Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides and Sezary syndrome. An updated experience of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation

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Bone Marrow Transplantation (2021) 56:1391–1401
https://doi.org/10.1038/s41409-020-01197-3

ARTICLE

Allogeneic hematopoietic stem cell transplantation for advanced mycosis fungoides and Sézary syndrome. An updated experience of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation

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Received: 12 May 2020 / Revised: 5 October 2020 / Accepted: 9 December 2020 / Published online: 8 January 2021

Abstract

Background Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative treatment option in advanced-stage mycosis fungoides (MF) and Sézary syndrome (SS). This study presents an updated analysis of the initial experience of the Lymphoma Working Party of the European Society for Blood and Marrow Transplantation (EBMT) describing the outcomes after allo-HSCT for MF and SS, with special emphasis on the impact of the use of unrelated donors (URD).

Methods and patients Eligible for this study were patients with advanced-stage MF or SS who underwent a first allo-HSCT from matched HLA-identical related or URD between January/1997 and December/2011. Sixty patients have been previously reported.

Results 113 patients were included [77 MF (68%)]; 61 (54%) were in complete or partial remission, 86 (76%) received reduced-intensity protocols and 44 (39%) an URD allo-HSCT. With a median follow up for surviving patients of 73 months, allo-HSCT resulted in an estimated overall survival (OS) of 38% at 5 years, and a progression-free survival (PFS) of 26% at 5 years. Multivariate analysis demonstrated that advanced-phase disease (complete remission/partial remission >3, primary refractory or relapse/progression in patients that had received 3 or more lines of systemic treatment prior to transplant or the number of treatment lines was not known), a short interval between diagnosis and transplant (<18 months) were independent adverse prognostic factors for PFS; advanced-phase disease and the use of URDs were independent adverse prognostic factors for OS.

Conclusions This extended series supports that allo-HSCT is able to effectively rescue over one third of the population of patients with advanced-stage MF/SS. High relapse rate is still the major cause of failure and needs to be improved with better strategies before and after transplant. The negative impact of URD is a matter of concern and needs to be further elucidated in future studies.

Highlights

- Allogeneic transplantation is a potentially curative option for advanced-stage mycosis fungoides and Sézary syndrome.
- Advanced-phase disease constitutes the most important prognostic factor for the long term outcome of the patients.
- The negative impact of the use of unrelated donors needs to be further elucidated.

Introduction

Mycosis fungoides (MF) and Sézary syndrome (SS) are the commonest types of primary cutaneous T-cell lymphomas (pCTCL), with an annual incidence of 4 cases per million people [1, 2]. Early-stage MF has a favorable prognosis and

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responds well to topical regimens, while advanced-stage (IIB-IV) or transformed forms of MF/SS are incurable despite combined systemic and topical therapies, and have a median survival of less than five years [3–5]. Thus, allo-HSCT has been explored as a potentially curative option in patients with advanced-stage MF/SS taking advantage of a clinically relevant graft-versus-lymphoma (GVL) effect [6–19].

The European Society for Blood and Marrow Transplantation (EBMT) has previously reported on the outcome of allo-HSCT for patients with advanced MF/SS [6, 8, 10]. Amongst several disease and transplant related factors influencing patient outcome, the use of unrelated donors (URD) emerged as the strongest independent factor negatively influencing both overall survival (OS) and progression-free survival (PFS). The main shortcoming of the original series was the limited number of cases ($n = 60$), of which only 15 had received an URD allo-HSCT. As URD have been increasingly used in recent years across all indications including MF/SS, we sought to extend our previous analysis (January/1997 – December/2007) to include patients with MF/SS transplanted between January/2008 and December/2011 in order to further analyze if this was the case in more recently allografted patients.

Patients and methods

Data source

EBMT is a voluntary organization comprising 583 transplant centers from 63 countries. EBMT membership requires submission of minimal essential data (MED-A form) from all consecutive transplant procedures to a central registry in which patients can be identified by underlying diagnosis and type of transplant. Informed consent for transplantation and data collection was obtained locally according to regulations applicable at the time of transplantation. Since January 2003, all transplant centers have been required to obtain written informed consent prior to data registration following the Helsinki Declaration 1975.

Patient eligibility

Eligible for this study were all patients with advanced-stage MF or SS (stages IIB and higher) who underwent a first allo-HSCT from a matched HLA-identical related donor or an URD between January/1997 and December/2011 including 60 patients previously reported [8, 10]. Baseline information and transplantation characteristics of eligible patients were downloaded from the EBMT registry and centers were contacted to provide additional information about characteristics of the patients and outcome. The diagnosis was based on local clinical and histologic review.

Definitions

Patients were staged according to the International Society for Cutaneous Lymphoma and the cutaneous lymphoma task force of the EORTC (ISCL/EORTC) Staging System [20, 21]. For the purpose of this analysis, disease status at the time of transplant was divided into early-phase disease [complete response (CR)1, CR2, partial response (PR)1, PR2 or relapse/progression in patients that had received less than 3 systemic therapies], and advanced-phase disease [CR/PR > 3, primary refractory or relapse/progression in patients that had received 3 or more lines of systemic treatment prior to transplant or the number of treatment lines was not known]. Performance status (PS) was defined according to the Karnofsky score criteria at time of transplant. Conditioning regimens were defined as myeloablative (MAC) or reduced intensity (RIC) according to previously established definitions [22].

