Allogeneic hematopoietic cell transplantation for multiple myeloma in Europe: trends and outcomes over 25 years. A study by the EBMT Chronic Malignancies Working Party

Allogeneic hematopoietic cell transplantation for multiple myeloma in Europe: trends and outcomes over 25 years. A study by the EBMT Chronic Malignancies Working Party

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Abstract

We describe the use and outcomes of allogeneic hematopoietic stem cell transplantation (allo-HSCT) for multiple myeloma (MM) in Europe between January 1990 and December 2012. We identified 7333 patients, median age at allo-HSCT was 51 years (range: 18–78), of whom 4539 (62%) were males. We distinguished three groups: (1) allo-HSCT upfront (*n*=1924), (2) tandem auto-allo-HSCT (*n*=2004) and (3) allo-HSCT as a second line treatment and beyond (*n*=3405). Overall, there is a steady increase in numbers of allo-HSCT over the years. Upfront allo-HSCT use increased up to year 2000, followed by a decrease thereafter and represented 12% of allo-HSCTs performed in 2012. Tandem auto-allo-HSCT peaked around year 2004 and contributed to 19% of allo-HSCTs in 2012. Allo-HSCT as salvage after one or two or three autografts was steadily increasing over the last years and represented 69% of allo-HSCTs in 2012. Remarkable heterogeneity in using allo-HSCT was observed among the different European countries. The 5-year survival probabilities from time of allo-HSCT for the three groups after year 2004 were 42%, 54% and 32%, respectively. These results show that the use of allo-HSCT is increasing in Europe, especially as second line treatment and beyond. There is an unmet need for well-designed prospective studies investigating allo-HSCT as salvage therapy for MM.

Introduction

Autologous hematopoietic stem cell transplantation (auto-HSCT) and the development of new agents with potent anti-myeloma activity has considerably improved the survival of multiple myeloma (MM) patients.[1, 2] The availability of many of these agents has led to several strategies in their use alone or in association either in the induction phase, the consolidation after auto-HSCT,

the maintenance phase and the post-relapse phase or at the minimal-residual disease stage.[3, 4, 5, 6, 7, 8] However, there is still a continuous risk of relapse mainly due to the inability of these agents to cure and eliminate definitively the MM cells. Allogeneic HSCT (allo-HSCT) remains a potentially curative treatment but its use is still controversial because of its high morbidity and mortality.[9, 10, 11, 12, 13, 14] Conventional myeloablative conditioning (MAC) regimens have given way in the last decade to reduced intensity conditioning (RIC) regimen that has been more frequently used in the last decade due to significantly reduced transplant-related mortality, which has decreased to 10–20% but was associated with high relapse rates compared with MAC.[15, 16]

The most important predictors of outcome are the low-tumor burden at the time of transplant and the management of chronic graft-versus-host disease (GvHD) after transplantation.[17, 18] In this regard, the use of auto-HSCT to reduce tumor burden followed by RIC allo-HSCT to obtain a benefit from the graft-versus-myeloma effect has been investigated.[19, 20] A total of six prospective randomized trials have compared tandem auto-allo-HSCT versus single/tandem auto-HCT in the upfront transplantation setting with conflicting conclusions.[21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31] In two studies, the auto-allo-HSCT showed an improved progression-free survival (PFS)/event-free survival (EFS) and overall survival (OS),[21, 22, 23, 24] while the rest of the studies failed to prove a significant difference in term of PFS/EFS or OS between the auto-HSCT and the auto-allo-HSCT strategies. These different results are in part explained by the substantial differences in design, patient eligibility, pre-transplantation induction therapy, conditioning regimen, GvHD prophylaxis and the important unknown information about treatment at relapse. In view of these uncertainties, the debate is still ongoing concerning the best time to propose allogeneic transplantation for patients with MM; while there is agreement in the scientific community to perform it preferentially within a clinical trial, the use of allo-HSCT for MM in Europe is usually based on individualized decision outside of a clinical trial.

The objective of this study is to describe the use of allo-HSCT for MM in Europe within EBMT centers over more than two decades and to evaluate its outcomes.

Materials and methods

The EBMT registry

The EBMT is a non-profit organization that was established in 1974 and maintains a patient database known as the EBMT Registry, which encompasses data on HSCT procedures for all indications. The EBMT has a centralized database located in Leiden, The Netherlands, where all the data requested through the standard data collection forms are stored. The data are submitted when 100 days have elapsed from the date of transplant, or when the patient dies, whichever comes first. All EBMT member centers need to forward these data to retain full membership. All centers must obtain informed consent from their patients before the data can be submitted to the EBMT.

