Autologous-allogeneic *versus* autologous tandem stem cell transplantation and maintenance therapy with thalidomide for multiple myeloma patients under 60 years of age: a prospective, phase II study

Nicolaus Kröger,[1] Gerald Wulf,[2] Ute Hegenbart,[3] Andreas Burchert,[4] Matthias Stelljes,[5] Nico Gagelmann,[1] Arne Brecht,[6,7] Martin Kaufmann,[8] Lutz Müller,[9] Arnold Ganser,[10] Dominik Wolf,[11,12] Wolfgang Bethge,[13] Martin Bornhäuser,[14] Michael Kiehl,[15] Eva-Maria Wagner,[16] Christoph Schmid,[17] Hans Christian Reinhardt,[18] Guido Kobbe,[19] Hans Salwender,[20] Thomas Heinicke,[21] Martin Kropff,[22] Marion Heinzelmann,[1] Francis Ayuk,[1] Lorenz Trümper,[2] Andreas Neubauer,[4] Andreas Völp,[23] Evgeny Kluychnikov,[1] Stefan Schönland[3] and Christine Wolschke[1]

[1]University Medical Center, Hamburg, Germany; [2]University Hospital, Göttingen, Germany; [3]University Hospital, Heidelberg, Germany; [4]University Hospital, Marburg, Germany; [5]Department of Medicine A, Hematology, Oncology, and Pneumology, University Hospital, Münster, Germany; [6]DKD HELIOS Hospital, Wiesbaden, Germany; [7]HELIOS Dr. Horst Schmidt Hospital, Wiesbaden, Germany; [8]Robert Bosch Hospital, Stuttgart, Germany; [9]University Hospital, Halle, Germany; [10]Medical School, Hannover, Germany; [11]Internal Medicine 3, University Hospital, Bonn, Germany; [12]Department of Hematology and Oncology, Comprehensive Cancer Center Innsbruck (CCCI), Medical University Innsbruck (MUI), Innsbruck, Austria; [13]University Hospital, Tübingen, Germany; [14]University Hospital, Dresden, Germany; [15]Frankfurt/Oder Hospital, Frankfurt/Oder, Germany; [16]University Hospital, Mainz, Germany; [17]University Hospital, Augsburg, Germany; [18]University Hospital, Essen, Germany; [19]University Hospital, Düsseldorf, Germany; [20]Asklepios Hospital Altona, Hamburg, Germany; [21]University Hospital, Magdeburg, Germany; [22]Osnabrück Hospital, Osnabrück, Germany and [23]Psy Consult, Hamburg, Germany

Correspondence: N. Kröger
nkroeger@uke.de

Received: February 11, 2023.
Accepted: November 2, 2023.
Early view: November 9, 2023.

https://doi.org/10.3324/haematol.2023.282920

Abstract

The role of autologous-allogeneic tandem stem cell transplantation (alloTSCT) followed by maintenance as upfront treatment for multiple myeloma is controversial. Between 2008 and 2014 a total of 217 multiple myeloma patients with a median age of 51 years were included by 20 German centers within an open-label, parallel-group, multicenter clinical trial to compare alloTSCT to autologous tandem transplantation (autoTSCT) followed by 2 years of maintenance therapy with thalidomide (100 mg/day) in both arms with respect to relapse/progression-free survival (PFS) and other relevant outcomes. A total of 178 patients underwent a second transplant (132 allogeneic, 46 autologous). PFS at 4 years after the second transplant was 47% (95% CI: 38-55%) for alloTSCT and 35% (95% CI: 21-49%) for autoTSCT (*P*=0.26). This difference increased to 22% at 8 years (*P*=0.10). The cumulative incidences of non-relapse mortality and of relapse at 4 years were 13% (95% CI: 8-20%) and 2% (95% CI: 0.3-2%) (*P*=0.044) and 40% (95% CI: 33-50%) and 63% (95% CI: 50-79%) (*P*=0.04) for alloTSCT and autoTSCT, respectively. The difference for relapse/progression increased to 33% (alloTSCT: 44%, autoTSCT: 77%) at a median follow-up of 82 months (*P*=0.002). Four-year overall survival was 66% (95% CI: 57-73%) for alloTSCT and 66% (95% CI: 50-78%) for autoTSCT (*P*=0.91) and 8-year overall survival was 52% and 50% (*P*=0.87), respectively. In conclusion, alloTSCT followed by thalidomide maintenance reduced the rate of recurrence or progression during a follow-up period of up to 10 years but failed to improve PFS significantly. This study was registered with ClinicalTrials.gov (NCT00777998).

Introduction

Multiple myeloma is the second most frequent hematologic malignancy and is considered to be an incurable disease. Novel agents which have been introduced into the treatment of multiple myeloma, such as proteasome

inhibitors, immunomodulatory agents, monoclonal antibodies and, more recently, chimeric antigen receptor T cells, have substantially improved overall survival (OS) and are included as induction, consolidation, and maintenance therapy in the context of autologous stem cell transplantation (SCT) in younger patients. However, despite high numbers of complete and measurable residual disease-negative remissions, the vast majority of patients will eventually relapse.

Allogeneic SCT carries the potential benefit of a graft-*versus*-myeloma effect resulting in a lower risk of relapse in comparison to that following autologous SCT but with the risk of higher morbidity and transplant-related mortality.[1-3] To lessen toxicity, reduced-intensity or non-myeloablative conditioning regimens have been introduced and have resulted in a decreased mortality rate in comparison to that associated with standard myeloablative conditioning.[4-6] To increase antimyeloma efficacy, sequential autologous-allogeneic tandem stem cell transplantation (alloTSCT) was introduced and investigated in several prospective studies in comparison to autologous-autologous stem cell transplantation (autoTSCT).[7-14] While in nearly all of the studies higher complete remission rates and lower relapse incidences were observed after the autologous-allogeneic approach, only two studies showed significantly improved event-free and OS rates due to the generally higher non-relapse mortality.[9,12] A recently published analysis with individual patients' data from four of these trials showed a significantly improved progression-free survival (PFS) as well as OS after alloTSCT after a median follow-up of 10 years.[15]

Despite these results allogeneic SCT as in the autologous-allogeneic tandem approach has not become standard of care in the treatment of younger myeloma patients and none of the studies has included maintenance therapy after allogeneic SCT. Here we report early and long-term results of a prospective, multicenter study of autoTSCT *versus* reduced-intensity alloTSCT, both followed by maintenance therapy with thalidomide for 2 years.

Methods

Major inclusion criteria were myeloma stage II or III according to Salmon and Durie staging system, age between 18 and 60 years, and a maximum of eight cycles of chemotherapy prior to registration independently of the response. Response was assessed according to the International Myeloma Working Group criteria. Major exclusion criteria were severe renal, hepatic, pulmonary, or cardiac diseases, and preceding autologous SCT.

The study was an open-label, parallel-group, multicenter clinical trial designed to compare outcomes (PFS and OS) after alloTSCT or autoTSCT followed by 2 years of maintenance therapy with thalidomide (100 mg/day) in both arms. The patients could have received a maximum of eight induction cycles and escalating prophylactic donor lymphocyte infusions were allowed after alloTSCT.

Patients received an autologous peripheral blood SCT followed by allogeneic peripheral blood SCT if a matched related or unrelated donor was available; otherwise, or if they declined the allogeneic transplant, they received a second autologous peripheral blood SCT. This happened in only two patients. The patients' characteristics are presented in Table 1. Appropriate donors were defined as a HLA-identical sibling or a 10/10 or 9/10 HLA-compatible unrelated donor.

