European Journal of Haematology

European Journal of Haematology 97 (479–488)

ORIGINAL ARTICLE

Outcome of allogeneic transplantation in newly diagnosed and relapsed/refractory multiple myeloma: long-term follow-up in a single institution

Laurens E. Franssen[1,2], Reinier A. P. Raymakers[1], Arjan Buijs[3], Marian F. Schmitz[1], Suzanne van Dorp[4], Tuna Mutis[2], Henk M. Lokhorst[1,2], Niels W. C. J. van de Donk[2]

[1]Department of Hematology, University Medical Center Utrecht, Utrecht; [2]Department of Hematology, VU University Medical Center, Amsterdam; [3]Department of Genetics, University Medical Center Utrecht, Utrecht; [4]Department of Hematology, Radboud University Medical Center, Nijmegen, the Netherlands

Abstract

Allogeneic stem cell transplantation (allo-SCT) has the potential to induce long-term remission in multiple myeloma (MM), but the role of allo-SCT in MM is controversial due to the high rate of treatment-related mortality (TRM). However, although proteasome inhibitors and immunomodulatory drugs have improved the outcome of patients with MM, high-risk patients still have a very poor prognosis. This indicates the need for new treatment strategies and identification of patients who might benefit from allo-SCT. We therefore analyzed the outcome of one hundred and forty-seven patients with MM who received an allo-SCT at our institution (58 in first line, 89 in relapsed/refractory setting) after a median follow-up of 88.8 months. For the first-line setting, median progression-free survival (PFS) and overall survival (OS) were remarkably good, with a CR rate of 48.3%, median PFS of 30.2 months, and 10-yr OS of 51%. We found no difference in outcome for patients with high-risk metaphase cytogenetics or FISH del(13q14), but efficacy in current standard high-risk patients could not be determined. The outcome in the relapsed/refractory setting was poor, especially in the subgroup of patients relapsing within 18 months after auto-SCT. Therefore, if applied at all in these patients, improvement of allo-SCT is needed, focusing on reduction of TRM and more effective immunotherapy.

Key words allogeneic stem cell transplantation; multiple myeloma; immunotherapy

Correspondence N. W. C. J. van de Donk, MD, PhD, Department of Hematology, VU University Medical Center Amsterdam, De Boelelaan 1118, 1081HZ Amsterdam, the Netherlands. Tel: 0031 20 444 2604; Fax: 0031 20 444 2601: e-mail: n.vandedonk@vumc.nl

Some patients were part of the HOVON 108 trial. Trial registered with trialregister.nl; HOVON 108: NTR 2958

Accepted for publication 29 March 2016 doi:10.1111/ejh.12758

Introduction

Allo-stem cell transplantation (SCT) has the potential to induce long-term remissions due to the graft-vs.-tumor effect (1–6). However, the role of allo-SCT in multiple myeloma (MM) is debated. Comparison of tandem autologous transplantation (auto-SCT) vs. upfront allo-SCT has shown conflicting results (7–12). This, together with the high rate of treatment-related mortality and established effectiveness of novel drugs as induction and/or maintenance therapy, led to the disappearance of allo-SCT as upfront therapy for MM. Although the introduction of proteasome inhibitors and immunomodulatory drugs (IMiDs) has markedly improved the outcome of patients with MM, patients with high-risk MM still have a very poor prognosis (13–17). This indicates the urgent need for new treatment strategies for these patients.

Current guidelines recommend allo-SCT to be performed in the setting of clinical trials, with candidates being newly diagnosed patients with ultra-high-risk myeloma or patients with an early relapse after first-line treatment including auto-SCT (18–20). The effectiveness of allo-SCT in these patients is however not well established. In the current study, we present the results of allo-SCT for patients with MM from a

single institution. We will describe the outcome of patients transplanted upfront, including the impact of cytogenetic aberrations that were considered high risk in the treatment period of this cohort of patients. In addition, the outcome of patients transplanted in a relapsed/refractory setting is analyzed, specifically looking at patients with early progression after auto-SCT.

Methods

Patients

Between April 2001 and January 2014, 147 patients with MM underwent an allo-SCT in the University Medical Center Utrecht (UMCU), Utrecht, the Netherlands. One patient received two additional transplantations because of non-engraftment and another patient received one additional transplantation because of non-engraftment. Total follow-up was until June 2014. During this period, standard practice in the UMC Utrecht was that all patients below 66 yr of age with a suitable sibling donor were offered an allo-SCT as part of their first-line therapy. The indication for allo-SCT in the relapsed setting was determined on an individual basis. Requirements included chemo-sensitive disease, a good performance status (WHO-2), and absence of severe organ abnormalities.