Patient population

We included patients who received allo-HSCT between 01 January 1990 and 31 December 2012 and were reported to the EBMT registry. Patients were divided into three groups according to the timing of allo-HSCT use—group 1 included patients who received allo-HSCT upfront after

induction therapy; group 2 included patients who received allo-HSCT after an upfront single auto-HSCT as auto-allo tandem transplantation with a maximum interval between auto-HSCT and allo-HSCT of 8 months; group 3 included patients who received allo-HSCT at a later time after one, two or three auto-HSCTs with at least 8 months between the first auto-HSCT and allo-HSCT, mainly as second line treatment and beyond. We evaluated the impact of the interval between auto-HSCT and allo-HSCT, up to 4 months and between 4 and 8 months. We then merged these patients together as their outcomes were similar. Patients with allo-HSCT performed beyond 8 months after auto-HSCT could not be considered as receiving tandem auto-allo-HSCT strategy and were therefore included in group 3. The three groups were each split into two, that is, including transplants performed before and after year 2004, assuming that 2004 was the time of introduction of novel drugs at the European centers.

Statistical analysis

OS was defined as the time from allogeneic transplantation until date of death or last follow-up. PFS was defined as the time from allo-HSCT to disease progression or death from any cause. OS and PFS probabilities were estimated by the Kaplan–Meier method, and the Log-Rank test was used for univariate comparison. Relapse/progression was defined according to the standard EBMT criteria as previously described.[32, 33] Cumulative incidence of relapse and of death without relapse after allo-transplantation (non-relapse mortality (NRM)) was estimated in a competing risks framework, and differences were evaluated using the Gray test.

Results

Patient characteristics

A total of 7333 patients from 38 different countries received allo-HSCT between 01 January 1990 and 31 December 2012 and were included in this study. There were 4539 (62%) males and 2794 (38%) females with a median age at allo-HSCT of 51 years (range: 18–78), of which 4726 (64%) have received allo-HSCT after year 2004. Group 1 included 1924 patients, group 2 included 2004 patients and group 3 included 3405 patients, and among them 514 (27%), 1446 (72%) and 2766 (81%) received allo-HSCT after year 2004, respectively. Patient characteristics are detailed in Table 1.

Table 1. Patient characteristics

Figures and tables index

	Allo-HSCT upfront*, N=*1924		***Tandem auto-allo-HSCT*, N=*2004***		***Later allo-HSCT*, N=*3405***	
	Before year 2004*, N=*1410	***After year 2004*, N=*514***	***Before year 2004*, N=*558***	***After year 2004*, N=*1446***	***Before year 2004*, N=*639***	***After year 2004*, N=*2766***

	Allo-HSCT upfront,* N=*1924		***Tandem auto-allo-HSCT,* N=*2004***		***Later allo-HSCT,* N=*3405***	
	Before year 2004,* N=*1410	***After year 2004,* N=*514***	***Before year 2004,* N=*558***	***After year 2004,* N=*1446***	***Before year 2004,* N=*639***	***After year 2004,* N=*2766***
Median age (range)	46 (18–77)	50 (18 – 78)	51 (21–68)	52 (19 – 72)	52 (27–71)	54 (24 – 73)
Gender (M/F)	857 (61%)/553 (39%)	308 (60%)/207 (40%)	339 (61%)/219 (39%)	879 (61%)/566 (39%)	415 (65%)/224 (35%)	1741 (63%)/1025 (37%)
Median time diagnosis—allo-HSCT (months)	11	13	11	11	39	39
International Staging System (ISS)						
I	249 (18%)	48 (9%)	82 (15%)	155 (11%)	105 (16%)	250 (9%)
II	30 (2°%)	12 (3%)	12 (2%)	30 (2%)	13 (2%)	32 (1%)
III	131 (9%)	36 (7%)	52 (9%)	109 (8%)	42 (7%)	157 (6%)
Missing	1000 (71%)	418 (81%)	412 (74%)	1152 (80%)	479 (75%)	2327 (84%)
Durie–Salmon stage						
I	122 (9%)	28 (5%)	55 (10%)	125 (9%)	54 (8%)	242 (9%)
II	206 (15%)	97 (19%)	93 (17%)	229 (16%)	98 (15%)	407 (15%)
III	599 (42%)	294 (57%)	340 (61%)	996 (69%)	355 (56%)	1863 (67%)
Missing	483 (34%)	95 (18%)	70 (13%)	96 (6%)	132 (21%)	254 (9%)
Disease status at allo-HSCT						
>PR	191 (14%)	133 (26%)	93 (17%)	421 (29%)	55 (9%)	738 (27%)
PR	711 (50%)	243 (47%)	320 (57%)	745 (52%)	268 (42%)	1213 (44%)
<PR	366 (26%)	114 (22%)	104 (19%)	188 (13%)	277 (43%)	635 (23%)

