Salvage use of allogeneic hematopoietic stem cell transplantation after reduced intensity conditioning from unrelated donors in multiple myeloma. A study by the Plasma Cell Disorders subcommittee of the European Group for Blood and Marrow Transplant Chronic Malignancies Working Party

Despite major improvements in the treatment of multiple myeloma (MM), the majority of patients will eventually relapse.[1] Those patients may benefit most from the potentially curative effect of graft *versus* myeloma effect of allogeneic hematopoietic stem cell transplantation (allo-HSCT) and its combination with potent anti-myeloma agents, especially if high-risk features are present at diagnosis.[2] Of late, different studies have evaluated the use of novel drugs including panobinostat, carfilzomib, daratumumab, elotuzumab and ixazomib in the context of relapse with very promising results.[3-8] We recently showed that the number of patients who received an allo-HSCT for MM in Europe is steadily increasing, and about 70% of cases are performed at a later stage of the disease, mainly following failure after one or two autologous HSCTs (auto-HSCT).[9] Herein, we aim to present a refined analysis considering the current most common indication for allogeneic HSCT in MM, namely salvage

Table 1. Patient and transplantation characteristics.

	10/10 HLA MUD N=419	9/10 HLA MMUD N=93	Cord Blood N=58
Median age at Allo-HSCT (range)	55 (30-74)	55 (19 - 69)	57 (24-69)
Sex (M/F)	260 (62%) / 159 (38%)	58 (62%) / 35 (38%)	28 (48%) / 30 (52%)
Previous number of Auto-HSCTs			
1 Auto-HSCT	257 (61%)	52 (56%)	27 (47%)
2 Auto-HSCTs	162 (39%)	41 (44%)	31 (53%)
Median time Auto-Allo HSCT (Months)	13	22	27
International Staging System (ISS)			
I	34 (11%)	6 (8%)	3 (8%)
II	60 (16%)	13 (18%)	6 (16%)
III	268 (73%)	53 (74%)	28 (76%)
Missing	N=57	N=21	N=21
Myeloma subtype			
IgG	299 (72%)	63 (69%)	43 (75%)
IgA	108 (26%)	25 (27%)	14 (25%)
Light chain	10 (2%)	4 (4%)	-
Missing	N=2	N=1	N=1
Cytogenetic abnormalities			
High-risk [t(4;14), del17p]	12	2	2
Other abnormalities (del13q, others)	94	3	6
Not reported in the registry	313	88	50
Disease status at Allo-HSCT			
>PR	155 (38%)	20 (22%)	15 (26%)
PR	145 (36%)	41 (45%)	23 (40%)
<PR	109 (26%)	30 (33%)	20 (34%)
Missing	N=10	N=2	-
T-cell depletion			
Yes/No	284 (68%) / 135 (32%)	72 (77%) / 21 (23%)	10 (17%) / 48 (83%)
Reduced-Intensity Conditioning			
BU-based	129 (31%)	27 (29%)	4 (7%)
TBI-based	125 (30%)	26 (28%)	48 (83%)
Others	165 (39%)	40 (43%)	6 (10%)
HLA matching			
MM on A locus	–	19 (20%)	–
MM on B locus	–	10 (11%)	–
MM on C locus	–	35 (38%)	–
MM on DQ locus	–	20 (22%)	–
MM on DR locus	–	9 (9%)	–
6/6 CB	–	–	2 (3%)
5/6 CB	–	–	14 (24%)
4/6 CB	–	–	42 (73%)
Year of Allo-HSCT			
2001-2007	54 (13%)	17 (18%)	13 (22%)
2008-2013	365 (87%)	76 (82%)	45 (78%)

HLA: human leukocyte antigen; MUD: matched unrelated donors; MMUD: mismatched unrelated donors; HSCT: hematopoietic stem cell transplantation; CB: cord blood; Auto: autologous; Allo: allogeneic; PR: partial response; BU: busulfan; TBI: total body irradiation; IgG: immunoglobulin G; IgA: immunoglobulin A.

allo-HSCT after one or two auto-HSCTs using reduced-intensity conditioning (RIC) and an alternative donor. Therefore, we contrasted the outcomes of patients receiving cord blood (CB) allo-HSCT with those of comparable patients receiving peripheral blood stem cells (PBSCs) during the same period of time from either 10/10 human leukocyte antigen (HLA)-matched unrelated donors (MUD) or 9/10 HLA-mismatched unrelated donors (MMUD).