Outcomes and definitions

Response to treatment and progression were determined according to the criteria formulated by the International Myeloma Working Group (21). Overall survival (OS) was measured in months and defined from the date of allo-SCT to the date of death from any cause. Patients alive at their last follow-up were censored. Progression-free survival (PFS) was defined from the date of allo-SCT to the date of progression or death from any cause. Patients alive without progression at their last follow-up were censored. Non-relapse mortality (NRM) was defined as death without previous occurrence of a relapse or progression. Relapse incidence (RI) was defined from the date of allo-SCT to the date of a relapse or progression. NRM and RI were considered competing events. Acute graft-vs.-host disease (GvHD) was defined as grade II-IV according to Seattle criteria (22). Chronic GvHD was defined as limited and extensive according to Shulman *et al.* (23). starting from d 100 after allo-SCT, with death or progression/relapse without chronic GvHD as competing events. Reactivation of cytomegalovirus (CMV) and Epstein–Barr virus (EBV) was determined by quantitative PCR. Invasive aspergillosis was diagnosed if the patient fulfilled criteria for possible, probable, or proven aspergillosis (24). Myeloablative conditioning (MAC) regimens included either busulfan and fludarabine or cyclophosphamide and TBI. Melphalan plus fludarabine and alemtuzumab, as was used in the HOVON 108 trial, was considered semi-ablative. Regimens not meeting these criteria were considered to be non-myeloablative (reduced intensity) conditioning.

Chromosomal and FISH analysis

Metaphase cytogenetics and analysis of deletion of chromosome 13 (del(13q14)) by FISH were carried out in 86 patients (58.5%). In three of these patients, only FISH analysis was performed. Any aberration found with metaphase cytogenetics (except hyperdiploidy) was considered as 'abnormal karyotype', as this has been described to be an adverse prognostic factor in MM (25–28). Although del (13q14) is not an optimal prognostic marker for outcome, it was the only chromosomal aberration that was adequately analyzed by FISH in these patients. In addition, it is often associated with other adverse cytogenetic abnormalities (del(17p), *t*(14;16), *t*(14;20)), and as such, it still is associated with adverse clinical outcome (14). Cytogenetic analysis was performed at the time of diagnosis in all patients.

High-risk patients

Two groups were defined as high-risk patients: the first being patients with high-risk cytogenetics. In our cohort, we separately looked at an abnormal karyotype (excluding hyperdiploidy) and del(13q14) by FISH; and the second being patients with early progression after auto-SCT (either within 12 or within 18 months).

Statistical analysis

Survival curves were estimated using the Kaplan–Meier method, with group comparison by the log-rank test. Prognostic factors for PFS and OS were analyzed for statistical significance using the Cox proportional hazard model. Factors that showed a significance of $P \leq 0.1$ were included in a multivariate Cox regression model (backward stepwise regression, likelihood ratio test).

For competing risk analyses, cumulative incidence functions were estimated with group comparison using the Gray test. NRM, RI, and chronic GvHD were analyzed using cumulative incidence curves. For prognostic influence of chronic GvHD, analysis was restricted to patients surviving >100 d. Differences in continuous variables were determined using the Mann–Whitney *U*-test or Kruskal–Wallis test. Differences in categorical variables were determined with Fisher's exact test for two-by-two tables and otherwise with Pearson's chi-square test. A level of $P < 0.05$ was considered significant. Analyses were performed using SPSS (IBM Statistics, version 20; IBM SPSS Inc., Armonk, NY, USA) and R (for WINDOWS Ri386 3.1.0).

Results

Patient and transplant characteristics

We included 147 patients with MM. Median follow-up was 88.8 months. Fifty-eight allo-SCTs were performed as part of first-line treatment (39.5%) and 89 for relapsed or refractory MM (60.5%). Induction therapy prior to the allo-SCT included novel agents in 39.7% of the patients treated with allo-SCT in first line and in 88.8% of the patients treated in the relapsed/refractory setting. Of the first-line patients, 57 (98.3%) received a tandem auto-allo-SCT according to the Seattle scheme (29). For first-line patients, the remission status pre-allo-SCT was VGPR in 50% of patients, PR in 34.5% and less than PR in 15.5%. For the relapsed patients, the remission status pre-allo-SCT was CR in 12.4% of patients, VGPR in 36%, PR in 41.6%, and less than PR in 10.1%. The majority of patients (93.2%) received peripheral blood stem cells. The conditioning regimen was myeloablative in only 3.4% of the transplantations. T-cell depletion was performed with antithymocyte globulin (ATG; *in vivo*) in case of an unrelated donor or HLA mismatch in 53 transplantations (36.1%), or with alemtuzumab (*in vivo* as well as 'in the bag') as part of the HOVON 108 trial in 30 transplantations (20.4%). In a subgroup of patients, cytogenetic analysis was performed (42 patients transplanted in first line (72.4%) and 44 patients transplanted in the relapsed/refractory setting (49.4%)). No consolidation treatment was given after allo-SCT or after DLI, except for four patients receiving lenalidomide maintenance post-allo-SCT. For detailed characteristics, see Table 1.