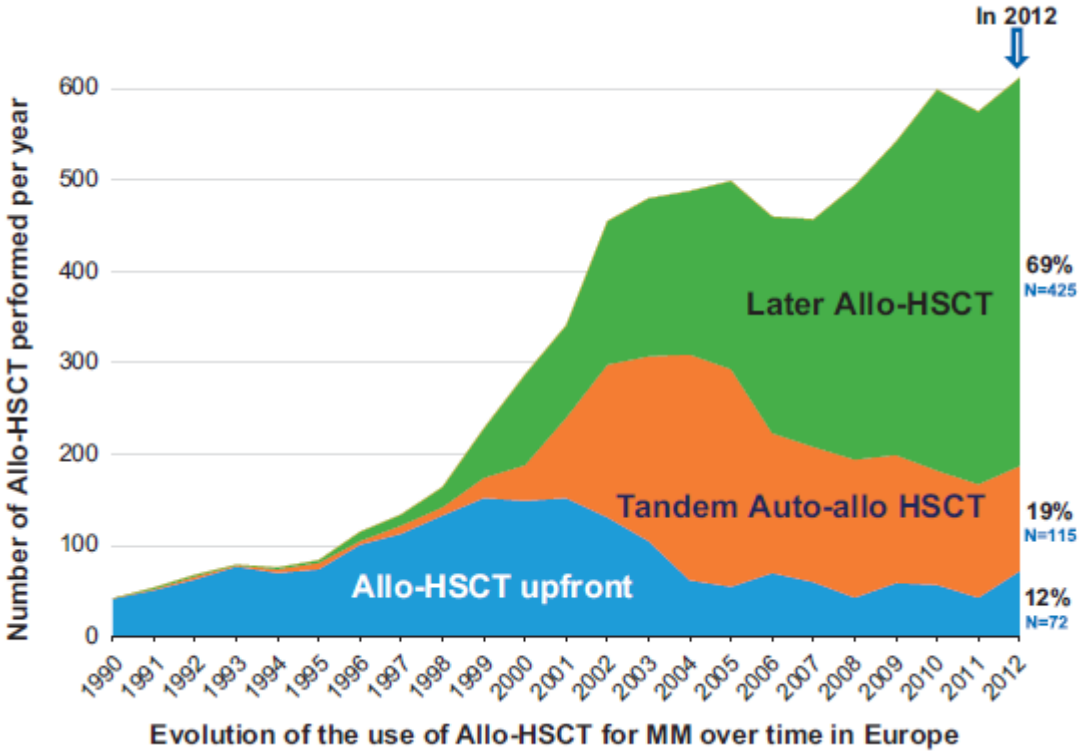
	Allo-HSCT upfront,* N=*1924		***Tandem auto-allo-HSCT,* N=*2004***		***Later allo-HSCT,* N=*3405***	
	Before year 2004,* N=*1410	***After year 2004,* N=*514***	***Before year 2004,* N=*558***	***After year 2004,* N=*1446***	***Before year 2004,* N=*639***	***After year 2004,* N=*2766***
Missing	142 (10%)	24 (5%)	41 (7%)	92 (6%)	39 (6%)	160 (6%)
Donor						
Matched related	1188 (84%)	313 (61%)	449 (80%)	978 (68%)	429 (67%)	1155 (42%)
Matched unrelated	121 (9%)	34 (7%)	83 (15%)	126 (9%)	158 (25%)	331 (12%)
Other	101 (7%)	167 (32%)	26 (5%)	342 (24%)	52 (8%)	1280 (46%)
Sex matching (R/D)						
Male/female	330 (23%)	96 (19%)	134 (24%)	318 (22%)	166 (26%)	588 (21%)
Others	1080 (77%)	418 (81%)	424 (76%)	1128 (78%)	473 (74%)	2178 (79%)
T-cell depletion						
Yes/no	417 (30%)/993 (70%)	137 (27%)/377 (73%)	148 (27%)/410 (73%)	475 (33%)/971 (67%)	202 (32%)/437 (68%)	1254 (45%)/1512 (55%)
Stem cells source						
BM	722 (51%)	78 (15%)	78 (14%)	69 (5%)	110 (17%)	264 (10%)
PBSC	688 (49%)	433 (84%)	480 (86%)	1370 (94%)	529 (83%)	2433 (88%)
CB	—	3 (1%)	—	7 (1%)	—	69 (2%)
Conditioning						

	Allo-HSCT upfront, N=*1924*		*Tandem auto-allo-HSCT,* N=*2004*		*Later allo-HSCT,* N=*3405*	
	Before year 2004, N=*1410*	*After year 2004,* N=*514*	*Before year 2004,* N=*558*	*After year 2004,* N=*1446*	*Before year 2004,* N=*639*	*After year 2004,* N=*2766*
MAC	1046 (74%)	295 (57%)	109 (20%)	278 (19%)	152 (24%)	704 (25%)
RIC	215 (15%)	212 (41%)	427 (77%)	1155 (80%)	421 (66%)	2051 (74%)
Missing	149 (11%)	7 (2%)	22 (3%)	13 (1%)	66 (10%)	11 (1%)
Number of auto-HSCT before allo-HSCT						
1	—	—	558 (100%)	1446 (100%)	354 (55%)	1237 (45%)
2	—	—	—	—	233 (37%)	1285 (46%)
3	—	—	—	—	52 (8%)	244 (9%)

Abbreviations: BM, bone marrow; CB, cord blood; D, donor; F, female; HSCT, hematopoietic stem cell transplantation; M, male; MAC, myeloablative conditioning; PBSC, peripheral blood stem cells; PR, partial response; R, recipient; RIC, reduced intensity conditioning.

