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Incidence and Outcome of Late Relapse after Allogeneic Stem Cell Transplantation for Myelofibrosis

Isik Kaygusuz Atagunduz[1,2], Maximilian Christopeit[1], Francis Ayuk[1], Gaby Zeck[1], Christine Wolschke[1], Nicolaus Kröger[1,*]

[1] *University Medical Center Hamburg-Eppendorf, Hamburg, Germany*
[2] *Marmara University Pendik Training and Research Hospital, Istanbul, Turkey*

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In this cross-sectional study, we retrospectively evaluated the files of 227 patients with myelofibrosis who underwent transplantation between 1994 and 2015 for relapse later than 5 years after allogeneic stem cell transplantation (SCT). A total of 94 patients who were alive and in remission at 5 years were identified with follow-up of at least 5 years (median, 9.15 years) after SCT. Thirteen patients (14%) experienced late molecular (n = 6) or hematologic (n = 7) relapse at a median of 7.1 years while 81 patients did not experience relapse. Relapse patients received either donor lymphocyte infusion (DLI) (n = 7) and/or second transplantation (n = 4). Of those, 72.7% achieved again full donor cell chimerism and molecular remission, and after a median follow-up of 45 months, the 3-year overall survival rates for patients with or without relapse were 90.9% (95% confidence interval [CI], 77% to 100%) and 98.8% (95% CI, 96% to 100%), respectively (P = .13). We conclude that late relapse occurs in about 14% of the patients and the majority can be successfully salvaged with DLI and/or second allograft. All patients with molecular relapse are alive and support the long-time molecular monitoring in myelofibrosis patients after allogeneic SCT.

Myelofibrosis (MF) is a chronic hematologic malignancy characterized by clonal ineffective hematopoiesis, a reactive reticulin deposition and fibrosis in bone marrow, circulating $CD34^+$ progenitor cells, extramedullary hematopoiesis, and leukemic progression [1]. MF has a heterogeneous clinical phenotype, and median survival of the disease varies from 16 months to 15 years according to the Dynamic International Prognostic Scoring System (DIPSS-PLUS) [2].

Although novel agents such as JAK-2 inhibitors may improve the symptoms and quality of life, the currently only curative therapy in MF is allogeneic hematopoietic stem cell transplantation (HSCT) with a cure rate of 30% to 65%. In prospective and retrospective studies, allogeneic HSCT for patients with primary myelofibrosis (PMF) was associated with 30% to 61% overall survival (OS) and 24% to 43% nonrelapse mortality at 3 to 5 years [2-7].

Despite advances in transplantation procedures and significant prolongation in survival, relapse following allogeneic HSCT (allo-HSCT) for MF remains a significant issue. Recent studies still report a high relapse rate of 10% to 43% after HSCT, and this is currently the common cause of death [2]. Most relapse occurs during the early period of allogeneic stem cell transplantation (allo-SCT). In an European Society of Blood and Marrow Transplantation (EBMT) retrospective study, the median time to relapse was 7.1 months (range, 1.4 to 111) [8]. Long-term follow-up of the EBMT prospective study of reduced-intensity conditioned (RIC) allo-HSCT reported relapse rates of 22% and 29% at 3 and 5 years, respectively [4]. In a recent EBMT retrospective study, long-term outcome after allogeneic hematopoietic cell transplantation for myelofibrosis was evaluated, and in patients who survived for 2 years, relapse incidence and nonrelapse mortality 10 years after transplant were estimated at 21% (1% to 24%) and 15% (12% to 18%) [2]. A graft-versus-myelofibrosis effect is confirmed by the observation of longer survival rates in patients with chronic graft-versus-host disease (GVHD) and the achievement of remission with donor lymphocyte infusion (DLI) after HSCT [9-11]. These data are based on case reports and studies with small patient numbers. DLI and second HSCT are the preferred treatment options in relapsed patients in general [8,12]. However, there are few studies and limited information about late relapse in myelofibrosis as well as the effect of DLI or second allograft on survival. In our study, we aimed to analyze patients who were alive and disease free at 5 years post-transplant and examined the eventual outcomes in this patient population.

