lower than 70 [11]. Thus, due to the exceedingly high TRM, myeloablative Allo-SCT was largely abandoned worldwide in the 1990s.

The use of reduced intensity conditioning (RIC) regimens in allo-SCT was introduced in an attempt to reduce the regimen-related toxicities while preserving an effect of graft versus tumor effect. First study was performed in a canine model conditioned with low-dose (2 Gy) total body irradiation (TBI) in combination of postgrafting mycophenolatemofetil (MMF) and cyclosporine (CSP). This approach permitted to stable engraftment with minimal toxicity [13, 14]. Seattle group introduced the strategy of autologous SCT followed by a RIC allo-SCT in 2-4 months with low-dose TBI as conditioning regimen [15]. Forty eight percent of 52 multiple myeloma patients had relapsed or refractory disease prior to SCT and the overall response rate was 81% (51% CR + 29% PR). In this tandem modality, the 100-day TRM after the allo-RIC was 2%, progression free survival (PFS) and overall survival (OS) at 2 years were 48% and 69%, respectively. Preliminary clinical studies [15-25] were also encouraging with low TRM rates (Table1). Kröger, et al performed tandem auto/Allo-RIC in 17 myeloma patients using unrelated or mismatched related donors and fludarabine, melphalan, anti-thymocyte globulin (ATG) as conditioning regimen [16]. Early TRM (day 100) was reported as 11% and estimated 1-year disease free survival (DFS) and OS were 56% and 74%.

One of the largest data related to a RIC-allograft in myeloma was published by the EBMT in which the outcome of 229 patients with MM from 33 centers was reported [18]. One-year TRM was 22%, the 3-year estimated PFS and OS were 41% and 21%, respectively. The adverse outcomes were seen in chemo-resistant disease prior to allo-SCT, transplantation to the pair of male recipient- female donor, no-chronic GvHD and the use of alemtuzumab.

The EBMT has also retrospectively compared 320 patients allografted a RIC regimen with 196 received a MAC regimen in multiple myeloma. They have reported markedly lower non relapse mortality in RIC than MAC setting (24% vs 32%, $p < .002$) [19]. However PFS and OS were not affected by the intensity of conditioning regimen. This was attributed to higher relapse rates in RIC group than the MAC group. Progressive disease at transplantation was

associated with an adverse effect on non-relapse mortality, PFS and OS. T cell depletion with alemtuzumab or other(s) led to high relapse rates as well.

Long-term follow-up data was reported in a RIC allo-graft for salvage setting of relapse and/or refractory myeloma patients (Table 1). These data showed that long term remission can be feasible for a subset of myeloma patients with allo-RIC performed in the salvage setting [21]. Seattle group reported the long term comparison data of RIC and MAC regimens [23]. Although the intensity of regimens changed time dependently, RIC regimens resulted in significantly lower overall mortality, improved PFS and much lower TRM.

Reference	Pa- tients (n)	Me- dian age (y)	Prior ASCT (n)	URD (n)	Regimens	GvHD prophy- laxis	Acute GvHDG rade II-IV	Chronic GvHD	TRM/ NRM	CR	PFS	OS
Maloney [15]	52	52	52	0	TBI (2 Gy)	CSP-MMF	38%	46%	2% (100 d)	57 %	48 % (2 y)	69% (2 y)
Kröger [16]	17	51	17	8	Fludarabine, Melphalan, ATG	CSP-MTX	38%	40%	11% (100 d)	73%	56% (2y)	74% (2y)
Giralt [17]	22	51	9	9	Fludarabine, Melphalan	TAC-MTX	73%	33%	19% (100 d) 40% (1y)	32%	19% (2 y)	30% (2y)
Crawley [18]	229	52	169	37	Fludarabine, Melphalan or Busulfan or cyclophospha- mide or TBI ± ATG or Alemtuzumab	CSP ± MTX	31 %	50%	11% 22% (1y)	25%	21% (3y)	41% (3y)
Rotta [20]	102	50	102	0	TBI (2Gy) ± Fludarabine	CSP-MMF; TAC-MMF	42%	74%	1% (100 d) 11 (1y) 18 (5y)	65%	36% (5y)	64% (5y)
Shimoni [21]	50	53	47	23	Fludarabine, Melphalan ±ATG	CSP-MTX	51%	63%	26 (5y)	58%	26% (7y)	34% (7y)
Cheikh [22]	40	56	11	17	Fludarabine, Busulfan, ATG; Fludarabine,TBI	CSP±MMF	47%	24%	0% (100 d)	44% (URD) 35% (MRD)	42% (URD) 44% (MRD)	59% (URD) 66% (MRD)
Bruno [24]	96	54	54	0	TBI (2 Gy)	CSP-MMF	38%	50%	11%	51%	53% (5 y)	65% (5y)
Vesole [25]	23		23	0	Fludarabine-Cyclop-hos- phamide	CSP-MP	17%	57%	8.7% (100 d)	30%	62% (2 y)	78% (2y)