The study had an observation period of 48 months, counting from the second SCT. A long-term follow-up of disease status and patients' survival covered a period of 10 years with a median follow-up of 82 months.

The primary endpoint was PFS, defined as the absence of relapse, progression or death from any cause, at 4 years after TSCT. Major secondary endpoints were cumulative incidence of relapse, disease-related mortality, non-relapse mortality and OS, all at 4 years, in both arms.

The study was approved by the "Ärztekammer Hamburg" Ethics Committee.

Statistics

Relapse-free/PFS and OS were compared between the treatment groups using Kaplan-Meier survival analysis. Confidence intervals for treatment group risk differences were determined using the Greenwood method.[16] Confirmatory testing for 4-year PFS was performed in the full analysis set (i.e., the patients who underwent TSCT) using a log-rank test and a two-sided type I error level of α=0.05. For relapse/progression, disease-related mortality and non-relapse mortality were analyzed as competing risks. Exploratory *post-hoc* Cox regression analysis was used for subgroup analysis and for determining the influence of recipient age (≤ median *vs.* > median), sex, myeloma classification, Salmon & Durie stage at baseline (I or II *vs.* III), cytogenetic risk (del17p or t4;14 *vs.* other), maximum response to induction (complete remission *vs.* other), disease status before the second SCT (complete remission *vs.* other), Eastern Cooperative Oncology Group grade before the second SCT (0 *vs.* >0), in addition to type of TSCT, on relapse/PFS and OS. In the multiple Cox models investigating the influence of the different co-variates, type of TSCT was always included (forced entry) whereas significant other co-variates were selected using backward elimination. Indicated *P* values are two-sided and are intended for descriptive interpretation except for the primary endpoint. All confidence intervals (CI) have a coverage of 95%.

The sample size was calculated on the basis of relapse-free/PFS at 4 years, assuming 48-month event rates of 50% for alloTSCT and of 70% for autoTSCT. A total sample size of 185 patients (111 for alloTSCT and 74 for

Table 1. Characteristics of the patients in the full analysis set.

Characteristics	All patients N=178	Auto-Allo TSCT N=132	Auto-Auto TSCT N=46
Age in years, median (range)	52 (26-61)	51 (26-61)	53 (34-61)
Sex, N (%)			
Male	101 (57)	74 (56)	27 (59)
Female	77 (43)	58 (44)	19 (41)
Multiple myeloma subtype, N (%)			
IgG	92 (52)	70 (53)	22 (48)
IgA	39 (22)	26 (20)	13 (28)
IgM	2 (1)	2 (2)	0 (0)
IgD	2 (1)	2 (2)	0 (0)
Light chain only	40 (22)	31 (22)	9 (20)
Missing data	3 (2)	1 (1)	2 (4)
International Staging System stage, N (%)			
I	49 (28)	33 (25)	16 (35)
II	43 (24)	32 (24)	11 (24)
III	33 (19)	27 (21)	6 (13)
Missing data	53 (30)	40 (30)	13 (28)
Extramedullary disease at diagnosis, N (%)			
No	134 (75)	97 (74)	37 (80)
Yes	19 (11)	14 (11)	5 (11)
Missing data	25 (14)	21 (16)	4 (9)
Cytogenetics,* N (%)			
Del17p or t(4;14)	32 (18)	24 (18)	8 (17)
Missing data	50 (28)	37 (28)	13 (28)
Time between diagnosis and study inclusion in months, median (range)	5 (1-118)	4 (1-118)	5 (1-47)
N of induction cycles, median (range)	3 (1-8)	3 (1-8)	3 (3-8)
Induction chemotherapy, N (%)			
VAD	12 (7)	11 (8)	1 (2)
ThalDex	2 (1)	2 (2)	0 (0)
BorDex	49 (27)	40 (30)	9 (20)
BorCyDex	68 (38)	46 (35)	22 (48)
Plus radiotherapy	3 (2)	3 (2)	0 (0)
Other	44 (25)	30 (23)	14 (30)
Best response after induction, N (%)			
Complete remission	16 (9)	13 (11)	3 (7)
Partial remission	136 (76)	99 (75)	37 (80)
Stable disease	6 (3)	4 (3)	2 (4)
Progressive disease	4 (2)	4 (3)	0 (0)
Missing data	16 (9)	12 (9)	4 (9)
Time between 1st and 2nd SCT in days, median (range)	84 (49-209)	84 (49-209)	82 (53-204)
ECOG performance status at 1st SCT, N (%)			
0	80 (45)	60 (46)	20 (44)
1	70 (39)	49 (37)	21 (46)
2	4 (2)	3 (2)	1 (2)
Missing data	24 (14)	20 (15)	4 (9)

*As determined by fluorescence *in situ* hybridization. Auto-Allo: autologous-allogeneic; TSCT: tandem stem cell transplantation; Auto-Auto: autologous-autologous; VAD: vincristine, doxorubicin and dexamethasone; ThalDex: thalidomide and dexamethasone; BorDex: bortezomib and dexamethasone; BorCyDex: bortezomib, cytarabine and dexamethasone; SCT: stem cell transplantation; ECOG: Eastern Cooperative Oncology Group.

autoTSCT) was estimated to provide at least 80% power to reject the null hypothesis in a log-rank test model.

Results

Patients' characteristics and transplants

Between October 2008 and July 2013, a total of 217 patients with stage II/III multiple myeloma were recruited into the trial in 20 centers in Germany. The median number of induction chemotherapy cycles was three in both arms. Two-hundred and eight patients underwent a first autologous transplant after conditioning with melphalan 200 mg/m^2. A second transplant was performed in 178 patients, who were analyzed for efficacy (full analysis set) and safety. Reasons for withdrawal before the second SCT are shown

in Figure 1. The second transplant was either allogeneic (n=132) or autologous (n=46). The allogeneic transplants were performed after conditioning with melphalan 140 mg/m^2, fludarabine 150 mg/m^2, and anti-T-lymphocyte globulin (Grafalon®, Fa Neovii, Switzerland) 60 mg/kg for those from matched unrelated donors and 30 mg/kg for those from HLA-identical siblings, divided into three doses given on days -3, -2, and -1. The conditioning regimen prior to a second autologous SCT was melphalan 200 mg/m^2. Seventy-nine patients (59.8%) received stem cells from an HLA-identical sibling and 53 (40.2%) from a matched unrelated donor, including four mismatched unrelated donors. One-hundred and eighteen patients of those receiving a second SCT (alloTSCT: 87, 66% of 132; autoTSCT: 31, 67% of 46) were alive at their individual endpoint of the original 48-month protocol. One-hundred and five patients (alloTSCT: n=78 [59%]; autoTSCT: n=27 [59%]) survived at the individual end of the long-term follow-up, with a follow-up duration of up to 124 months (last patient last seen alive). The patients' characteristics are summarized in Table 1.

Time-to-event endpoints

Cumulative event rates for time-to-event endpoints are presented in Table 2.

For PFS, treatment group event rates were similar during the first 1.5 years after the second SCT whereas increasingly lower rates were observed in the alloTSCT group (as compared to the autoTSCT group) as the follow-up progressed, with event rate differences of 12% at month 48 and of 22% at 8 years. The median PFS was 40.1 months (95% CI: 26.9-53.3 months) for alloTSCT and 29.8 months (29.8-37.7 months) for autoTSCT. However, treatment group differences at 48 months (primary endpoint) and at 8 years did not reach the nominal level of being statistically significant.