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*Correspondence and reprint requests: Nicolaus Kröger, MD, Department of Stem Cell Transplantation, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, D-20246 Hamburg, Germany.
E-mail address: nkroeger@uke.uni-hamburg.de (N. Kröger).

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METHODS

Patient Selection

In this cross-sectional study, we retrospectively evaluated incidence and outcome of late relapse in 227 patients with myelofibrosis who received allogeneic stem cell transplantation between December 1994 and December 2015 at the University Medical Center Hamburg-Eppendorf, Germany. Late relapse was defined as relapse after 5 years post-HSCT. Of the 227 patients, 94 were identified as being alive and disease free at 5 years after transplant. Study patients were then grouped into "late relapse" and "no relapse" for the purposes of comparison. Relapse was defined as disease recurrence according to International Working Group-Myeloproliferative Neoplasms Research and Treatment and European LeukemiaNet Consensus Criteria for Treatment Response in Myelofibrosis [13]. Highly sensitive PCRs of JAK2V617F and CALR mutations were used as markers of minimal residual disease (MRD) in relapsed patients after treatment as previously described [11].

Statistical Analysis

Statistical analysis of demographic variables was expressed descriptively. Data distribution was assessed using the Kruskal-Wallis test. We used the Student *t* test to compare continuous data with the normal distribution. Skewed data comparisons were performed using the Wilcoxon rank-sum test. We used chi-square or Fisher exact tests for the comparison of categorical variables, where appropriate. The survival data were estimated using the Kaplan-Meier method and log-rank test, respectively. OS was calculated from the date of documented relapse until death or last observation alive.

RESULTS

A total of 94 patients with MF were identified with a minimum of at least 5 years after allografting with a median follow-up of 9.15 years (range, 5.12 to 19.61). Median age at transplantation of these 94 patients was 56 years (range, 29 to 75). Sixty-two patients (65.9%) had PMF, 18 (19.1%) had post-polycythemia vera, and 14 (14.9%) had post-essential thrombocythemia myelofibrosis.

Overall, 13 patients (14%) (male/female = 7/6) experienced late molecular (n = 6) or hematologic (n = 7) relapses at a median of 7.1 years (range, 5.02 to 10.20) (group A). Eighty-one patients (male/female = 48/33) with a median follow-up of 8.76 years (range, 5.02 to 19.61) did not experience relapse (group B). Patient characteristics are shown in Table 1. Median age at transplant was similar in both groups (group A versus group B: 55 [36 to 73] versus 57 [29 to 75]).

Although numerically smaller, the median time from diagnosis to transplantation, 20 months (3 to 100) in group A and 13 months (1 to 353) in group B, had no effect on relapses. Other clinical and laboratory parameters analyzed were not associated with a significantly higher risk of late relapses such as cytogenetic and molecular abnormalities, including JAK2, CALR, and MPL mutations; type of HSCT; DIPSS score, type of conditioning regimens (myeloablative conditioning versus RIC); anti-thymocyte globulin dosing; achievement of molecular complete remission after SCT; development of acute or chronic GVHD; pretransplant percentage of blasts in peripheral blood; or degree of bone marrow fibrosis at the time of transplantation.

Seven patients had hematologic relapses (HRs). Three patients with HRs received 1 to 5 doses of DLI and additionally a second SCT for nonresponsiveness or progression. These patients achieved full donor cell chimerism and MRD negativity. One patient with PMF received 3 doses of DLI for HR. This patient had full donor cell chimerism and MRD negativity. One post-essential thrombocythemia myelofibrosis patient with HR received a second SCT and had full chimerism and MRD negativity. One patient (patient 2, Table 2), who achieved complete molecular remission with 2 doses of DLI, died of secondary malignancy after 2 years of therapy. A second patient (patient 6, Table 2) died of progressive disease, before starting salvage therapy.