We included MM patients who received RIC allo-HSCT from unrelated donors after one or two auto-HSCTs between January 2001 and December 2013, as reported in the European Group for Blood and Marrow Transplant (EBMT) registry. Only patients with complete data on HLA typing were included. HLA results were reviewed and classified by an independent HLA expert on HLA A,B,C,DR,DQ for patients receiving allo-HSCT from PBSCs and on HLA A,B (generic level) DR (allelic level) for those receiving allo-HSCT from CB. There were 570 patients in total; 346 (61%) were males, median age at allo-HSCT was 55 years (range: 19-74), the immunoglobulin subtype was immunoglobulin G (IgG) in 48% of patients, light chain in 26% and immunoglobulin A (IgA) in 20%. Overall, 62% were in stage III according to the International Staging System (ISS) classification. Cytogenetic data was absent in 451 (79%) patients; this could be due to the fact that in most cases cytogenetic testing was not done, was done but not reported in the registry, or, the least likely scenario, was done and found to be normal. For the remaining 119 (21%) patients, karyotype abnormalities were reported, with the majority affecting del(13q), and there were 12 high-risk patients with t(4;14) and/or del (17p). Allo-HSCT was performed after a median time of 15 months (range: 3-46) following one (n=336, 59%) or two (n=234, 41%) auto-HSCTs. Unrelated donors were 10/10 HLA-MUD for 419 (74%) patients, 9/10 HLA-MMUD for 93 (16%) patients and at least 4/6 HLA-matched CB in 58 (10%) patients (19 single, 39 double). In the 9/10 MMUD group, the mismatch concerned the A locus in 19 (20%) patients, the B locus in 10 (11%), the C locus in 35 (38%), the DQ locus in 20 (22%) and the DR locus in 9 (9%) patients. In the CB