The treatment group differences in PFS were mainly driven by significantly lower incidences of myeloma relapse and progression in the alloTSCT group, with cumulative incidence rate differences of 23% at month 48 (*P*=0.011) and of 33% at 8 years (*P*=0.002) (Figure 2A). Moreover, mortality following relapse or progression was also lower in the alloTSCT arm (Figure 2B). The cumulative incidence of non-relapse mortality at 4 years was lower after autoTSCT at 2% (95% CI: 0.3-2%) *versus* 13% (95% CI: 8-20%) after alloTSCT (*P*=0.01) (Figure 2C).

The mean OS was 82.2 months (95% CI: 73.5-90.8 months) for patients who underwent alloTSCT and 80.1 months (95% CI: 75.7-94.2 months) for those who underwent autoTSCT (Figure 2D).

Graft-*versus*-host disease

Any grade of acute graft-*versus*-host disease (GvHD) after allogeneic SCT was observed in 38% of the patients, and was grade 1 in 17%, grade 2 in 15% and grade 3 in 6%. GvHD after donor lymphocyte infusion (DLI) was observed in 55% (95% CI: 47-64%) of the patients, a rate only slightly higher than in those who did not receive DLI. Chronic GvHD was assessed during the first 4 years of the follow-up; the cumulative incidence at month 48 was 61% (95% CI: 54-70%),

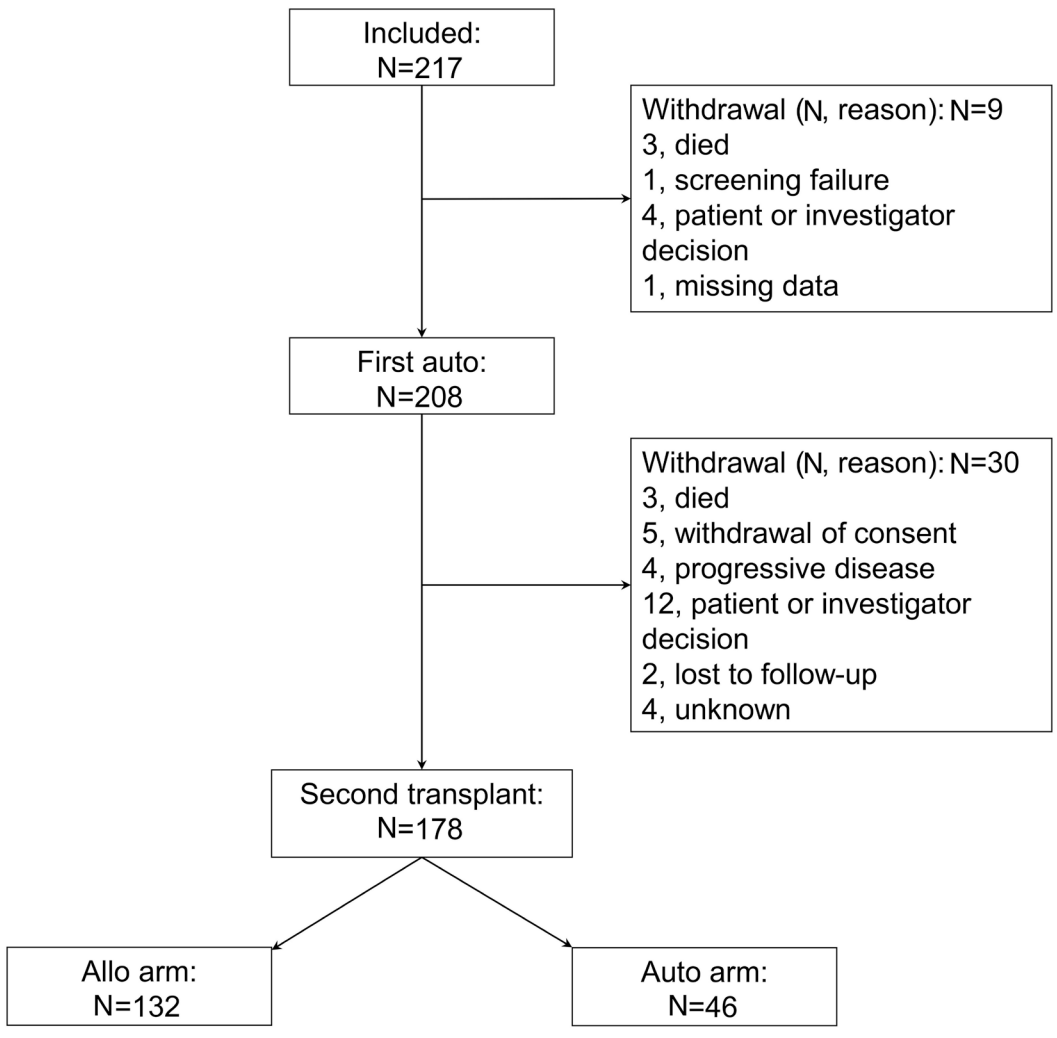


Figure 1. A CONSORT diagram of the patients' disposition in the trial. Auto: autologous stem cell transplantation. Allo: allogeneic stem cell transplantation.

and the last case of a first occurrence of chronic GvHD was observed at 26 months after the second SCT. No obvious increase in GvHD was seen after thalidomide treatment.

Thalidomide maintenance

According to protocol thalidomide 100 mg/day was to be given in both arms from day 120 after the second transplant (whether allogeneic or autologous) for a maximum of 2 years unless progression or intolerable toxicity occurred.

Thirty-two patients (24%) in the alloTSCT arm and eight patients (17%) in the autoTSCT arm did not receive any thalidomide in accordance with either the patients' wishes or physicians' decision, or because they did not survive until or progressed before the scheduled start of the treatment. Twenty-one percent of patients in the alloTSCT group received thalidomide for at least 700 days and 55% received the drug for less than 700 days, compared to 24% and 59%, respectively, in the autoTSCT group. About 77% of the patients in both groups who were administered thalidomide received an initial daily dose of 100 mg while the remaining patients started at a dose of 50 mg/day. The maintenance dose for all patients except four in the alloTSCT group and one in the autoTSCT group was also 100 mg/day in accordance with the study protocol. Among those receiving any dose of thalidomide, 44% in the alloTSCT arm and 53% in the autoTSCT arm stopped the drug because of toxicity.

Across both treatment groups, patients receiving thalidomide had a longer mean PFS (69.0 months, compared to 60.8 months for all patients) and mean OS (91.0 months *vs.* 81.8 months for all patients). The results are, however, likely biased by the fact that relapse, progression or mortality occurring before the start of thalidomide administration

Table 2. Results after the second transplantation.