Table 1
Demographic and Clinical Data of Myelofibrosis Patients >5 Years after Stem Cell Transplantation with (Group A) or without (Group B) Relapse

Variable	Group A (n = 13)	Group B (n = 81)
Age at HSCT, median (range), yr	55 (36-73)	57 (29-75)
Sex		
Male	7	48
Female	6	33
Disease at time of transplant		
Primary myelofibrosis	6 (46.2)	54 (66.6)
Secondary myelofibrosis	7 (53.8)	21 (25.9)
Post-PV myelofibrosis	4	10
Post-ET myelofibrosis	3	11
Transformation into acute leukemia	—	5
MDS	—	1
Cytogenetic abnormalities		
Yes	3	26
No	5	39
Unknown	5	16
Molecular abnormalities		
Yes	13	77
No	0	3
Unknown	—	4
Grade of bone marrow fibrosis at HSCT		
Grades 1-2	6	20
Grade 3	7	53
Unknown	—	8
Blasts in PB at HSCT	12 (1.7)	76 (2.4)
DIPSS at HSCT		
Low to intermediate 1	7	18
Intermediate 2 to high	5	56
Unknown	1	7
Time to transplant, median (range), mo	20 (3-100)	13 (1-353)
Conditioning regimen		
RIC	11	72
MAC	2	9
Donor type		
MRD	4	16
MUD	9	65
ATG dose		
60 mg/kg	7	46
<60 mg/kg	3	32
Unknown	3	3
Maximum response after transplant (mCR)		
Yes	5 (38.4)	22 (27.8)
No	8 (61.5)	57 (72.2)
Acute GVHD		
Yes	10 (77)	52 (64)
No	3 (23)	29 (36)
Chronic GVHD		
Yes	11 (85)	66 (81.4)
No	2 (15.3)	15 (18.6)

Values are presented as numbers or numbers (%) unless otherwise indicated.
PV indicates polycythemia vera; ET, essential thrombocythemia; MDS, Myelodysplastic Syndrome; PB, peripheral blood; RIC, reduced-intensity conditioning; MAC, myeloablative conditioning; MRD, minimal residual disease; MUD, matched unrelated donor; ATG, anti-thymocyte globulin; mCR, molecular complete remission.

Six patients had only molecular relapses (MRs). One with post-polycythemia vera myelofibrosis with active chronic GVHD received interferon therapy. This patient is still on interferon therapy with stable mix chimerism and improvement in MRD. The remaining patients were transfused with 1 to 7 doses of DLI. Three achieved full chimerism and a negative MRD. Two patients did not respond to 3 and 5 doses of DLI and are still on follow-up.

In the whole relapsed patient group, 7 patients received DLI only, 3 patients received DLI in conjunction with second transplantation, and 1 patient had only a second HSCT. Eight patients (72.7%) achieved full donor cell chimerism and molecular remission with these treatments. No treatment-related mortality after DLI therapy was observed. Three patients with MR had a previous HSCT. All 3 relapsed within 2 years after their first HSCT, and 2 did not respond to DLI (Table 2).

Nonrelapsing patients after the fifth year of SCT had significantly longer 3-year event-free survival when compared to relapsed patients for a median follow-up of 45 months (range, 1 to 166): 98.8% (95% confidence interval [CI], 96% to 100%) versus 73.4% (95% CI, 50% to 100%; P= .011) (Figure 1A).

At the time of analysis and a median follow-up of 7 years 11 months (range, 5.3 to 12.6) in the relapsed patient group, 11 of 13 patients were alive. Three-year OS rates for patients with or without relapse were 90.9% (95% CI, 77% to 100%) and 98.8% (95% CI, 96% to 100%), respectively (P= .126) (Figure 1B).

DISCUSSION

Post-transplant relapse is a relevant clinical problem in MF and is the main cause of death in the long-term follow-up. Relapse occurs most frequently in the first 2 years in these patients, but late relapses have been described [2]. According to the risk profile of patients with MF, 10% to 30% relapse is observed within 3 years after transplantation [12]. When the 3-year relapse rates were evaluated according to the intensity of the preparation regimen, relapse was reported as 10% to 18% in patients who underwent transplantation with the myeloablative conditioning regimen and 29% to 43% with RIC [14]. In studies with long-term follow-up, cumulative relapse rates at 3 and 5 years were reported as 22% and 29%, respectively [15].