Abbreviations: ASCT: Autologous Stem Cell Transplantation; GvHD: Graft versus Host Disease; TRM: Transplant-Related Mortality; NRM: Non-Relapse Mortality; CR: Complete Remission; PFS: Progression-Free Survival; OS: Overall Survival; TBI: Total Body Irradiation; ATG: Anti-Thymocyte Globulin; CSP: Cyclosporine; MMF: Mycophenolate Mofetil; TAC: Tacrolimus; MTX: Methotrexate; MP: Methyl-Prednisolone; URD: Unrelated Donor; MRD: Matched Related Donor

Table 1. Reduced intensity allogeneic transplantation alone or following autogous-SCT

A prospective multicenter study by the Gruppo Italiano Trapianti di Midollo Osseo (GITMO) enrolled 100 newly diagnosed multiple myeloma patients who were < 65 years of age and who had a sibling donor [24]. Allo-RIC transplantation was performed 2 to 4 months after ASCT in 96 patients. Disease sensitivity at the transplantation was significantly associated with longer OS and event-free survival (EFS). Overall survival were not significantly affected by the presence of del(13q) whereas EFS was better in patients without del(13q). Similarly, the Eastern Cooperative Oncology Group (ECOG) performed a trial of ASCT followed by RIC-allo from matched sibling donor to provide maximal tumor cytoreduction to allow for a subsequent graft versus myeloma (GvM) effect [25]. With a median follow up of 4.6 years from registration, 23 patients who completed both transplantations had a median PFS of 3.6 years and a 2-year survival rate of 78%. Cumulative non-relapse mortality on day 100 was 8.7%. In contrast to Italian study, plateau in PFS or OS was not observed with this treatment approach even in patients achieving CR.

Another prospective study for myeloma as part of first-line therapy, a donor versus no-donor analysis was performed of the patients treated in the HOVON-50 study [26]. This study allowed the patients with an HLA-identical sibling donor to proceed to the HOVON-54 study of allo-RIC between 2 and 6 months after ACST. Their results did not support allo-SCT as a frontline therapy.

3. Tandem autologous vs Allo-RIC transplantation

Recent trials have compared tandem auto-allo HSCT with a tandem autologous modality (Table 2). The IFM initiated two trials in high-risk (β -2 microglobulin level greater than 3 mg/L and chromosome 13 deletion at diagnosis) de novo multiple myeloma [27]. Patients with an HLA-identical sibling donor were randomized with allo-RIC arm following 1st ASCT (IFM99-03) (n=65), and patients without an HLA identical sibling donor were randomly assigned to undergo 2nd ASCT with or without anti-IL-6 monoclonal antibody (IFM99-04) (n=219). In IFM99-03 trial, 46 patients completed the entire program. When compared the OS and EFS between two trials, IFM99-03 and 04 did not significantly differ (OS: 35 months versus 41 months, p=.27; 25 months vs 30 months, p=.56). IFM group submitted the updated results in 2008 [28]. When the results of patients in IFM99-04 were compared with those of the 46 patients completed the tandem ASCT/Allo-RIC program, there was a trend of better OS for ASCT followed by allo-RIC transplantation (47.2 months vs 35 months, p=.07). As they compared of the results of the 166 patients out of 219 who completed the whole tandem ASCT protocol with those of the 46 patients out of 65 who underwent the entire auto/allo-RIC program, no difference was observed regarding EFS (median 25 vs 21 months, p=.88), but there was a trend for a superior OS in favor of double ASCT (57 vs 41 months, P=.08), due to a longer survival after relapse in the tandem ASCT arm.

These findings suggest that patients with high-risk myeloma did not benefit from a mini-allo transplantation following ASCT in comparison of tandem ASCT.