Trend of allo-HSCT use over time

The number of allo-HSCTs is continuously increasing to reach its maximum at time of study analysis with a total of 612 transplantations performed in 2012. The upfront use of allo-HSCTs decreased after year 2000 to represent 12% of allo-HSCTs performed in 2012, while the peak of allo-HSCT use directly after one auto-HSCT in a context of tandem auto-allo-HSCTs was around year 2004 to reach 19% of usage in 2012. It is clear that allo-HSCT performed at a later time after single, double or even three auto-HSCTs, which could be translated in a context of relapse post auto-HSCT, was used at the highest rate during the last years to reach 69% of usage in 2012. Evolution of allo-HSCT use between years 1990 and 2012 for the different strategies is shown in Figure 1.



Interestingly, when taking into consideration the use of allo-HSCTs according to the top six countries in Europe, we found that not only the trend of usage is different between each country, (that is, increase in Germany compared with others) but also the treatment strategy is different between early use versus late use (Figure 2).

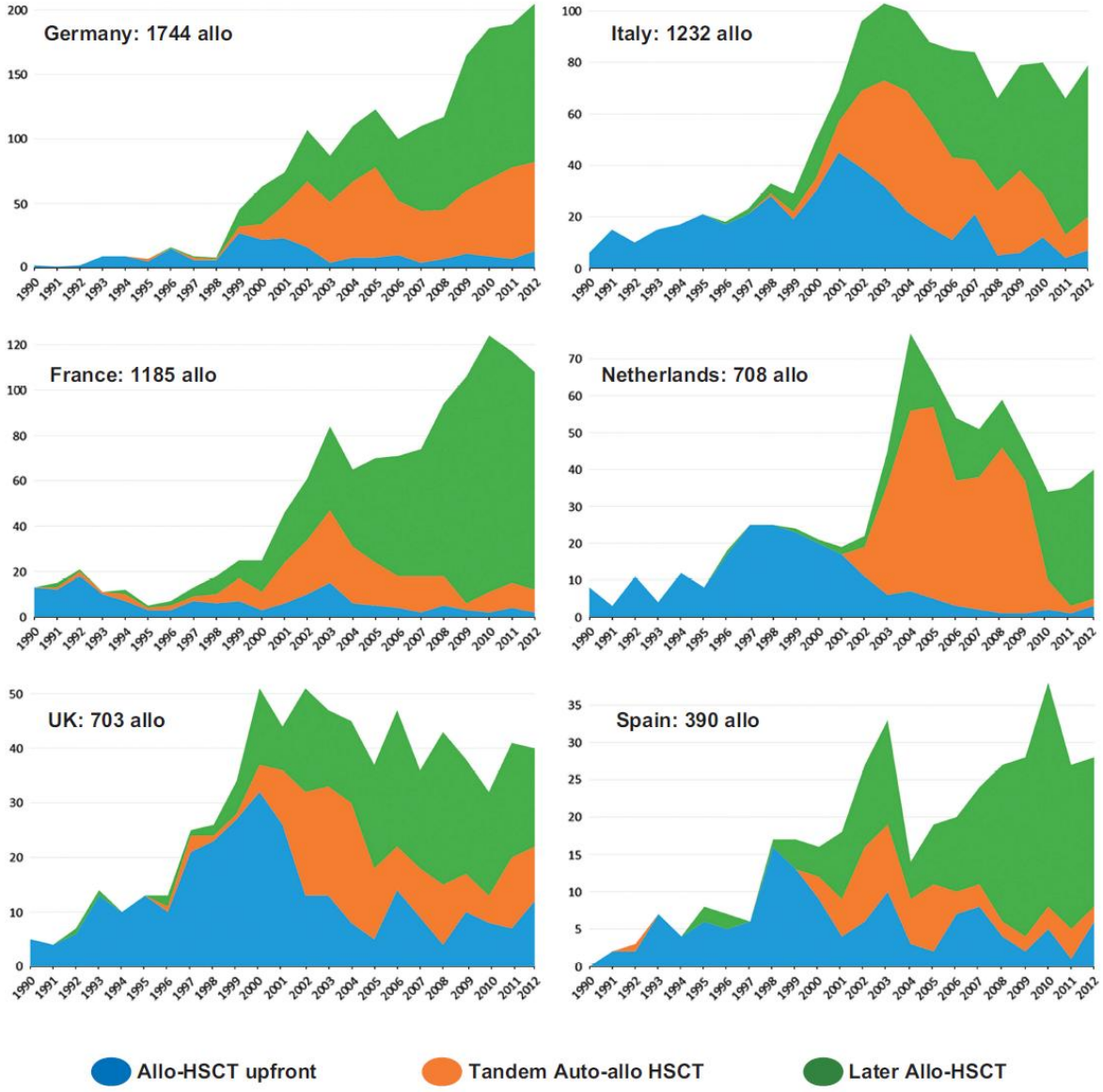


Figure 2. Evolution of allogeneic HSCT in the top six countries in Europe according to different strategies.