With its long median follow-up of 9.15 years (range, 5.12 to 19.61), our study contributes to the current literature since the long-term outcome and late relapse in MF are currently scarcely addressed. In our study of patients with MF, with a long-term follow-up after the fifth post-transplant year, the late-relapse rate was 13.8%. To the best of our knowledge, our study has the longest post-transplant median follow-up of patients with MF in the current literature that allows the investigation of late relapse (>5 years) in this patient cohort. A similar previous study, although with a shorter follow-up, conducted by the Chronic Malignancies Working Party of EBMT, reported additional long-term follow-up data based on a retrospective analysis of a cohort of 1371 patients with MF. In this cohort, the relapse rate was 18.3% for a median follow-up of 52.5 months (range, 4 to 116) [8]. The estimated 10-year relapse rate, using the data derived from a landmark MF patient group of EBMT consisting of 1055 patients who were alive and disease free at the second post-transplant year, and with an additional median follow-up of 49.7 months, was 21% (range, 17% to 24%) [2]. In another study with a similar median follow-up of 78 months (range, 49 to 101), the fifth year cumulative relapse rate at 5 years was reported as 26% [16].

It is worth to emphasize that the estimated 10-year relapse rate based on the cumulative relapse rate within the first 5 years of follow-up differs substantially from the 13.8% long-term relapse rate observed in our study and underlines the

Table 2
Patient Characteristics with Late Relapse (n = 13)

Patient No.	Age, yr/Sex	Diagnosis	Type of SCT	Regimen	Response	Time to Relapse, mo	Type of Relapse	Relapse Therapy	Response	2. SCT	Duration of Follow-up after Relapse, mo	Last Follow-up Current Status
1	53/M	Post-ET MF	MRD	MAC: Bu/Flu/ATG30	CR	111.8	HR	1 × DLI + HU	No	Yes	92.1	Alive, full chimerism, MRD(−)
2	56/M	PMF	MMUD	RIC: Bu/Flu/ATG60	hCR	72.6	HR	2 × DLI + ruxolitinib	CR	No	37.1	Dead (secondary malignancy) 01.07.2015
3	36/F	PMF	MMUD	RIC: Bu/Flu/ATG60	hCR	120.7	MR	5 × DLI	No	No	32.8	Alive, stable mixed chimerism, improvement in MRD
4	51/M	Post-PV MF	MUD	RIC: Treo/Flu/Thym6 (2. SCT)	CR	86.5	MR	1 × DLI	mCR	No	58.5	Alive, full chimerism, MRD(−)
5	43/F	Post-PV MF	MRD	RIC: Bu/Flu/ATG30	CR	82.9	HR	5 × DLI + ruxolitinib	NR	Yes	73.2	Alive, full chimerism, MRD(−)
6	63/M	PMF	MUD	RIC: Bu/Flu/ATG60	CR	81.1	HR	–	NR	No	19.8	Dead (progressive disease) 15.01.2016
7	56/M	Post-PV MF	MMUD	MAC: Treo/Flu/Thym4 (2. SCT)	CR	111.3	MR	IFN	PR	No	35.0	Alive, stable chimerism, improvement in MRD
8	68/F	PMF	MUD	RIC: Bu/Flu/ATG60	mCR	70.6	HR	2 × DLI	Progression		59.7	Alive, full chimerism, MRD(−)
9	59/M	Post-PV MF	MUD	RIC: Treo/Flu/Thym6 (2. SCT)	mCR	116.6	MR	2 × DLI	Stable	No	3.8	Alive, stable chimerism, improvement in MRD
10	73/F	PMF	MUD	RIC: FLAMSA/Bu/Flu/ATG60	hCR	94.5	HR	3 × DLI	mCR	No	5.4	Alive, full chimerism, MRD(−)
11	47/M	Post-ET MF	MUD	RIC: FLAMSA/Bu/Flu/ATG60	mCR	58.1	HR	–	–	Yes	40.2	Alive, full chimerism, MRD(−)
12	54/F	PMF	MRD	RIC: FLAMSA/Bu/Flu/ATG30	mCR	60.9	MR	7 × DLI	mCR	No	27.1	Alive, full chimerism, MRD(−)
13	55/F	Post-ET MF	MRD	RIC: Bu/Flu/ATG60	mCR	101.3	MR	2 × DLI	mCR	No	29.2	Alive, full chimerism, MRD(−)

Bu, Busulfan; Flu, Fludarabine; HU, Hydroxyurea; MMUD, mismatched unrelated donor; hCR, hematologic complete remission; CR, complete remission; Treo, Treosulfan; Thym, Thymoglobulin; NR, not reported; FLAMSA, Fludarabine/Amsacrine.