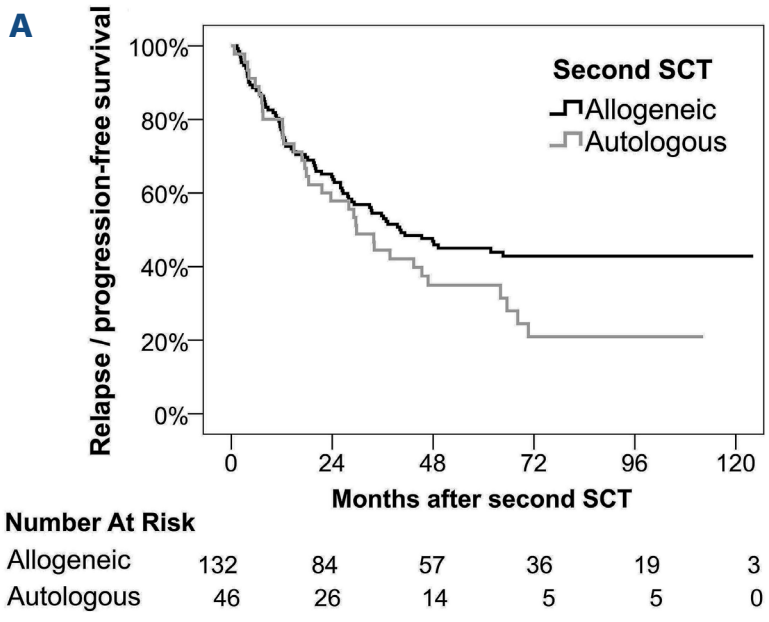
Responses and outcomes	Auto-Allo TSCT N=132	Auto-Auto TSCT N=46	*P*
Responses			
Time to engraftment in days, median (IQR)			
Leukocytes >1x10^9/L	17 (14-22)	12 (11-16)	<0.001
Platelets >50x10^9/L	18 (13-29)	11 (10-15)	<0.001
Best response after 2nd SCT, N (%)			0.029
Complete remission*	93 (71)	25 (54)	
Partial remission*	27 (21)	14 (30)	
Stable disease	1 (1)	1 (2)	
Progressive disease	5 (4)	4 (9)	
Missing data	6 (5)	2 (4)	
Disease status at end of the 48 month study, N (%)			0.019
Complete remission*	47 (36)	9 (20)	
Partial remission*	20 (15)	7 (15)	
Stable disease	1 (1)	0 (0)	
Progressive disease	54 (41)	28 (61)	
Missing data	10 (8)	2 (4)	
Outcomes, % (95% CI)			
Relapse-/progression-free survival			
At month 48	47 (38-55)	35 (21-49)	0.26
At end of follow-up	43 (34-51)	21 (9-36)	0.10
Relapse/progression*			
At month 48	40 (33-50)	63 (50-79)	0.01
End of follow-up	44 (36-54)	77 (64-92)	0.002
Disease-related mortality*			
At month 48	21 (15-30)	32 (21-50)	0.15
At end of follow-up	35 (26-47)	47 (32-69)	0.09
Non-relapse mortality (death in remission)			
At month 48	13 (8-20)	2 (0.3-15)	0.04
At end of follow-up	13 (8-20)	2 (0.3-15)	0.04
Overall survival			
At month 48	66 (57-73)	66 (50-78)	0.90
At end of follow-up	52 (41-62)	50 (32-67)	0.86

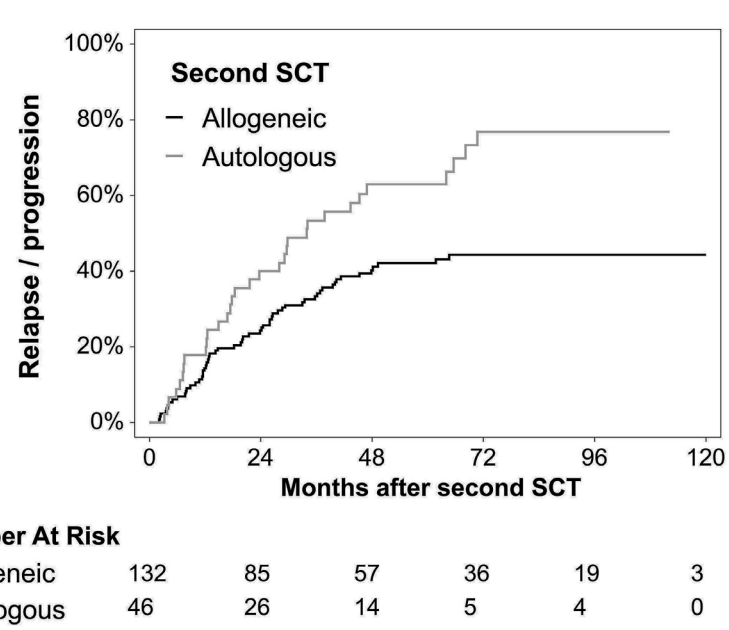
*Includes patients who died in remission. Auto-Allo: autologous-allogeneic; TSCT: tandem stem cell transplantation; Auto-Auto: autologous-autologous; IQR: interquartile range; SCT: stem cell transplantation; 95% CI: 95% confidence interval.

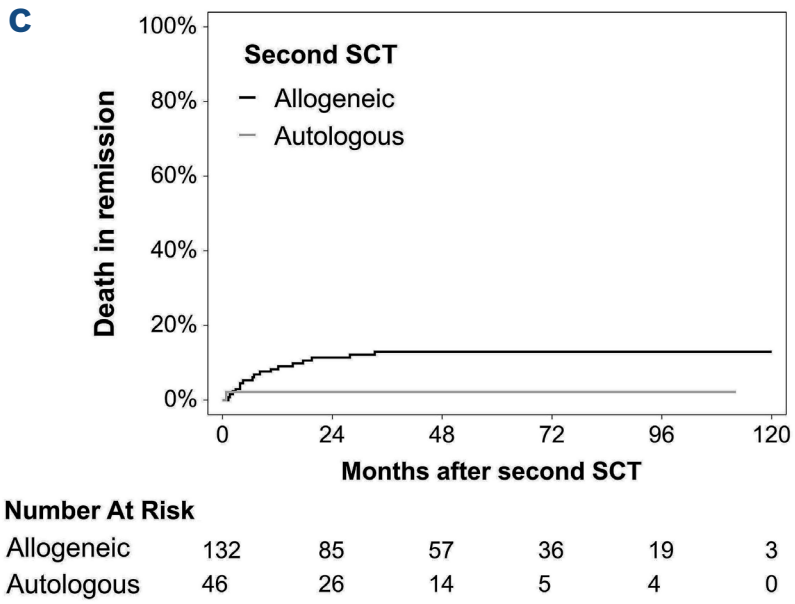
decreased PFS and OS in the full analysis set but not in the subset of patients who received thalidomide.

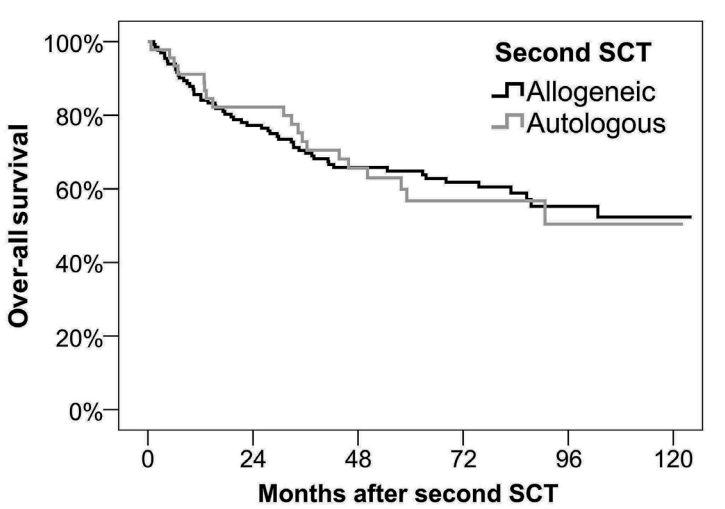
Donor lymphocyte infusion

Prophylactic DLI could be given according to a local investigator's discretion in an escalating fashion after stopping immunosuppressive medication and in the absence of signs of GvHD. Fifty-eight patients (50.4%) in the alloTSCT group received between one and six DLI. Of those 58 patients, 35 received between one and three DLI and 23 received