Outcome

Response. Outcome after transplantation is shown in Table 2. Overall response rate (defined as a remission status of ≥PR after allo-SCT) was 87.9% in first-line setting vs. 87.6% in relapsed/refractory setting ($P = 0.79$). Complete response rates after allo-SCT were higher in the first-line setting compared with the relapsed setting (48.3% vs. 30.3%) ($P = 0.06$).

Survival. In the first-line setting, median PFS was 30.2 months (95% CI: 21.4–39.0) and median OS was not reached (10-yr OS was 51%). PFS and OS were significantly shorter in the relapsed/refractory setting. Median PFS was 8.0 months (95% CI: 6.4–9.7) and median OS was 28.7 months (95% CI: 16.4–41.0) ($P < 0.0001$, Fig. 1). To exclude worse survival due to multiple lines of relapse treatment before allo-SCT was given, we compared PFS and OS of patients treated with allo-SCT after first relapse/progression ($n = 58$) with patients treated with allo-SCT after one or more lines of relapse treatment ($n = 31$) which did not show any significant differences.

Table 1 Clinical characteristics

Clinical characteristics	First-line setting $N = 58$	Relapsed/refractory setting $N = 89$
Sex		
Male	37 (63.8)	63 (70.8)
Female	21 (36.2)	26 (29.2)
Age (years)		
Mean	53.30	55.64
Range	35–66	32–68
Line of therapy		
1	N.A.	N.A.
2		58 (65.2)
3		22 (24.7)
>3		9 (10.1)
Source		
PB	56 (96.6)	81 (91.0)
BM	1 (1.7)	7 (7.9)
Missing data	1 (1.7)	1 (1.1)
Donor		
Sibling	55 (94.8)	32 (36.0)
MUD	3 (5.2)	57 (64.0)
Sex mismatch		
Patient/donor M/F	13 (22.4)	21 (23.6)
Myeloablation		
MA	3 (5.2)	2 (2.2)
NMA	55 (94.8)	58 (65.2)
Semi-ablative	0	29 (32.6)
T-cell depletion		
ATG/Alemtuzumab	7 (12.1)	76 (85.4)
None	51 (87.9)	13 (14.6)
Type original M protein		
IgA	7 (12.1)	21 (23.6)
IgG	43 (74.1)	52 (58.4)
IgM	1 (1.7)	1 (1.1)
IgD	1 (1.7)	0
FLC only	3 (5.1)	13 (14.6)
Non-secretory	3 (5.2)	1 (1.1)
Novel agents pre-allo		
Bortezomib based	6 (10.3)	6 (6.7)
Lenalidomide based	0	4 (4.5)
Thalidomide based	17 (29.3)	19 (21.3)
Multiple types	0	50 (56.2)
None	35 (60.3)	10 (11.2)
Time auto-SCT to allo-SCT (months)		
Mean	4.08	32.79
Range	1.63-15.37	2.13-81.13
Relapse after auto-SCT†		
<12 months	N.A.	17 (25.8)
<18 months		29 (43.9)
Remission status pre-allo		
CR	0	11 (12.4)
VGPR	29 (50)	32 (36.0)
PR	20 (34.5)	37 (41.6)
Less than PR	9 (15.5)	9 (10.1)
Cytogenetic aberrations		
Metaphase cytogenetics (excluding hyperdiploidy)		
Yes	15 (25.9)	13 (14.6)
No	27 (46.6)	29 (32.6)

(continued)

Table 1. (continued)

Clinical characteristics	First-line setting $N = 58$	Relapsed/refractory setting $N = 89$
Unknown	16 (27.6)	49 (53.9)
FISH del(13q)		
Yes	17 (40.5)	18 (40.9)
No	25 (59.5)	26 (59.1)
Unknown	16 (27.6)	45 (50.6)

[†]Only patients in relapsed setting, $n = 89$. Of those, we could determine time from auto-stem cell transplantation (SCT) to relapse/progression in 66 patients.