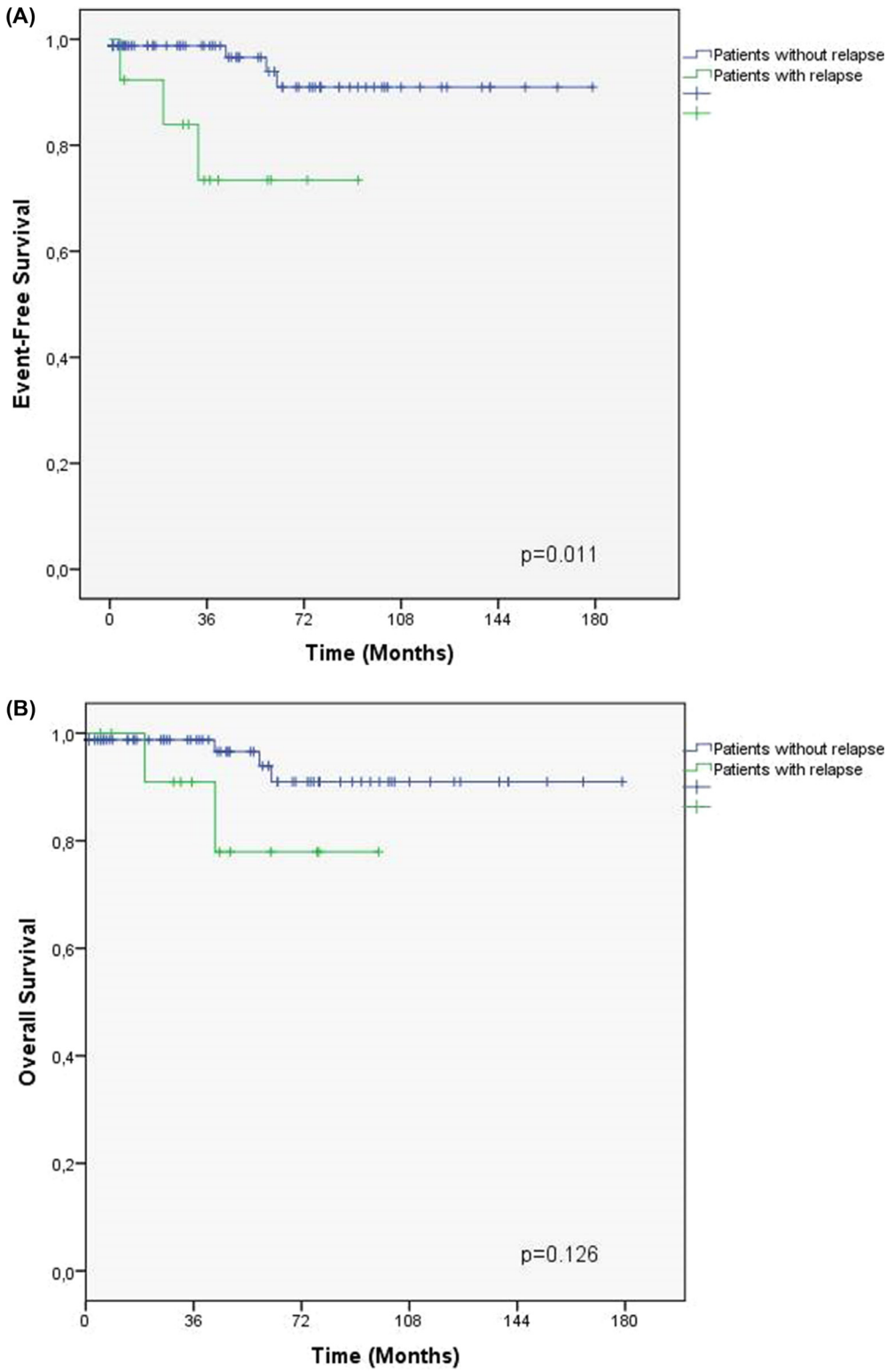

Figure 1. Landmark analyses of overall survival (A) and progression-free survival (B) in 13 patients starting from 5 years post-transplant and at time of relapse.

necessity for real-life data. In fact, the late relapse rate decreased as the follow-up lengthened.