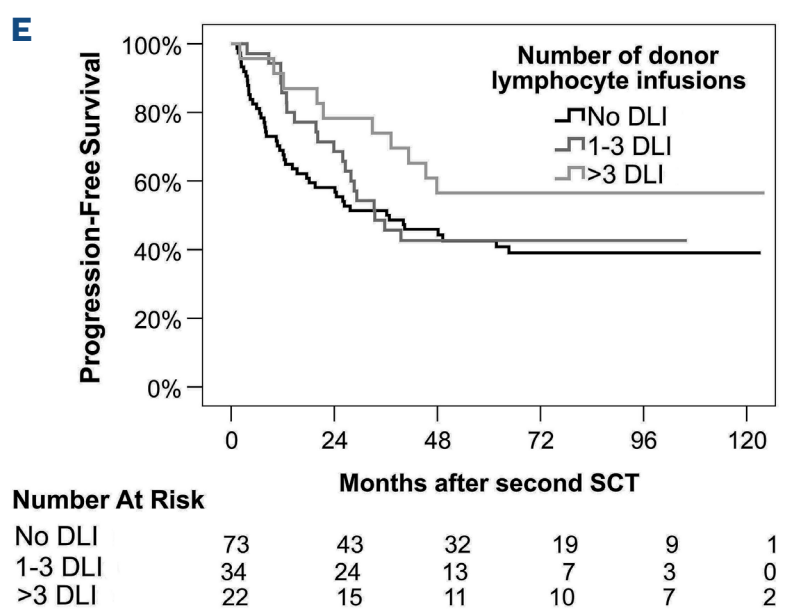


Figure 2. Outcomes after autologous-allogeneic *versus* autologous-autologous tandem stem cell transplantation followed by 2 years of thalidomide maintenance therapy in patients with newly diagnosed multiple myeloma. (A) Relapse/progression-free survival. (B) Cumulative incidence of relapse or progression. (C) Cumulative incidence of non-relapse mortality. (D) Overall survival. (E) Landmark analysis of progression-free survival according to whether the patients received no, one to three, or more than three prophylactic donor lymphocyte infusions. SCT: stem cell transplant; DLI: donor lymphocyte infusions.

more than three DLI. In a subgroup analysis of the alloTSCT group, the 6-year PFS rates of patients who did not receive DLI, patients who received one to three DLI, and patients who received more than three DLI were 39% (95% CI: 27-51%), 43% (95% CI: 27-59%), and 57% (95% CI: 37-77%), respectively (*P*=0.24) (Figure 2E)

Treatment effects in subsets of patients

The effects of alloTSCT or autoTSCT in subsets of patients defined by various covariates were compared in a series of Cox regression analyses whose main results are presented in Figure 3A (PFS) and 3B (OS). For both outcomes, none of the covariates investigated showed a significant interaction with the type of TSCT. For PFS, trends for autoTSCT were observed for disease status before the second SCT, while patients with active multiple myeloma, those aged 52 years or less and patients with high-risk cytogenetics had a more favorable outcome with alloTSCT.

Covariates of relapse/progression-free and overall survival

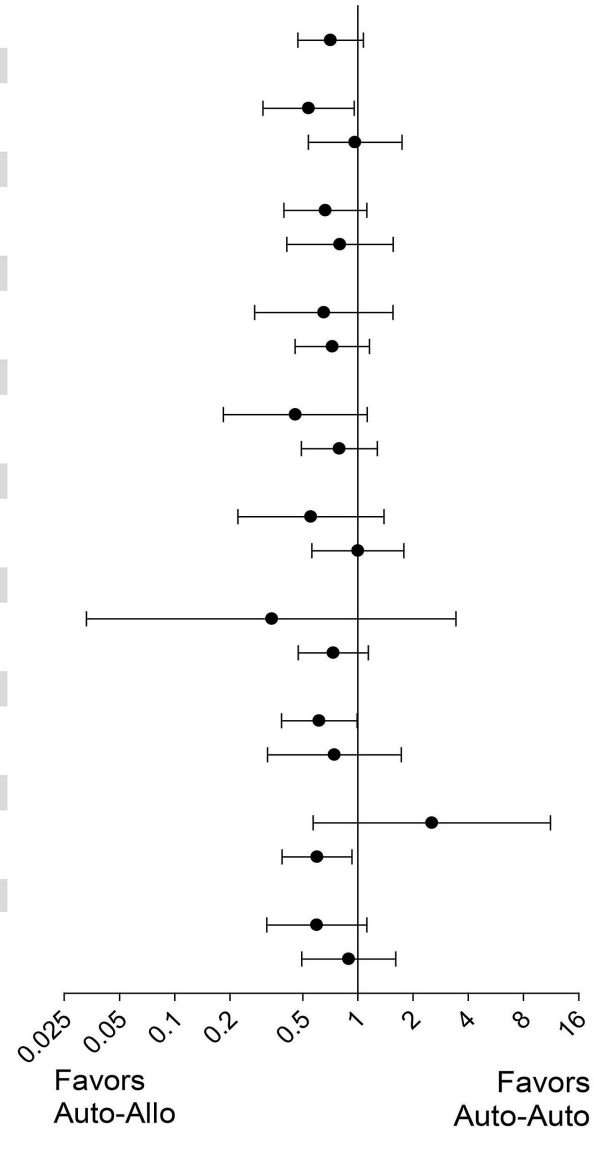
Figure 4 presents the main results for the final step of the multivariate Cox regression analyses for PFS and OS. Accounting for all covariates in the final models, an allogeneic graft as the second SCT improved PFS by 38% and OS by 15% (point estimates) even though the associated coefficients were not statistically significant. For PFS, complete remission after induction treatment was a significant positive prognostic factor while high-risk cytogenetics and delayed start of thalidomide treatment (or none at all) were associated with poor outcome. The latter two covariates were also prognostic factors for poor OS whereas complete remission before the second SCT was associated with improved OS. No difference in OS was noted between recipients of grafts from HLA-identical siblings or matched unrelated donors (*P*=0.6)

Engraftment, remission, and disease status after the second transplant

The median period to leukocyte as well as platelet engraftment was significantly shorter after autoTSCT (Table 2). No graft failure was observed. For best response after the second SCT as well as for disease status at the end of the 48-month clinical trial period, the proportions of patients in complete remission were greater after alloTSCT. Across all categories of response, treatment group differences were statistically significant favoring alloTSCT, as also shown in Table 2. During the post-trial follow-up

A

Subgroup	Auto-Allo	Auto-Auto	Hazard Ratio [95% CI]	*P*
All patients	132	46	0.71 [0.47; 1.07]	-
Age				
≤52 years	71	22	0.54 [0.30; 0.95]	0.16
>52 years	61	24	0.96 [0.54; 1.74]	
Sex				
Male	74	27	0.66 [0.39; 1.12]	0.70
Female	58	19	0.80 [0.41; 1.56]	
Myeloma classification				
Light chain	31	9	0.65 [0.27; 1.55]	0.79
Other	101	37	0.72 [0.45; 1.16]	
Salmon & Durie stage				
I - II	24	11	0.46 [0.18; 1.12]	0.34
III	107	34	0.79 [0.49; 1.28]	
Cytogenetic risk				
High (17p / t4;14)	24	8	0.55 [0.22; 1.39]	0.21
Low	71	25	1.00 [0.56; 1.78]	
Best response to induction				
Complete remission	13	3	0.34 [0.03; 3.42]	0.44
Other	107	39	0.73 [0.47; 1.14]	
Thalidomide administered				
Yes	100	38	0.61 [0.38; 0.99]	0.75
No	32	8	0.74 [0.32; 1.72]	
Status before 2nd SCT				
Complete remission	24	8	2.53 [0.57; 11.23]	0.07
Other	99	38	0.60 [0.39; 0.93]	
ECOG grade before 2nd SCT				
Grade 0	65	19	0.60 [0.32; 1.12]	0.34
Grade >0	51	22	0.89 [0.49; 1.61]	



Continued on following page.