Table 2 Outcome after allo-SCT

	Allo-SCT in first line $N = 58$	Allo-SCT in relapsed setting $N = 89$
Remission status after allo-SCT		
CR	28 (48.3)	27 (30.3)
VGPR	18 (31.0)	33 (37.1)
PR	5 (8.6)	18 (20.2)
Less than PR	7 (12)	9 (10.1)
Too early to evaluate		1 (1.1)
EBV reactivation	8 (13.8)	31 (34.8)
CMV reactivation	10 (17.2)	33 (37.1)
Aspergillus infection	3 (5.2)	12 (13.5)
Acute GVHD grade II-IV	29 (50)	27 (30.3)
Chronic GVHD		
Limited	6 (10.3)	12 (13.5)
Extensive	23 (39.7)	21 (23.6)
Median PFS (months)		
Whole group (95% CI)	30.20 (21.44–38.96)	8.03 (6.38–9.68)
Median PFS2 (months)		
Whole group (95% CI)	61.63 (31.75–91.51)	14.97 (11.60–18.34)
Median OS (months)		
Whole group (95% CI)	NR (10-yr survival of 51%)	28.70 (16.39–41.01)

CMV, cytomegalovirus; EBV, Epstein–Barr virus; OS, overall survival; PFS, progression-free survival; allo-SCT, allogeneic stem cell transplantation

NRM and relapse/progression incidence. In the first-line setting, cumulative incidence of NRM at 10 yr was 15.5% (95% CI: 7.6–26.0), compared with 18.8% (95% CI: 10.8–28.5) in the relapsed/refractory setting ($P = 0.72$). Causes of NRM were infections in eight patients, heart failure of unknown origin in one, and GvHD in all others ($n = 41$). Cumulative incidence of relapse or progression at 10 yr was 53.3% (95% CI: 39.0–65.6) in the first-line setting, compared with 75.1% (95% CI: 56.3–86.7) in the relapsed/refractory setting ($P < 0.001$, see Fig. 2).

GvHD. The incidence of acute GvHD (grade II-IV) in the first-line setting was 50.0%, compared with 30.3% in the relapsed setting ($P = 0.024$). Cumulative incidence of limited and extensive chronic GvHD at 10 yr was higher in the first-line setting compared with allo-SCT in the relapsed setting (50% vs. 36.5%, $P = 0.133$).

High-risk cytogenetic abnormalities. In the first-line setting, cytogenetic aberrations defined by metaphase cytogenetics or FISH del(13q14) did not significantly influence PFS and OS in our cohort (Table 3).

In the relapsed/refractory setting, FISH del(13q14) was an unfavorable prognostic factor for OS, but not for PFS. Median OS was 13.4 months in patients with del(13q14) compared with 64.3 months in patients without this abnormality ($P = 0.007$, HR 2.845, 95% CI: 1.330–6.082) (Table 4). Cytogenetic aberrations defined by metaphase cytogenetics did not influence survival in this group.

Early relapse after auto-SCT. For 66 patients receiving allo-SCT for relapse/progression after previous treatment, we were able to define the time from auto-SCT to relapse or progression (according to IMWG criteria). The other 23 patients did not receive auto-SCT ($n = 5$), were primary refractory to auto-SCT ($n = 5$), received tandem auto-allo-SCT for progression after previous non-high-dose treatment ($n = 2$), and progressed without reaching the IMWG progression criteria ($n = 2$), and for nine patients, the exact interval between auto-SCT and relapse/progression could not be calculated.

A relapse or progression within 18 months after auto-SCT significantly influenced both PFS and OS. Median PFS in patients relapsing within 18 months after auto-SCT ($n = 29$) was 6.5 months (95% CI: 4.5–8.4) compared with 9.7 months (95% CI: 6.4–13.1) in patients relapsing after 18 months ($n = 37$) ($P = 0.020$). Median OS was 22.8 months (95% CI: 14.9–30.8) compared with 52.4 months (95% CI: 20.5–84.4) in patients relapsing within and after 18 months, respectively ($P = 0.012$) (see Fig. 3). For patients relapsing within 12 months after auto-SCT ($n = 17$), survival was not significantly different from patients relapsing within 18 months (median PFS 6.6 months and median OS 19.4 months, $P = 0.061$ and $P = 0.068$, respectively).

Predictive factors for PFS and OS. Next to the defined 'high-risk myeloma' group described above, we also analyzed other possible predictive factors for PFS and OS.

For the upfront setting, univariate analysis for possible predictive factors for PFS and OS is depicted in Table 3. In the multivariate analysis, a remission status of ≥VGPR after allo-SCT was an independent predictor for longer PFS (HR 0.196, $P < 0.001$) and OS (HR 0.259, $P = 0.001$).