In our study, we found that 8 of 11 (72.7%) late-relapse patients who received DLI and/or second SCT achieved molecular complete remission and full donor chimerism. All patients with HR, but only 60% of patients with MR, achieved molecular complete remission and full donor chimerism. Reason for this higher response rate in HR patients may be that 4 of 6 HR patients received additional HSCT after insufficient response to DLI. Still, the achieved 60% full molecular remission in

patients with MR treated with DLI only should not be underestimated.

Prognostic factors affecting the risk of relapse after HSCT are not well understood. The results of studies addressing the factors associated with relapse risk are not always in accordance. A previous important study reported that the absence of GVHD, transplantation from another than an HLA-matched related donor, and the use of the RIC regimen were associated with increased relapse risk [2]. In another study, the development of chronic GVHD significantly decreased the risk of relapse [17]. Contradictorily, 2 retrospective studies showed that the intensity of the conditioning regimen did not affect the risk of relapse [18,19]. Other factors suggested to increase the risk of relapse are the longer time to transplant, absence of acute GVHD, transplantation from HLA-matched donors, and the persistence of JAK2V617F mutation positivity after transplantation [15,18,20]. A very recent study reported that transfusion dependency at day +100 together with an unfavorable molecular state is associated with shorter Relapse-free Survival [21].

We did not find any significant factors that increased the risk of late relapse. In our study, the high DIPSS score was not a risk factor for relapse, and most patients who did not relapse had higher DIPSS scores. A few studies evaluated the relationship between pretransplant DIPSS score and transplant course. In one of these studies, the relapse rate, similar to our study, was found to be lower in the DIPSS intermediate 2/high-risk group in comparison to the low-risk patients [5]. However, the remaining studies have shown that relapsing is less and OS is better in patients with a low DIPSS score before transplant [16,20,22]. However, this might be due to the fact that those high-risk patients had already experienced earlier relapse.

DLI and second SCT are the 2 main treatment options for patients with MF who relapse after transplantation [8,12]. Studies with small sample sizes and case reports suggest that DLI is safe and effective in the treatment of post-transplant relapses (especially molecular relapse) and residual disease [9-12,23,24]. Similarly, studies evaluating the second SCT in patients with MF who relapse after transplantation also consist of only case reports and studies involving a small number of patients [8,12,25].

In 27 patients with late relapse and 3 patients with graft rejection, our group has shown that DLI and a second HSCT are effective and safe in the treatment of myelofibrosis as a 2-step salvage approach. They reported that out of 26 patients treated with DLI, 39% achieved complete remission. Thirteen patients with DLI failure and 4 patients not suitable for DLI treatment achieved 60% complete remission and 80% Overall Responserate with second HSCT [12].

In addition to the above findings, another study addressing the JAK2-V617F-triggered preemptive and salvage DLI therapy in 17 patients with MF with relapse found that this treatment was more effective in patients with MRD recurrence than patients with full clinical relapse. Also, the rates of complete molecular remission for salvage DLI and preemptive DLI were 33.3% and 100%, respectively [11].

The number of studies investigating the postrelapse survival of patients with MF is limited. In our study focusing on late relapse after a median follow-up of 35 months (range, 3.8 to 92.1) of the relapsed patients, the 2-year Progression-free Survival and OS are very encouraging with 83.9% and 92.3%, respectively.

In conclusion, late relapse after 5 years occurs in about 14% of patients with MF after allogeneic stem cell transplantation. To detect possible late relapse, chimerism and minimal residual disease activity should be monitored even after the fifth year of HSCT based on our observation that the majority of all relapses can be successfully salvaged by DLI and/or second allogeneic SCT.

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