B

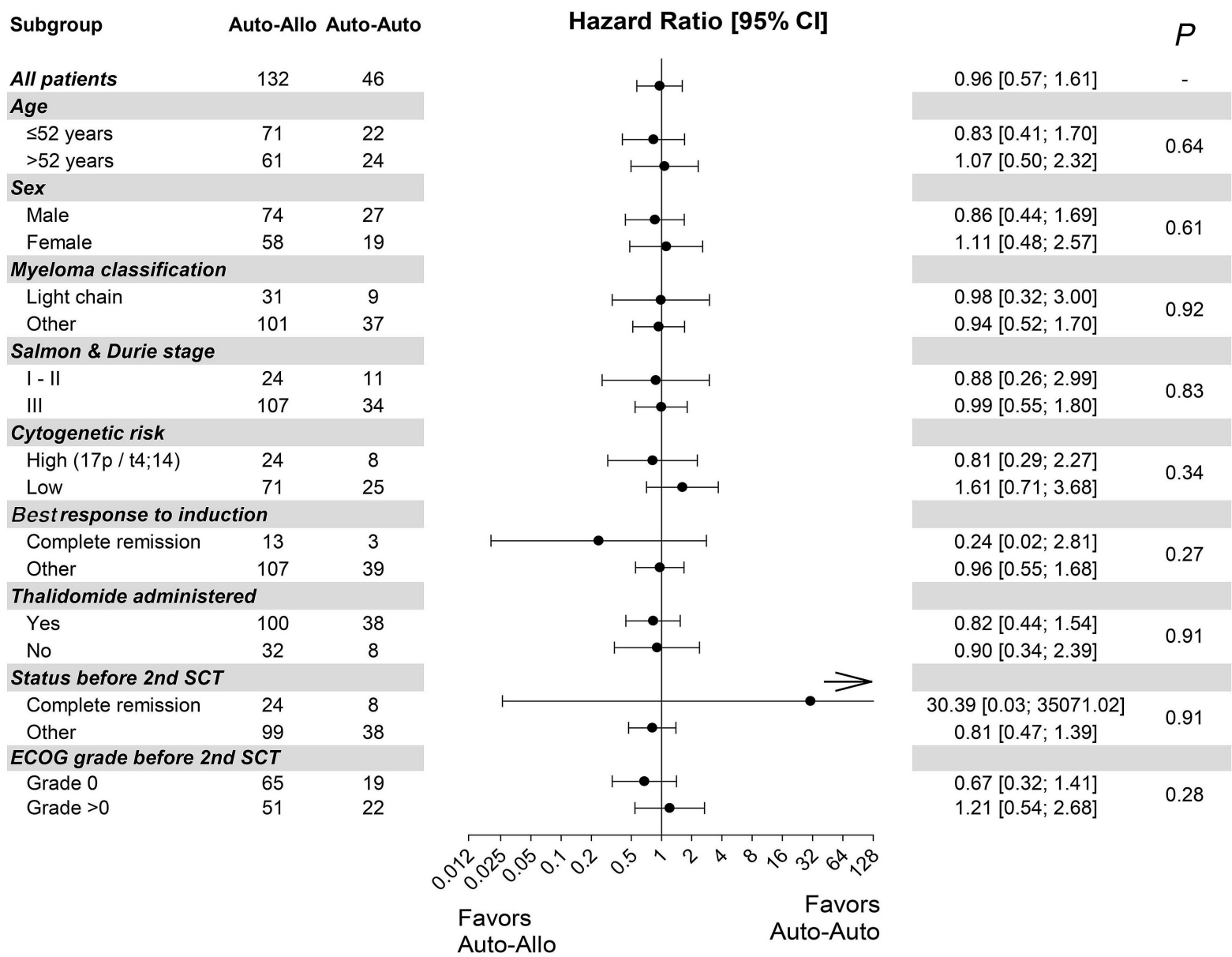


Figure 3. Subgroup survival hazard ratios for patients with multiple myeloma who underwent autologous-allogeneic or autologous-autologous tandem stem cell transplantation. *P* values for treatment by covariate interactions are shown. (A) Relapse/progression-free survival. (B) Overall survival. Auto-Allo: autologous-allogeneic tandem stem cell transplantation; Auto-Auto: autologous-autologous stem cell transplantation; SCT: stem cell transplantation; ECOG: Eastern Cooperative Oncology Group.

period, the proportion of progression-free patients at 8 years was about twice as high in the alloTSCT group as in the autoTSCT group.

Discussion

Allogeneic SCT can induce molecular remission in about 50% of cases, as determined by highly sensitive patient-specific allele-specific oligonucleotide primers.[17-19] This can result in long-term freedom from disease and eventually in cure.[20] However, due to high therapy-related mortality, myeloablative conditioning allogeneic SCT has not become standard care of treatment, not even in younger patients or patients with high-risk features.[20] The separation of a graft-*versus*-myeloma effect and high-dose chemotherapy-related tumor killing by combining autologous SCT followed by reduced-intensity allografting has raised interest in investigating allogeneic SCT in myeloma patients, with the hope of similar efficacy of myeloablative conditioning but less therapy-related toxicity and mortality.[4-6,8] Meanwhile results of prospective studies comparing tandem autologous-allogeneic approaches with single or tandem autologous SCT have been published,[7,9-14,21] but the findings have been contradictory.

Despite lower non-relapse mortality after reduced-intensity conditioning than after myeloablative conditioning, in all studies non-relapse mortality was higher after allogeneic SCT, but due to a lower relapse incidence in two studies a significant benefit regarding PFS and OS was reported.[9,12,13] A long-term follow-up of individual patients' data from four prospective trials has shown a significant benefit for PFS and OS in patients who underwent allogeneic SCT.[15] Importantly, due to the higher early mortality after allogeneic SCT and the lower relapse rate, long-term follow-up is needed to see differences, and in most studies the Kaplan-Meier curves cross at about 3 years.

In none of the mentioned studies was maintenance therapy included, although this has become the standard of care after autologous SCT.[22-24]

In the present study we aimed to show that alloTSCT, including transplants from matched unrelated donors, and tha-