Disease and transplantation characteristics

Baseline disease characteristics are available mainly as disease stage according to Durie–Salmon staging. Data were available for 85% of patients and 72% among them were in stage III at the time of transplantation (Table 1). Cytogenetic information was missing for the majority of patients with data reported only for 483 (6.6%) patients. This lack of data is probably due to the absence of routine use of such testing in the past years across centers or it could be missing at the transplantation center but available at the referring center. However, since this was outside the scope of this descriptive study we did not request those data from the corresponding centers.

Response status at transplantation was available for 93% of patients, among them only 24% had a response status at transplantation in at least very good partial (VGPR) (Table 1). For conditioning regimen, a fast shift was observed around year 2000 from MAC to RIC reaching respective rates of 34 and 66% of total use in 2012 (Figure 3a). For stem cells source, in 81% of patients, peripheral blood stem cells were used while bone marrow was used in 18% of patients and only 1% used cord blood. Another shift was also seen in terms of HSC donors, where the usage of HSC from unrelated donors have gained over related donors in the recent years with a maximum reached in 2012 representing 56% versus 44%, respectively (Figure 3b). The use of T-cell depletion *in vitro* and *in vivo* represented 36% of the total number of performed transplantations.

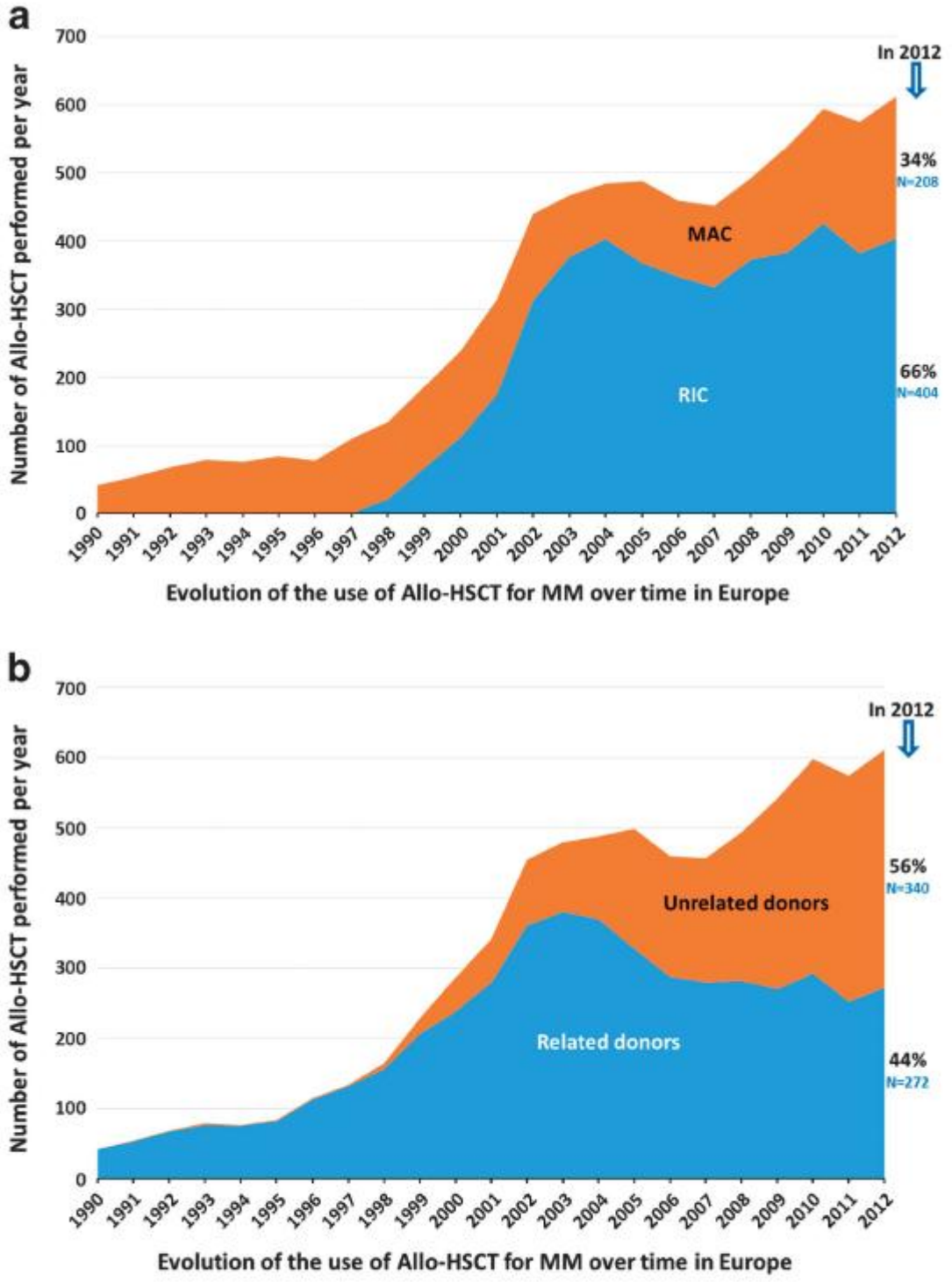


Figure 3. (**a**) Evolution of allogeneic HSCT use over time in Europe according to conditioning. (**b**) Evolution of allogeneic HSCT use over time in Europe according to HSC donors.

Transplantation outcomes

At time of analysis, a total of 3140 patients were alive with a median follow-up of 36 months (range: 1–270) after date of transplantation. When comparing survival before and after year 2004, OS rates have improved after year 2004 with a median OS going from 29 to 40 months in the upfront allo-HSCT group (P=0.017); from 63 to 70 months in the tandem auto-allo-HSCT group (P=0.11); and from 16 to 26 months in the later allo-HSCT group (P<0.0001) (Figure 4). The respective 5-year OS probabilities went from 38% (35–40) before year 2004 to 42% (36–47) after year 2004 (P=0.017), from 51% (46–55) to 54% (50–57) (P=0.11) and from 25% (22–29) to 33% (30–35) (P<0.0001). When considering only RIC in the tandem auto-allo-HSCT group, the 5-year OS according to year of transplant before or after 2004 was 53% and 55% with a median of 74 months versus 76 months, respectively, (P=0.26).