For the relapsed/refractory setting, univariate analysis is depicted in Table 4. In multivariate analysis, independent predictive factors for PFS were age at allo-SCT (HR 1.059, $P = 0.012$), ≥VGPR after allo-SCT (HR 0.395, $P = 0.006$), and chronic GvHD (HR 0.371, $P = 0.002$). For OS, FISH del(13q14) (HR 4.149, $P = 0.006$), Aspergillus infection

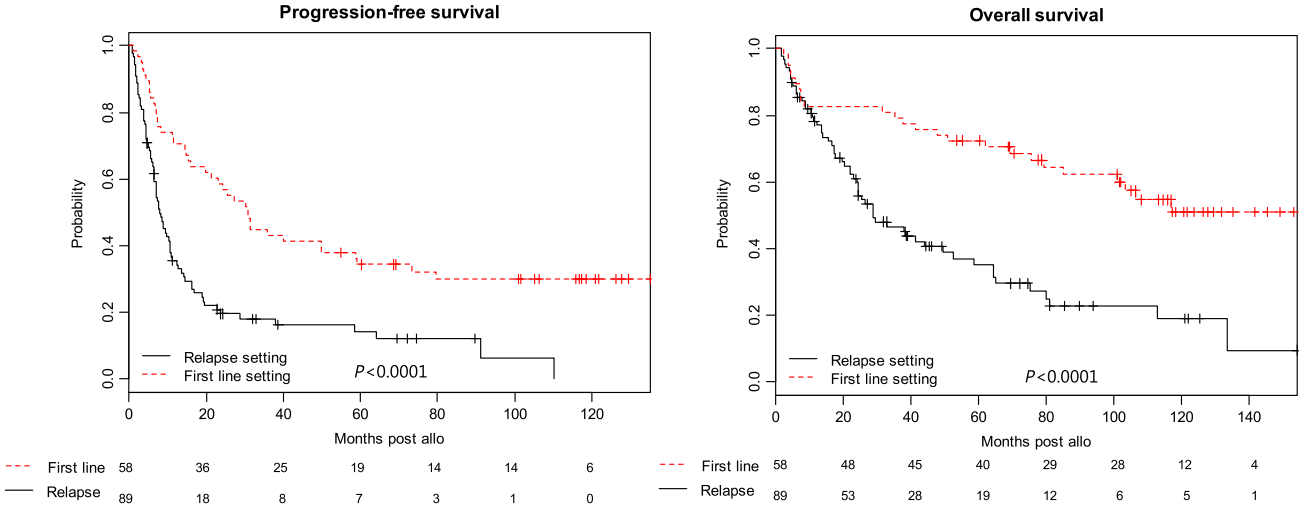

Figure 1 Progression-free and overall survival in upfront vs. relapsed/refractory setting. Progression-free survival and overall survival for patients transplanted upfront vs. patients transplanted in a relapsed/refractory setting. The log-rank test was used to test the statistical significance of the difference between the survival curves.

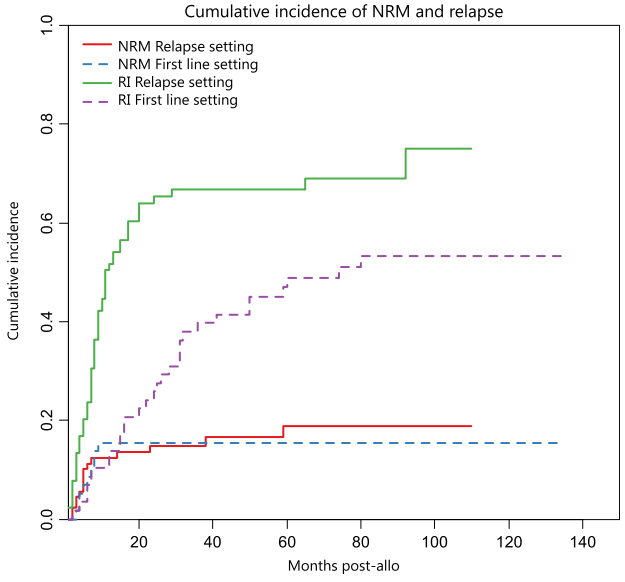

Figure 2 Cumulative incidence functions of non-relapse mortality (NRM) and relapse incidence (RI) in upfront vs. relapsed/refractory setting. Cumulative incidence functions showing NRM and the RI in patients transplanted upfront and patients transplanted in a relapsed/refractory setting.

(HR 7.336, P = 0.003), and CR after allo-SCT (HR 0.184, P = 0.010) were independent predictive factors.

Relapse treatment and outcome. After allo-SCT, 90 patients (61.2%) had a relapse or progression of disease. Seventy patients were treated with novel agents post-allo-SCT (15 bortezomib, 26 lenalidomide, 18 thalidomide, and 11 lenalidomide plus bortezomib). ORR (≥PR) to relapse treatment was 51.4%, with a CR rate of 13.2%. Response rate was not significantly different between patients receiving allo-SCT as part of first-line or relapse treatment. Median time from start of relapse treatment to subsequent progression or death (second PFS) was 8.1 months (95% CI: 6.6–9.7) and not significantly different between different types of novel agents. Median overall survival from the time of first relapse was 76.8 months (95% CI: 44.6–109.0) in newly diagnosed patients, compared with 22.1 months (95% CI: 10.3–33.9) in the relapsed/refractory setting (P = 0.001). Thirty-seven of the 90 patients received a DLI, which was preceded by novel agents in 28 patients. Novel agents combined with DLI (n = 28) resulted in an ORR (≥PR) of 60.7% and a CR rate of 10.7%. DLI without novel agents (n = 9) resulted in an ORR of 77.8% and CR rate of 11.1%. For all patients receiving DLI as part of relapse treatment, median second PFS was 8.7 months (95% CI: 4.6–12.7).