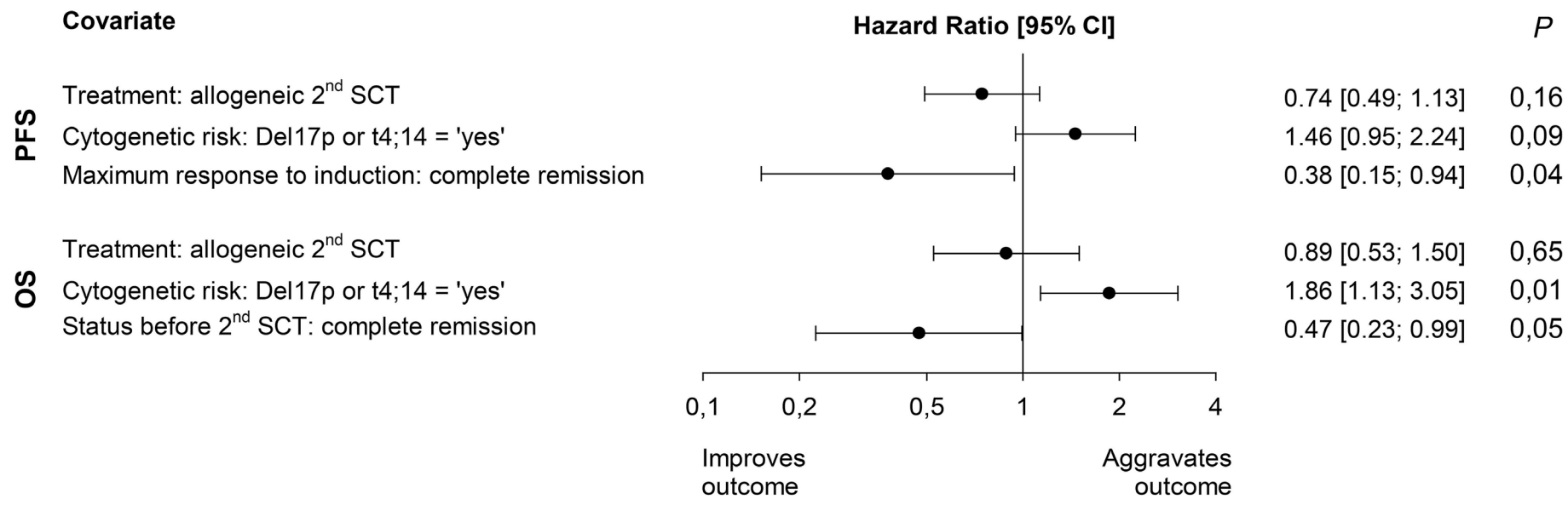


Figure 4. Covariates of relapse/progression-free and overall survival – predictors in the final step of multivariate Cox regression models. 95% CI: 95% confidence interval; SCT: stem cell transplantation; PFS: progression-free survival; OS: overall survival.

lidomide maintenance therapy as well as DLI would result in an improved PFS in comparison to tandem autologous transplantation followed by thalidomide maintenance. The well-documented graft-*versus*-myeloma effect delivered by DLI[1,2] and the capacity to enhance remission status after allograft[25] by combining DLI with immunomodulatory drugs[26,27] were the rationale for this post-transplant therapy after allografting, further encouraged by the likewise well-documented effect of immunomodulatory drugs after autografting.[28] Overall, the incidence of acute GvHD was 38% and only 6% experienced grade 3 acute GvHD. Notably the risk of GvHD was not obviously higher after DLI and thalidomide and the best PFS was seen in patients who received more than three DLI. Similarly to other studies, premature discontinuation of thalidomide due to toxicity was noted in 44% of the patients after allografting and in 53% after autologous transplantation. However, those patients who received thalidomide, regardless of the duration of the treatment, had a longer PFS compared to those not given thalidomide, but this might be biased by the fact that some patients progressed, relapsed or died before the scheduled start of thalidomide – these cases were necessarily counted as 'failures' in the non-thalidomide subset.

Overall, the study failed to demonstrate its hypothesized primary endpoint which was a 20% improved PFS at 4 years by alloTSCT. At 4 years, the difference in PFS was only 12%. However, after the long-term follow-up at 8 years, the difference was 22% and no further relapses occurred after 5 years in the alloTSCT arm. The observed 22% difference in PFS after 8 years did not reach statistical significance because of a lower number of patients who received a second autograft as planned and the overall rate of relapse after autoTSCT was lower than anticipated. In the study proposal we expected about 60% of the patients to receive allografts and 40% autografts, but in fact 74% of the participants received an allograft and only 26% received an autograft due to greater availability of matched unrelated donors, which reduced the statistical power substantially. The non-relapse mortality of 13% after alloTSCT is in line with that in other studies including unrelated donors but it is still too high to be able to recommend alloTSCT for all patients regardless of the lower incidence of relapse. A major factor for improved outcome was complete remission after induction chemotherapy, whereas detection of del17p or t4;14 by fluorescence *in situ* hybridization was predictive of a worse outcome. Even if no statistical significance for alloTSCT was seen in patients with high-risk cytogenetics and aged less than 52 years, in a similar and recently published, prospective trial, also including matched unrelated donors, a benefit was reported for patients harboring del17p who received alloTSCT. In our study the number of patients was too low to draw a meaningful conclusion on whether patients with high-risk cytogenetics will benefit more from allogeneic SCT.[14] While maintenance therapy after autologous SCT is standard treatment, more studies are needed to investigate post-transplant maintenance therapies after allografting in myeloma. Given that all the patients in our study were scheduled to receive thalidomide, the impact of this maintenance therapy on PFS or OS cannot be determined.

What is the current role of allogeneic SCT in myeloma – if any? There has been rapid development of novel agents, especially antibodies and more recently chimeric antigen receptor-T cells, which induce high rates of minimal residual disease-negative complete remissions with less toxicity and mortality compared to allografting. A recently published report of real-world evidence from the European Society of Blood and Marrow Transplantation documented decreased use of allogeneic SCT as upfront treatment in myeloma in more recent years, but an increasing use as salvage therapy after failure of an autograft. This analysis also showed that if allogeneic SCT is performed after multiple lines of pretreatment, long-term survival is unlikely.[29]

Unfortunately, clinical studies including allogeneic SCT are very rare, but according to the current data, which suggest long-term benefits in some patients, the scientific community should not abandon allogeneic transplants, and a prospective comparison between allogeneic SCT and approved triple therapies in patients with relapsed multiple myeloma is ongoing in Germany, supported by health authorities in that country.

In summary, alloTSCT, as compared to autoTSCT, reduced the rate of recurrence or progression of multiple myeloma by 23% at 4 years and by 33% at 8 years. During the same period, alloTSCT was also associated with an approximately one-third reduction of disease-related mortality, from 30% to 21%. However, the advantage in PFS after alloTSCT did not reach statistical significance.

Disclosures

NK has received research grants and honoraria (for lectures and advisory board participation) from Neovii and Novartis; honoraria (for lectures and advisory board participation) from Sanofi, Amgen, and Gilead/Kite; research grants and honoraria (for advisory board participation) from Jazz; research grants and honoraria from Celgene/BMS and Riemser; and honoraria (for lectures) from AOP Pharma. GW has received consultancy fees and honoraria for lectures, presentations, and manuscript writing from Gilead Sciences, Novartis, Takeda, and Clinigen; and has received travel/meeting attendance support from Medac. UH has received honoraria for talks and advisory board participation, financial support for congress participation and financial sponsorship of an amyloidosis registry from Janssen; honoraria for talks and advisory board participation, and financial support for congress participation from Pfizer and Prothena; and honoraria for talks from Alnylam and Akcea. AB has received grants or contracts and honoraria for lectures, presentations and manuscript writing from Incyte; and has received consultancy fees, and honoraria for lectures, presentations, and manuscript writing from AOP Health, Novartis, BMS, and Gilead. NG and LM have received travel/meeting attendance support from Neovi. MK has received travel/meeting attendance support from Janssen; and honoraria from Kite/Gilead for advisory board participation. MB has received consultancy fees and honoraria for lectures, presentations, and manuscript writing from Jazz Pharmaceuticals; and travel/meeting attendance support from Gilead. CS has received consultancy fees and honoraria for lectures, presentations, and manuscript writing from Novartis, Jazz, and Neovii; consultancy fees and honoraria for lectures, presentations, manuscript writing, and advisory board participation from Pfizer; and travel/meeting attendance support from Abbvie. HCR has received consultancy/lecture fees from AbbVie, Roche, Janssen-Cilag, Novartis, Vertex, and Merck; has received consultancy/lecture fees, and research funding from AstraZeneca; has received research funding from Gilead; and is a co-founder of CDL Therapeutics GmbH. GK has received consultancy fees, honoraria for lectures and advisory board participation, and research funding from BMS/Celgene. HS has received payment for presentations from Abbvie, Amgen, BMS/Celgene, Chugai, GSK, Janssen, Oncopeptides, Pfizer, Roche, Sanofi, Sebia, Stemline, TAD, and Takeda; and has received travel/meeting attendance support from Amgen, BMS/Celgene, Janssen, and Sanofi. AN has received honoraria for presentations from Medupdate. AV has received grants from and has contracts with UKE. SS declared that research support and honoraria for lectures/presentations, and advisory board participation were given to his institution by Janssen, Prothena, Neuroimmune, Sanofi, Takeda, and Pfizer; he has received honoraria for advisory board participation from Telix, and travel/meeting attendance support from Janssen, Prothena, Celgene, Jazz, and Binding Site. MS, AB, AG, DW, WB, MK, EMW, TH, MK, MH, FA, LT, EK, and CW have no conflicts of interest to disclose.