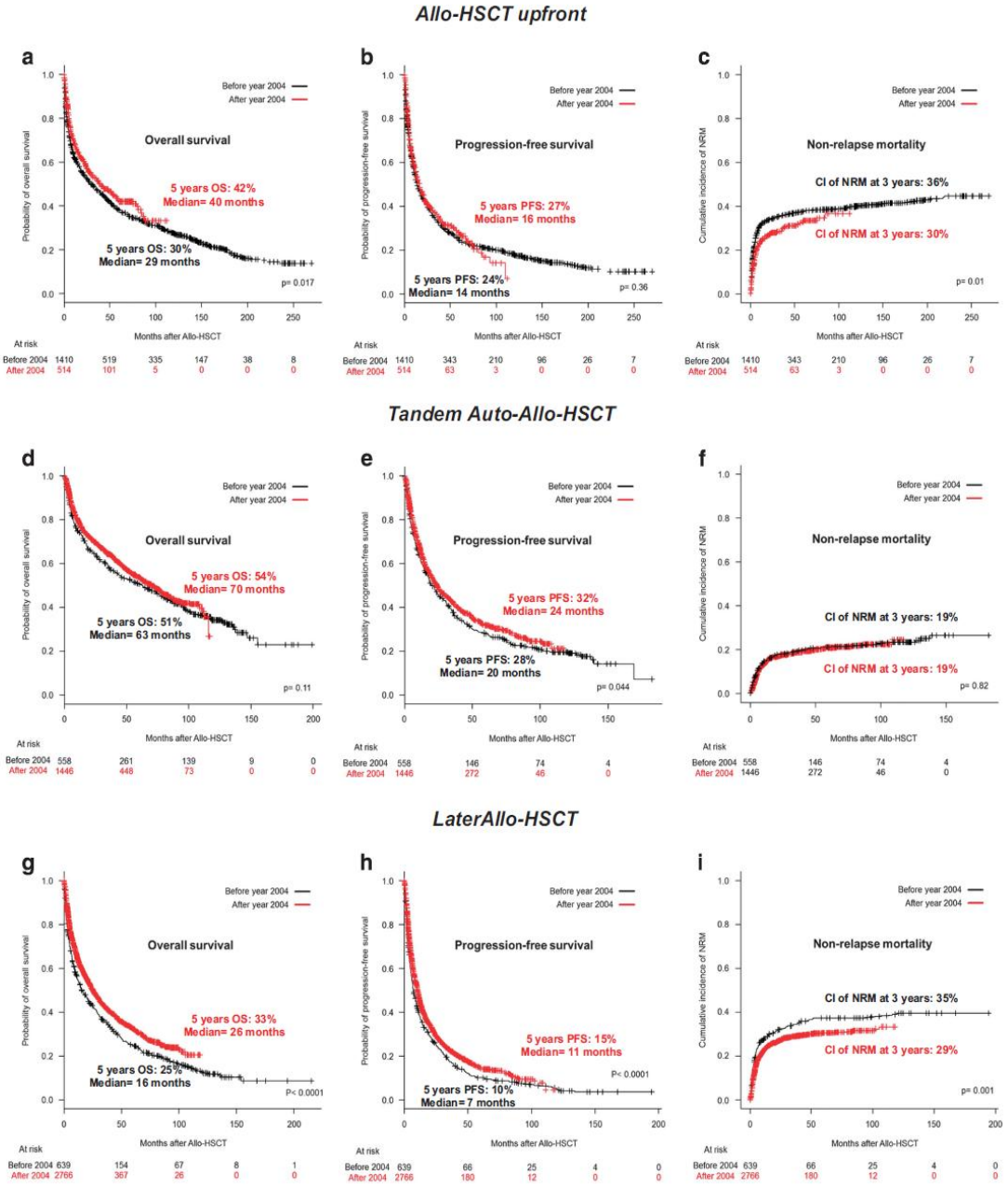


Figure 4. Overall survival (**a**, **d**, **g**), progression-free survival (**b**, **e**, **h**) and non-relapse mortality (**c**, **f**, **i**) rates according to the year of allo-HSCT before and after year 2004 for the three allo-HSCT groups. Number of patients at risk is shown under each panel for the three groups.

Relapse rates were not very different overall after year 2004, with 5-year cumulative incidence going from 39 to 38% in the upfront group (P=0.043); from 51 to 47% in the tandem auto-allo-HSCT group (P=0.12); and from 53 to 55% in the later allo-HSCT group (P=0.59).

There was a significant improvement in PFS after year 2004 in the auto-allo-HSCT group and the later allo-HSCT group, with a median going from 20 to 24 months (P=0.044) and from 7 to 11 months (P<0.0001) in the two groups, respectively. The PFS difference according to the date cut-off was not significant in the upfront allo-HSCT group (median going from 14 to 16 months, P= 0.36). The 5-year PFS probabilities for groups 1, 2 and 3 before and after year 2004 went from 24%

(22–27) to 27% (22–32) (P=0.36); from 28% (24–32) to 32% (29–35) (P=0.044); and from 10% (8–13) to 15% (13–16) (P<0.0001) respectively (Figure 4).

NRM improved overall after year 2004 with 3-year cumulative incidence going from 36 to 30% in the upfront allo-HSCT group (P=0.014), it was similar in the tandem auto-allo-HSCT group with 19% (P=0.82) and from 35 to 29% in the later allo-HSCT group (P=0.001).

Discussion

Despite the continuous controversy about the use of allogeneic transplantation for treatment of MM, the number of patients who received an allogeneic stem cell transplantation in Europe is steadily increasing from year 1990 to 2012. A major reason might be that the improvement in outcome with novel drugs has yet not translated in cure of the disease and most patients will ultimately relapse. Autologous transplantation has improved the outcome, but even when combined with novel drugs relapse continues to be the main cause of death. The present study also shows that the timing of allogeneic