Of the 90 patients receiving treatment for first progression after allo-SCT, eight developed chronic GvHD, while 18 developed acute GvHD. There was no significant difference in GvHD occurrence between the different types of treatment, including DLI.

Of the 29 high-risk patients relapsing within 18 months after auto-SCT, 24 received treatment for their first progression after allo-SCT. Strikingly, the ORR to first relapse treatment in these patients was only 25% compared with 72% in patients relapsing beyond months after auto-SCT (P = 0.002). In addition, duration of response was significantly shorter in these patients (4.7 compared with 12.1 months, P = 0.020). Median overall survival from the time of first relapse in these high-risk patients was 16.2 months (95% CI: 5.3–27.2), compared with 36.1 months (95% CI: 3.8–68.4) in patients relapsing after 18 months post-auto-SCT (P = 0.028). For patients with cytogenetic high-risk features (in this cohort defined as either an abnormal

Table 3 Univariate analysis of possible predictive factors for PFS and OS after allo-SCT in the upfront setting

	PFS; *P*-value	HR	95% CI	OS; *P*-value	HR	95% CI
Sex (female)	0.036	0.464	0.226–0.953	0.111	0.474	0.189–1.188
Age	0.256	1.023	0.984–1.064	0.110	1.042	0.991–1.096
Remission status pre-allo						
CR	N.A.			N.A.		
CR and VGPR	0.007	0.415	0.219–0.786	0.024	0.378	0.163–0.878
Stem cell source (BM)	0.461	2.126	0.286–15.818	0.146	4.571	0.590–35.419
Donor type (Sib)	0.947	0.953	0.229–3.956	0.331	0.487	0.114–2.078
Remission status after allo						
CR	<0.001	0.217	0.109–0.432	<0.001	0.160	0.059–0.435
CR and VGPR	<0.001	0.196	0.093–0.414	0.001	0.259	0.115–0.582
Aspergillus infection	0.806	0.837	0.202–3.473	0.699	0.673	0.091–5.003
EBV reactivation	0.434	1.414	0.593–3.373	0.123	2.176	0.810–5.844
CMV reactivation	0.562	1.273	0.563–2.883	0.318	1.651	0.618–4.416
Acute GVHD (grade II-IV)	0.798	1.084	0.582–2.019	0.987	1.007	0.457–2.220
Chronic GVHD (limited and extensive)[†]	0.169	0.646	0.347–1.204	0.196	0.593	0.268–1.311
Prior treatment with novel agents	0.668	0.867	0.453–1.662	0.297	1.523	0.690–3.361
Patient/donor (male/female)	0.462	1.309	0.639–2.681	0.148	1.861	0.803–4.317
T-cell depletion with ATG or alemtuzumab	0.469	0.682	0.243–1.919	0.945	0.959	0.286–3.209
Karyotyping abnormal (excluding hyperdiploidy)	0.654	0.834	0.377–1.845	0.160	0.459	0.151–1.396
FISH del(13q)	0.351	1.425	0.677–2.997	0.798	0.883	0.342–2.282

CMV, cytomegalovirus; EBV, Epstein–Barr virus; OS, overall survival; PFS, progression-free survival; allo-SCT, allogeneic stem cell transplantation
[†]Chronic GVHD was analyzed including the time-dependent variable >100 d

karyotype or FISH del(13q14)), response to and duration of first relapse treatment were not different compared to patients without these aberrations.

Discussion

In the present study, we describe our single-center experience with allo-SCT in 147 patients with MM. This is one of the largest single-center reports on the outcome of allo-SCT in MM. Our goal was to describe the outcome of allo-SCT for newly diagnosed and relapsed/refractory MM, including the outcome in patients with abnormal metaphase cytogenetics or del(13q14) determined by FISH, and in the relapsed setting in patients with an early relapse or progression after auto-SCT (13–17, 20). As almost all patients were treated with allo-RIC and peripheral blood stem cells (PBSC), we were not able to draw any conclusions on the use of PBSC vs. bone marrow as stem cell source, or the difference of allo-MAC vs. allo-RIC.