Contributions

NK, CW, and SS conceived and designed the study. NK also wrote the manuscript. All the authors gave their final approval of the manuscript and are accountable for all aspects of the work.

Funding

The study was supported by a research grant from BMS (formerly Celgene and Pharmion, Germany).

Data-sharing statement

The data supporting the findings of this study are available upon request to the author for correspondence.

References

1. Aschan J, Lonnqvist B, Ringden O, Kumlien G, Gahrton G. Graft-versus-myeloma effect. Lancet. 1996;348(9023):346.
2. Tricot G, Vesole DH, Jagannath S, Hilton J, Munshi N, Barlogie B. Graft-versus-myeloma effect: proof of principle. Blood. 1996;87(3):1196-1198.
3. Gahrton G, Tura S, Ljungman P, et al. Allogeneic bone marrow transplantation in multiple myeloma. European Group for Bone Marrow Transplantation. N Engl J Med. 1991;325(18):1267-1273.
4. Kroger N, Schwerdtfeger R, Kiehl M, et al. Autologous stem cell transplantation followed by a dose-reduced allograft induces high complete remission rate in multiple myeloma. Blood. 2002;100(3):755-760.
5. Maloney DG, Molina AJ, Sahebi F, et al. Allografting with nonmyeloablative conditioning following cytoreductive autografts for the treatment of patients with multiple myeloma. Blood. 2003;102(9):3447-3454.
6. Crawley C, Iacobelli S, Bjorkstrand B, Apperley JF, Niederwieser D, Gahrton G. Reduced-intensity conditioning for myeloma:

lower nonrelapse mortality but higher relapse rates compared with myeloablative conditioning. Blood. 2007;109(8):3588-3594.
7. Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood. 2006;107(9):3474-3480.
8. Kroger N, Sayer HG, Schwerdtfeger R, et al. Unrelated stem cell transplantation in multiple myeloma after a reduced-intensity conditioning with pretransplantation antithymocyte globulin is highly effective with low transplantation-related mortality. Blood. 2002;100(12):3919-3924.
9. Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med. 2007;356(11):1110-1120.
10. Rosinol L, Perez-Simon JA, Sureda A, et al. A prospective PETHEMA study of tandem autologous transplantation versus autograft followed by reduced-intensity conditioning allogeneic transplantation in newly diagnosed multiple myeloma. Blood. 2008;112(9):3591-3593.
11. Krishnan A, Pasquini MC, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol. 2011;12(13):1195-1203.
12. Bjorkstrand B, Iacobelli S, Hegenbart U, et al. Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. J Clin Oncol. 2011;29(22):3016-3022.
13. Gahrton G, Iacobelli S, Bjorkstrand B, et al. Autologous/reduced-intensity allogeneic stem cell transplantation vs autologous transplantation in multiple myeloma: long-term results of the EBMT-NMAM2000 study. Blood. 2013;121(25):5055-5063.
14. Knop S, Engelhardt M, Liebisch P, et al. Allogeneic transplantation in multiple myeloma: long-term follow-up and cytogenetic subgroup analysis. Leukemia. 2019;33(11):2710-2719.
15. Costa LJ, Iacobelli S, Pasquini MC, et al. Long-term survival of 1338 MM patients treated with tandem autologous vs. autologous-allogeneic transplantation. Bone Marrow Transplant. 2020;55(9):1810-1816.
16. Greenwood M. A report of the natural duration of cancer. H. M. Stationery Office, London, UK. 1926.
17. Corradini P, Voena C, Tarella C, et al. Molecular and clinical remissions in multiple myeloma: role of autologous and allogeneic transplantation of hematopoietic cells. J Clin Oncol. 1999;17(1):208-215.
18. Martinelli G, Terragna C, Zamagni E, et al. Molecular remission after allogeneic or autologous transplantation of hematopoietic stem cells for multiple myeloma. J Clin Oncol. 2000;18(11):2273-2281.
19. Ladetto M, Ferrero S, Drandi D, et al. Prospective molecular monitoring of minimal residual disease after non-myeloablative allografting in newly diagnosed multiple myeloma. Leukemia. 2016;30(5):1211-1214.
20. Kroger N, Einsele H, Wolff D, et al. Myeloablative intensified conditioning regimen with in vivo T-cell depletion (ATG) followed by allografting in patients with advanced multiple myeloma. A phase I/II study of the German Study-group Multiple Myeloma (DSMM). Bone Marrow Transplant. 2003;31(11):973-979.
21. Giralt S, Costa LJ, Maloney D, et al. Tandem autologous-autologous versus autologous-allogeneic hematopoietic stem cell transplant for patients with multiple myeloma: long-term follow-up results from the Blood and Marrow Transplant Clinical Trials Network 0102 trial. Biol Blood Marrow Transplant. 2020;26(4):798-804.
22. Gay F, Jackson G, Rosinol L, et al. Maintenance treatment and survival in patients with myeloma: a systematic review and network meta-analysis. JAMA Oncol. 2018;4(10):1389-1397.
23. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1782-1791.
24. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012;366(19):1770-1781.
25. Kroger N, Kruger W, Renges H, et al. Donor lymphocyte infusion enhances remission status in patients with persistent disease after allografting for multiple myeloma. Br J Haematol. 2001;112(2):421-423.
26. Kroger N, Shimoni A, Zagrivnaja M, et al. Low-dose thalidomide and donor lymphocyte infusion as adoptive immunotherapy after allogeneic stem cell transplantation in patients with multiple myeloma. Blood. 2004;104(10):3361-3363.
27. Wolschke C, Stubig T, Hegenbart U, et al. Postallograft lenalidomide induces strong NK cell-mediated antimyeloma activity and risk for T cell-mediated GvHD: results from a phase I/II dose-finding study. Exp Hematol. 2013;41(2):134-142.e3.
28. Spencer A, Prince HM, Roberts AW, et al. Consolidation therapy with low-dose thalidomide and prednisolone prolongs the survival of multiple myeloma patients undergoing a single autologous stem-cell transplantation procedure. J Clin Oncol. 2009;27(11):1788-1793.
29. Sobh M, Michallet M, Gahrton G, et al. Allogeneic hematopoietic cell transplantation for multiple myeloma in Europe: trends and outcomes over 25 years. A study by the EBMT Chronic Malignancies Working Party. Leukemia. 2016;30(10):2047-2054.