transplantation, as well as the strategy how to perform it varied considerably within the European countries. While allo-HSCT is still currently proposed for a good percentage of patients in the upfront setting in some countries, other countries have postponed it for a use in second line and beyond. The different trends in using allo-HSCT among the European countries might be related to the reimbursement by the health authorities and insurance companies, as well as the policy of the national myeloma study groups. The descriptive nature of this study gives an idea on outcomes for allo-HSCT in the different context of use. Nevertheless, a direct comparison between results from different strategies is not possible as there is no adjustment for the different characteristics, as well as for the time scale, which was not among our objectives. The actual rational of upfront use of allo-HSCT in MM remains in high-risk patients. In this context, encouraging results are obtained with the upfront tandem auto-allo-HSCT procedure where debulking by a previous autologous transplant appears to maximize the graft-versus-myeloma effect by the allogeneic transplant.[17] The 5-year OS of 55% and a median of 76 months in the tandem auto-RIC-allo-HSCT performed after year 2004 are comparable with most trials including auto or auto/auto and novel drugs.[34] However, the most important fact seems to be that long-term survival of up to 15 years is obtained in more than 20% of the patients in the auto-allo-HSCT group. Upfront allogeneic transplantation, without previous autologous transplantation, is a less advantageous approach mainly due to a higher NRM of 34% at 3 years, which is close to the NRM in patients transplanted in later stages of the disease. The main reason for this high-NRM upfront is that MAC was used in the majority of patients (70 %) while in the tandem modality it was the opposite—79% received RIC. The higher NRM with myeloablation translated into poorer OS. However, improvement in supportive treatment has reduced NRM even following myeloablative allogeneic transplantation in the recent years.