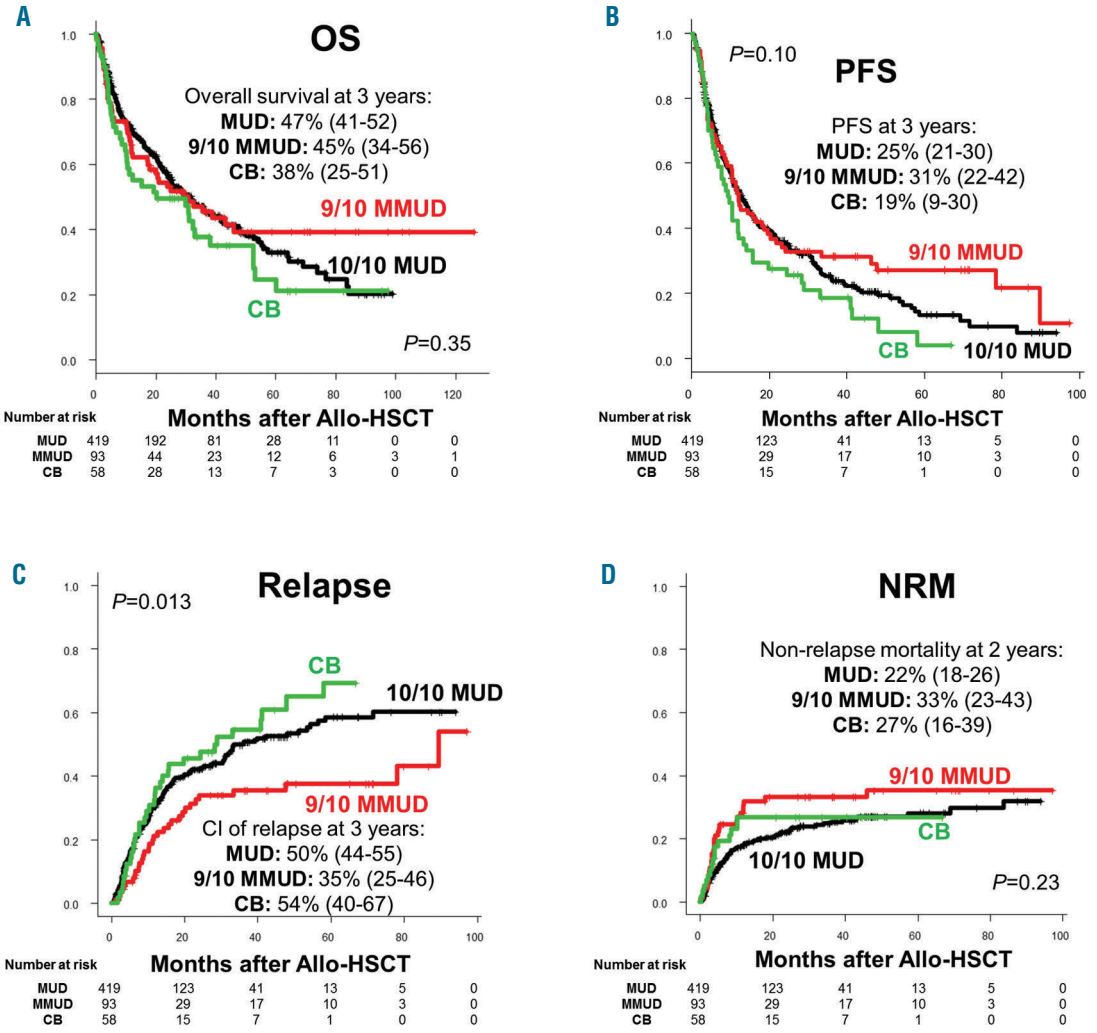

Figure 1. Transplantation outcomes according to the different hematopoietic stem cells sources. (A) Overall survival, (B) Progression-Free Survival, (C) Relapse incidence and (D) Non-Relapse Mortality. MUD: matched unrelated donors; MMUD: mismatched unrelated donors; CB: cord blood; Allo-HSCT: allogeneic hematopoietic stem cell transplantation; CI: confidence interval.

group, the degree of HLA matching was as follows: 6/6 HLA-matched in 2 (3%) patients, 5/6 HLA-mismatched in 14 (24%) patients, and 4/6 HLA-mismatched in 42 (73%) of patients. At transplantation, at least 399 (70%) of patients were in partial response (PR), among them, 122 (21%) reached complete remission (CR). In the MUD and MMUD groups, RIC included fludarabine, busulfan and anti-thymocyte globulin (ATG) in 45% of patients, fludarabine and low-dose total body irradiation (TBI) in 30% of patients, and fludarabine and melphalan in addition to either ATG, campath or bortezomib in 26% of patients. In the CB group, RIC mainly included cyclophosphamide, fludarabine and low-dose TBI (83% of patients). There were no significant differences between the three groups according to the different diseases and patients' characteristics as cited above. Disease and transplantation characteristics according to the different donor groups are described in Table 1.