The outcome of patients transplanted as part of first-line therapy (being a tandem auto-allo approach in 98.3%) in our cohort is remarkably good and compares favorably to results described in the literature where 'upfront' allo-SCT has mostly been compared to high-dose chemotherapy and single auto-SCT or tandem auto-SCT in donor-vs.-no-donor comparisons, with conflicting results (8–12, 30–34). We observed a high CR rate after allo-SCT of 48.3%. Median PFS was 30.2 months and median OS was not reached (10-yr OS was 51% in our cohort). We also observed a plateau in the PFS and OS curves; however, it remains unclear whether these patients can be considered to be cured. Despite these encouraging survival outcomes, we also found a cumulative incidence of chronic graft-vs.-host disease of 50% in this group. This probably has a major impact on quality of life (35, 36). Unfortunately, however, due to lack of collection of standardized quality-of-life data in this cohort, we were not able to report on quality of life in this analysis. Our subgroup analysis in patients with cytogenetic aberrations showed no difference in outcome compared with standard-risk patients, suggesting that allo-SCT in the upfront setting might overcome the unfavorable prognosis of these cytogenetic aberrations.

Very few studies have described the outcome of high-risk cytogenetic patients after allo-SCT in an upfront setting. Long-term results of the EBMT-NMAM2000 study show an equal outcome for patients with and without del(13q14) (31). In addition, Kroger *et al.* (37) found that allo-SCT overcomes the adverse prognosis of del(17p) and *t*(4;14), but it is unclear whether they included only upfront allo-SCT. In a prospective study comparing patients with del (13q14), Knop *et al.* (7) found a significantly increased PFS for the auto-allo arm, compared with double auto-SCT and also a significantly better OS in the allo-SCT arm for the subgroup with del(17p). In contrast to these studies, the French group found no difference in outcome, in high-risk patients with MM also carrying del(13q14), when double auto-SCT was compared with tandem auto-allo (33, 34). However, the high-dose ATG used in that protocol may have negatively influenced the outcome of the allogeneic transplantation.

Table 4 Univariate analysis of possible predictive factors for PFS and OS after allo-SCT in the relapsed/refractory setting

	PFS; *P*-value	HR	95% CI	OS; *P*-value	HR	95% CI
Sex (female)	0.301	0.749	0.434–1.294	0.583	1.187	0.644–2.187
Age	0.061	1.030	0.999–1.062	0.130	1.026	0.992–1.061
Relapse after auto-SCT						
<12 months	0.061	1.743	0.976–3.116	0.068	1.796	0.957–3.372
<18 months	0.022	1.860	1.094–3.160	0.014	2.140	1.165–3.930
Remission status pre-allo						
CR	0.543	0.796	0.382–1.660	0.240	0.576	0.230–1.445
CR and VGPR	0.224	1.336	0.838–2.130	0.312	1.302	0.781–2.172
Stem cell source (BM)	0.031	2.401	1.083–5.320	0.989	0.994	0.394–2.506
Donor type (Sib)	0.487	1.180	0.740–1.883	0.658	0.886	0.518–1.516
Extent of prior therapy (2nd vs 3rd vs 4th line allo)	0.156	1.240	0.922–1.668	0.057	1.369	0.991–1.892
Remission status after allo						
CR	0.001	0.400	0.234–0.683	0.018	0.464	0.246–0.875
CR and VGPR	0.005	0.495	0.302–0.812	0.203	0.704	0.410–1.209
Aspergillus infection	0.110	1.662	0.892–3.097	<0.001	3.568	1.788–7.119
EBV reactivation	0.023	0.565	0.345–0.923	0.058	0.583	0.334–1.018
CMV reactivation	0.176	0.714	0.438–1.163	0.424	0.798	0.458–1.389
Acute GVHD (grade II-IV)	0.133	0.673	0.402–1.129	0.889	1.041	0.590–1.838
Chronic GVHD (limited and extensive)[†]	0.001	0.434	0.263–0.715	0.012	0.488	0.278–0.856
Prior treatment with novel agents	0.261	1.498	0.740–3.030	0.305	1.491	0.695–3.198
Patient/donor (male/female)	0.152	1.453	0.871–2.424	0.856	1.054	0.598–1.858
T-cell depletion with ATG or alemtuzumab	0.361	1.337	0.717–2.494	0.150	1.713	0.822–3.570
Karyotyping abnormal (excluding hyperdiploidy)	0.846	1.076	0.514–2.252	0.141	1.813	0.812–4.049
FISH del(13q)	0.528	1.237	0.638–2.397	0.007	2.845	1.330–6.082

ATG, antithymocyte globulin; CMV, cytomegalovirus; EBV, Epstein–Barr virus; OS, overall survival; PFS, progression-free survival; allo-SCT, allogeneic stem cell transplantation