Although later transplants result in shorter OS than early transplants, the long-term outcome is encouraging. Out of the patients who received the transplant >8 month from first auto-HSCT, usually in progression or relapse, 25% survived at 10 years from the transplant, some of these patients may well be cured. Most of the allo-transplants reported in this study were performed before the use of novel drugs. Better results when incorporating second- and third-generation proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies and histone deacetylase inhibitors may well be obtained.[35] The introduction of these new compounds before and/or after transplantation capable of inducing high-response rates with limited side effects has greatly

challenged its role, although recent reports have shown that their use and graft-versus-myeloma effect are not mutually exclusive and a strong synergistic effect may be established.[36, 37, 38, 39, 40] In our study, the impact of novel drugs could be seen in significant improvement in terms of PFS for the auto-allo-HSCT group and the later allo-HSCT group after year 2004. Data concerning maintenance therapy after allo-HSCT, including the use of donor lymphocyte infusions in this retrospective registry study, especially the reason for their use, were not reliable to evaluate their impact on outcomes. Compared with other treatment modalities for MM, allo-HSCT induces a high rate of clinical complete response (CR) where at least half of patients with CR also achieve CR at the molecular level.[41, 42] Although remission rates before and after transplantation are important, the use of molecular evaluation of minimal-residual disease has been demonstrated to have a highly significant impact on disease recurrence detection, where an immediate therapeutic intervention could offer a low-risk opportunity to extend the duration of remission and survival.[43, 44, 45] Considering the poor outcome for high-risk patients, that is, those with the del(17p), gain(1q), t(4;14) and t(14;16) abnormalities, with current treatments, studies of upfront auto-RIC-allo-HSCT, including novel drugs, are warranted in such high-risk young patients. Previous prospective and retrospective reports evaluating allo-HSCT in MM, in the majority of cases, high-risk patients were classified mainly according to beta2 microglobulin and del(13q) that in absence of other poor prognostic abnormalities is no longer considered as a high-risk feature.[46] This prognostic classification in addition to differences in design, patient eligibility, pre-transplantation induction therapy, conditioning regimen and GvHD prophylaxis may explain the different results between the large studies evaluating allo-HSCT in MM and which have substantially impacted on the local experience in each country leading to the heterogeneity of allo-HSCT use observed today within European countries. In our study, cytogenetic information was missing for the majority of patients with data reported only for 6.6% of patients. This lack of data is due to the absence of routine use of such testing in the past years across centers or it could be missing at the transplantation center but available at the referring center. However, since this was outside the scope of this descriptive study, we did not request those data from the corresponding centers. In terms of transplantation settings, there was a big shift toward using RIC which also enlarged the use of allo-HSCT for more unfit and older patients. There was a remarkable increase in the use of transplants from unrelated donors during the last decade. This was supported by encouraging results when optimizing the donor selection especially in the human leukocyte antigen settings.[47] We showed that the majority of allo-HSCTs performed in the last years were in a context of relapse after one or two autologous transplantations. The spectrum of treatment options for patients with relapsed MM had changed dramatically after the introduction of novel drugs including the option of using a second auto-HSCT. However, allo-HSCTs have shown better freedom from disease intervals in these patients.[48, 49] Recently, different studies have evaluated the use of novel drugs including panobinostat, carfilzomib, elotuzumab and ixazomib, in the context of relapse with very promising results,[50, 51, 52, 53] however, a longer follow-up is needed to perform a specific sub analysis regarding those combinations and allo-HSCT. The International Myeloma Working Group together with the Blood and Marrow Transplant Clinical Trials Network (BMT-CTN), the American Society of Blood and Marrow Transplantation (ASBMT) and the European Society of Blood and Marrow Transplantation (EBMT) reported consensus on salvage options in patients with relapsed MM.[12] The authors recommended that allogeneic HSCT should be considered as an appropriate therapy for any eligible patient with early relapse (<24 months) after primary therapy that included an autologous HSCT and/or high-risk features.

In conclusion, we showed that the use of allo-HSCT for MM patients is still increasing in Europe despite the introduction of novel drugs. The use of allo-HSCT is different between the different European countries which reflects the heterogeneous health policies and treatment option availabilities, which translates into different local experiences and results. Furthermore, there is a clear trend to less perform allo-HSCT at an early stage of the disease (upfront allo-HSCT and tandem auto-allo-HSCT), but more in the context of relapsed and/or high-risk patients. While we do not give any recommendation for timing of or even any allo-HSCT in myeloma, we want to stress out that the increasing use of allo-HSCT after relapse to an autograft needs to be validated in prospective comparative studies, which do not exist so far. Despite several consensus and recommendations for the use of allo-HSCT in a context of clinical trials, the use of allo-HSCT for MM in Europe is actually based on individualized decision outside of a clinical trial.

Conflict of interest

The authors declare no conflict of interest.

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