The engraftment rate was 94%, 96% and 89% in the MUD, MMUD and CB groups, respectively. Acute graft-*versus*-host disease (GvHD) grade II-IV occurred in 33%, 41% and 42% of patients in the three groups, respectively, while chronic GvHD was present in 152/373 (41%) patients (56 limited, 96 extensive), 39/83 (47%) (15 limited, 24 extensive) and 15/49 (31%) (11 limited, 4 extensive), respectively. After a median follow-up of 26 months, the probability of overall survival (OS) for patients at three years was 47% (95% confidence interval (CI): 41-52), 45% (95% CI: 34-56) and 38% (95% CI: 25-51) in the MUD, MMUD and CB groups, respectively. At five years the probability of OS was 33% (95% CI: 26-40), 39% (95% CI: 28-51) and 25% (95% CI: 12-39), respectively, with a median OS of 32 months, 31 months and 20 months, respectively (P=0.35) (Figure 1A). At three years the probability of progression-free survival (PFS) for the MUD, MMUD and CB groups was 25% (95% CI: 21-30), 31% (95% CI: 22-42) and 19% (95% CI: 9-30), respectively, P=0.10. At five years the probability of PFS was 14% (95% CI: 9-19), 27% (95% CI: 18-38) and 4% (95% CI: 1-16), respectively, with a median PFS of 12.7 months, 12 months and 9.2 months, respectively (Figure 1B). The cumulative incidence of relapse for the MUD, MMUD and CB groups at three years was 50% (95% CI: 44-55), 35% (95% CI: 25-46) and 54% (95% CI: 40-67), and at five years it reached 58% (95% CI: 52-65), 37% (95% CI: 27-48) and 69% (95% CI: 52-81), respectively (P=0.013 for MMUD *versus* all others) (Figure 1C). The non-relapse mortality (NRM) rate at two years was 22% (95% CI: 18-26), 33% (95% CI: 23-43) and 27% (95% CI: 16-39) in the MUD, MMUD and CB groups, respectively, P=0.23, at five years the rate was 28% (95% CI: 23-33), 35% (95% CI: 25-46) and 27% (95% CI: 16-39), respectively. Among those patients considered high-risk according to cytogenetics, no significant difference was observed in terms of OS and PFS between the three groups.

The principal finding of our study is the similar outcome of HLA 9/10 mismatched unrelated donors and HLA 10/10 matched unrelated donors. Notably, even if not significant, the Kaplan-Meier curves of PFS and OS in the HLA 9/10 MMUD group suggest a trend for a better outcome in the long-term. This may be caused by a stronger graft *versus* myeloma effect after HLA 9/10 MMUD as supported by a significantly lower incidence of relapse. Despite its low number, the CB group shows the feasibility of this kind of cell source, as published studies on this topic are very limited; apart from a recent study by the EBMT reporting results of 95 CB allo-HSCT in MM,[10] there is one additional study which was performed using data from the Japanese registry,[11] reporting on a total of 86 patients between 2001 and 2011. In both of these aforementioned studies, myeloablative chemotherapy and RIC were included, along with patients with different allo-HSCT indications (first-line, tandem auto-allo HSCT and further treatments). In our study, we considered the current most used indication for allogeneic HSCT in MM, which is the salvage allo-HSCT after one or two auto-HSCTs using RIC. Even if not significant, the outcome following CB transplantation seems to be worse in comparison to HLA 10/10 MUD or 9/10 MMUD. The main concern for all alternative donor options is the high risk of relapse. In the manner of autologous transplantation, maintenance strategies with novel agents alone or in combination with donor lymphocyte infusions should be investigated following salvage allogeneic transplantation in order to reduce the risk of relapse. Similar to other registry studies, the main weakness of our study is the unknown patient selection. However, the short median interval of only 15 months between the last autograft and allogeneic stem cell transplantation suggests a selection of high-risk patients in the presented registry study. Finally, it might not be feasible to perform the necessary clinical trials to compare different regimens or drug association to allogeneic transplantation, and determine which are most suitable for particular subgroups of relapsed/refractory MM patients, however, gaining cautious insights from subgroup analyses as we present herein could help in guiding clinicians in their daily practice. In conclusion, salvage RIC allo-HSCT from alternative unrelated donors after a short remission duration of one or two auto-HSCTs is a feasible treatment option which offers a degree of long-term survival. HLA 9/10 mismatched or HLA10/10 matched unrelated donors are the preferential alternative donor sources.

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