[†]chronic GVHD was analyzed including the time-dependent variable >100 d

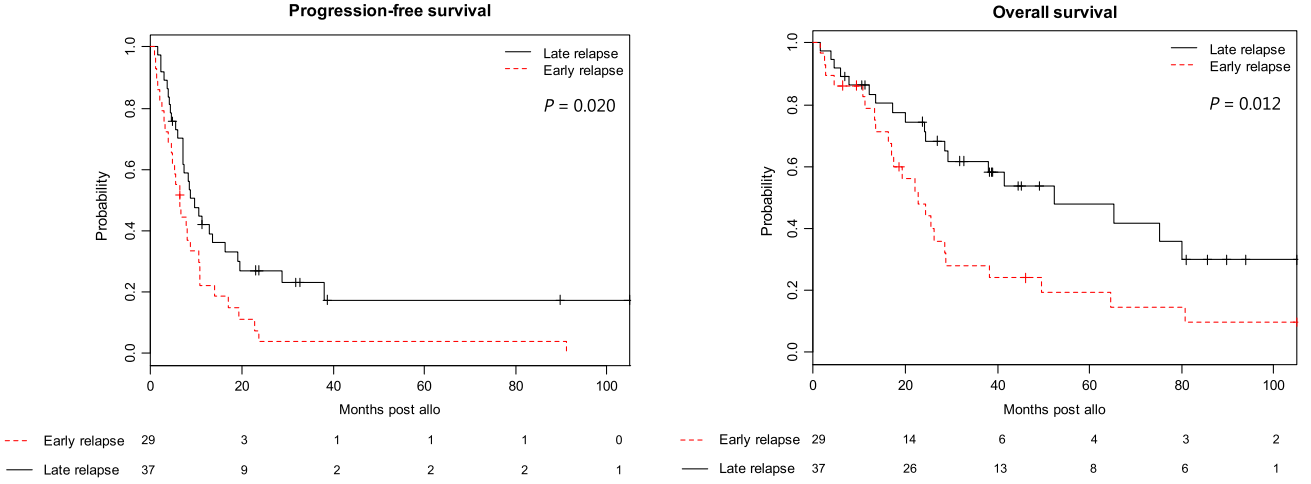

Figure 3 Progression-free and overall survival for patients with an early vs. a late relapse after auto-stem cell transplantation (SCT). Progression-free survival and overall survival for patients transplanted for a relapse after auto-SCT within 18 months (early relapse) vs. patients transplanted for a relapse after auto-SCT beyond 18 months (late relapse). The log-rank test was used to test the statistical significance of the difference between the survival curves.

Unfortunately, we were not able to obtain data on the presence of *t*(4;14), del(17p), and *t*(11;14) due to the retrospective character of this study and the fact that assessment of these cytogenetic aberrations was not routine practice at the time of transplant for most of these patients. Although del(13q) as determined by FISH is no longer seen as an

independent risk factor because it often coincides with other adverse cytogenetic abnormalities, as such it still is associated with adverse clinical outcome (14).

The discussion on whether allo-SCT should be considered an option for relapsed/refractory patients is still ongoing. A recent guideline by Giralt *et al.* (20) describes that allo-SCT should be considered appropriate therapy for any patient with a relapse within 24 months after a primary auto-SCT. We found a very poor outcome of allo-SCT in relapsed patients, with a short median PFS of 8.0 months and a median OS of 28.2 months. If we focus only on patients relapsing within 18 months after auto-SCT, median PFS was 6.5 months compared with 9.7 months in patients relapsing after 18 months. In addition, patients relapsing within 18 months after auto-SCT had inferior response rates and response duration to relapse treatment after allo-SCT, which translated in a worse median OS of 22.8 months compared with 52.4 months in patients relapsing within or after 18 months, respectively. Although the overall survival of patients relapsing after 18 months is promising, the short PFS in this group suggests a poor graft-vs.-myeloma effect and the extended OS probably reflects effective relapse treatment after allo-SCT with novel agents. For patients relapsing beyond 1.5-2 yr after auto-SCT, we generally recommend novel agent-based therapy or, in case of transplant eligible patients, a second auto-SCT (38–47).

In conclusion, although our results of allo-SCT as part of first-line therapy are very encouraging, upfront allo-SCT is not considered an option for standard-risk MM due to the high non-relapse mortality and currently available superior alternatives with novel agent-based combination therapies. For the subgroup of patients with ultra-high-risk myeloma (ISS 3 and high lactate dehydrogenase and del (17p) and/or *t*(4;14)), the chances of achieving a long-term remission are still very low (16). In these patients, upfront allo-SCT in the setting of a clinical trial might be an option.

In the relapsed/refractory setting, outcome after allo-SCT is very poor, especially for patients with an early relapse after auto-SCT. If applied at all, new treatment options for allo-SCT are urgently needed. In this respect, the value of optimal induction, maintenance therapy, and post-allo-SCT immunotherapy should be explored, as well as strategies to lower NRM and acute and chronic GvHD.

Acknowledgements

None.

Conflicts of interest

None.

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