	Auto/auto vs Auto/allo RIC (n)	Conditioning for allo- RIC	CR (%) (auto/auto vs auto/allo RIC)	PFS/EFS (months) (auto/auto vs auto/allo RIC)	OS (months) (auto/auto vs auto/allo RIC)	TRM % P(auto/auto vs auto/allo RIC)
Moreau [28]	166 vs 46	Fludarabine, busulfan, ATG	-	25 vs 21 p=.88	57 vs 41 p=.08	Not evaluated
Bruno [29]	80 vs 82	Low-dose TBI	26 vs 55 p=.004	35 vs 29 p=.02	80 vs 54 p=.01	46 pts. vs 58pts. P=.09
Rosinol [30]	85 vs 25	Fludarabine, Melphalan	40 vs 11 p=.001	31 vs not reached p=.08 26 vs 19.6 p=.4	60% vs 61.8% (5y) p=.9	5 vs 16 p=.09
Krishnan [31]	366 vs 156	Low-dose TBI	13 vs 9 p=.0004	46% vs 43% (3 y) p=.7	3 years 80% vs 77% P:0.19	Not evaluated
Giaccone [32]	46 vs 58	Low-dose TBI	26 vs 55 p=.003	33 vs 39 p=0.02	5.3 years vs not reached P=.02	16 vs 2

Abbreviations: CR: Complete Remission; PFS: Progression-Free Survival; EFS: Event-Free Survival; OS: Overall Survival; TRM: Transplant-Related Mortality; TBI: Total Body Irradiation; ATG: Anti-Thymocyte Globulin

Table 2. Double transplantation comparing tandem ASCT with auto/allo RIC

The Italian group enrolled 162 consecutive younger patients ≤ 65 years of age with newly diagnosed myeloma who had at least one sibling [29]. Patients with an HLA-identical sibling donor received NMA TBI (2Gy) and stem cells median 94 days after ASCT (n=58). Patients without an HLA-identical sibling received tandem ASCT with high-dose melphalan (n=46). The rate of complete remission was significantly higher in the auto-allograft group (55% vs 26%, p=.004). Treatment-related mortality was similar (p=.009) but disease-related mortality was significantly higher in the double ASCT group (43% vs 7%, p<.001). There was a trend of higher EFS in auto-allograft arm (p=.07) while survival in the auto-allo setting was superior to the patients received double ASCT (p=.002).

Another prospective study has been performed by the Spanish PETHEMA group [30]. They enrolled 110 patients with newly diagnosed failing to achieve at least near-CR after a 1st ASCT were scheduled to receive either 2nd ASCT (n=85) or allo-RIC (n=25), depending on the

availability of HLA-identical donor. There was a higher increase in CR rate (40% vs 11%, $p=.001$) and a trend toward a longer PFS ($p=.08$) in favor of tandem auto-allo transplantation. In contrast, TRM was higher in the tandem auto-allo transplantation (16% vs 5%, $p=.07$), EFS and OS was not significantly different between 2nd ASCT and allo-RIC.

The Blood and Marrow Transplant Clinical Trials Network reported a multicenter phase III trial (BMT CTN 0102) in which patients were biologically assigned based on the availability of a matched related donor to either tandem ASCT using melphalan 200sqm or tandem auto-alloHCT using melphalan 200 sqm followed by alloHCT with 2 Gy TBI [31]. Among the 710 patients enrolled between 2003 and 2007 from 37 US centers, 625 patients had standard risk. Patients assigned to receive an ASCT followed by an allo-SCT or tandem ASCT on the basis of the availability of an HLA-matched sibling donor. The study showed no difference of median estimated PFS and OS in comparison of double auto with tandem auto-allo.

Recently, the long-term results of a trial in which treatment of newly diagnosed myeloma patients ($n=245$) was based on the presence or absence of HLA-identical donor was reported from Italy [32]. Patients with HLA-identical siblings were offered by a standard autograft with high-dose melphalan (200sqm) followed by an allograft with NMA TBI (2 Gy) ($n=82$), while patients without HLA-identical siblings were assigned to double ASCT after intermediate-dose (100 sqm) or high-dose (140-200 sqm) melphalan ($n=80$). At a median follow-up of 7.1 year, both OS and EFS were significantly longer in patients with HLA-identical siblings than those without, and median OS and EFS remained significantly longer in the patients transplanted with tandem auto-allo than those patients treated double ASCT. This comparative study showed that allograft conferred a long-term survival and disease-free survival advantage over standard autografting.

4. Post-transplant approaches

High rate of CR after allo-SCT was reported in above studies. But relapse still seems to be a remaining problem. The importance of molecular remission on long-term disease control has been mentioned in the studies of allogeneic transplantation with MAC or RIC regimes. Therefore, post-transplant strategies for preventing and treatment of relapse/refractory disease are of clinical importance. The role of adaptive immunotherapy, donor lymphocyte infusion (DLI), and novel agents has been assessed in several studies.

Donor lymphocyte infusion can enhance GvM and also induce graft versus host disease (GvHD) rates [33,34] Van de Donk, et al evaluated DLIs given in eight European transplantation centers for relapsed ($n=48$) or persistent ($n=15$) myeloma following NMA allo-SCT [35]. Overall response was 38%, acute GvHD was 38% and chronic GvHD was 42%. The development of GvHD and response to DLI seems to be associated with GvM effect, and durable remissions are restricted to a minority of patients who achieve CR in this retrospective evaluation. Escalating doses of DLI were found to have lower GvHD risk and better survival rates [36-38].

Immunomodulatory agents, thalidomide or lenalidomide have both have T cell and NK cell activity [39]. Effect of low dose thalidomide after allo-SCT was evaluated in the French study and found that 13 of 31 patients responded [40]. Nineteen percent of patients stopped treatment due to toxicity. Although thalidomide is used for treatment of GvHD, authors observed GvHD in the follow up of 5 patients. Kröger et al, showed improved responses with low dose thalidomide followed by DLI in patients who were refractory to sole DLI [41]. Lenalidomide increased the frequency of human leukocyte antigen-DR (+) T cells and regulatory T cells. Improved response rates were reported with lenalidomide with / without dexamethasone for relapsed/refractory patients [42,43]. Recently, HOVON group investigated maintenance of lenalidomide after allo-SCT; it is not found a feasible treatment due to induction of GvHD [44].

The use of proteasome inhibitor, bortezomib for in vitro depletion of alloreactive T cells after allo-SCT can control GvHD [45]. In retrospective analyses bortezomib administration in relapse or progression of MM after allo-HSCT was shown to be effective treatment without worsening of GVHD symptoms (46).

5. Conclusion

The role and timing of allo SCT still cannot be defined clearly. Due to high TRM rates, myeloablative conditioning in allo-SCT has shifted to reduced intensity conditioning. The studies can be summarized as: (1) -early-day 100 TRM as low as 0 -20%, (2) Acute grade II-IV GvHD and chronic GvHD rates as 30 to 70%, (3) chemosensitivity prior to the transplantation as main factors of survival after transplantation (4) negative PFS effects of in vitro T cell depletion with Alemtuzumab or other(s).

Most of the studies were performed in the relapsed/refractory setting and currently there is no strong data to support allo-RIC as part of a frontline therapy. Reduction of tumor burden by high dose therapy with autologous stem cell rescue has found to have impacts on the transplant outcome and these results brought the comparative studies of auto/auto vs auto/allo transplantation. There are contradictory results in this era and lack of strong evidence to support one to the other procedure.

Relapse after allo RIC transplantation is still a remaining problem to be solved. Introduction of novel agents such as bortezomib, thalidomide, and lenalidomide with/without DLI(s) can provide solutions to this problem.

In conclusion, allo-SCT has been recognized as a potential therapeutic modality in MM, especially since the introduction of RIC regimens and the use of a tandem auto-allo transplants has shown promise by reducing the TRM and inducing high CR rates. Nevertheless, long-term control of the disease remains a key issue, even in patients treated first by RIC allo-SCT. The role of allo-SCT should be re-evaluated when taking into consideration of promising effects of novel agents in myeloma treatment in randomized clinical trials.

Author details

Pervin Topcuoglu¹, Sinem Civriz Bozdog² and Taner Demirer³

*Address all correspondence to: topcuogl@medicine.ankara.edu.tr

*Address all correspondence to: scivriz@hotmail.com

*Address all correspondence to: demirer@medicine.ankara.edu.tr

1 Ankara University, School of Medicine, Dept of Hematology, Stem Cell Transplantation Unit, Ankara, Turkey

2 Ankara Oncology Research and Education Hospital, Hematology and Stem Cell Transplantation Unit, Ankara, Turkey

3 Ankara University, School of Medicine, Dept of Hematology, Stem Cell Transplantation Unit, Ankara, Turkey

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