Statistical analysis

Primary endpoints studied were PFS and OS. PFS was defined as the time from allo-HSCT to relapse or progressive disease or death from any cause, and OS was defined as the time from allo-HSCT to death from any cause. Acute and chronic graft-versus-host disease (GVHD), non-relapse mortality (NRM) and disease relapse or progression were also analyzed. NRM was defined as the time from allo-HSCT to death in the absence of prior relapse or progression. Disease relapse/progression was calculated as the time from allo-HSCT to relapse or progression. NRM and relapse/progression events were considered as competing risks. Grades II-IV acute GVHD (aGVHD) were defined according to standard criteria [23]. Chronic GVHD was determined according to the evaluations by treating physician. Chronic GVHD (cGVHD) was also analyzed in a competing risks setting with death and relapse as competing events.

The database was closed for analysis as of July 2017. Demographics were compared between groups using the X^2 test or Fisher's exact test for categorical variables and Mann-Whitney U test for continuous variables. The probabilities of OS and PFS were estimated using the Kaplan-Meier product limit method and compared using the log-rank test. Estimates of NRM, incidence of relapse/progression and cGVHD were calculated using cumulative incidence curves and compared with Gray's test, to accommodate competing risks. Survival and cumulative incidence results were calculated as estimates and 95% confidence intervals (95%CI). Multivariate analyses were performed with Cox regression models, variables were selected using a backward-selection procedure. The variables included in the multivariate analysis were: age at HSCT, histology (MF or SS), disease status at HSCT (early-phase vs advanced-phase), donor type,

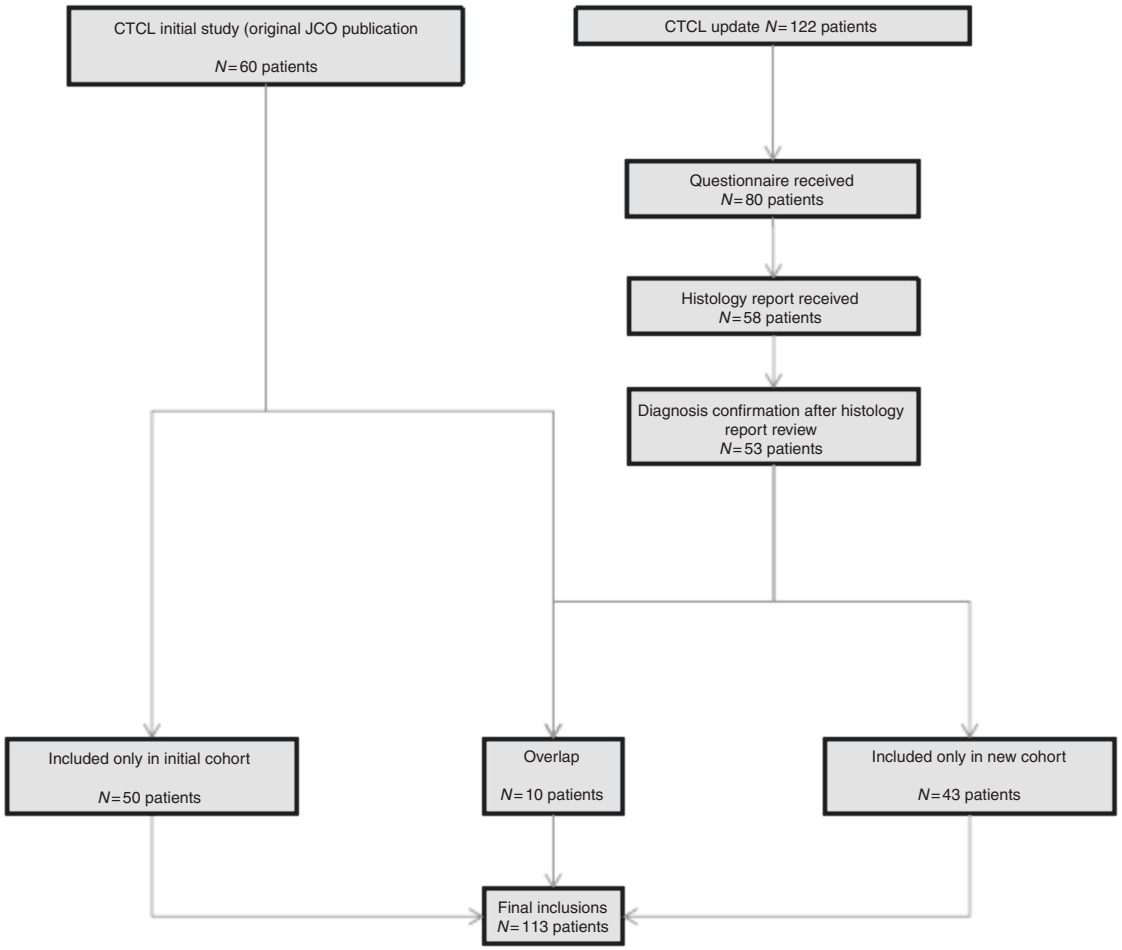

Fig. 1 Flowchart of the inclusion of patients in the study.

source of stem cells [bone marrow (BM) vs peripheral blood (PB)], conditioning (MAC vs RIC), PS at HSCT, time from diagnosis to HSCT (≤18 months vs >18 months), disease stage, T-cell depletion (TCD) and study cohort (initial vs recent). All tests were two-sided and p values <0.05 were considered as indicating significant associations. All analyses were performed using R version 3.1.1 with the R packages survival version 2.38, cmprsk version 2.2–7 and Hmisc version 3.16-0 (R Core Team. R: a language for statistical computing. 2014. R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

One hundred and thirteen patients met the eligibility criteria for this study. The flowchart of the final population of patients included in the present study is depicted in Fig. 1. Baseline patient demographics, disease and transplant characteristics are shown in Table 1. Of note, there were some significant clinical differences between the first group of patients analyzed ($n = 60$, January/1997 to December/2007) and the more recent one ($n = 53$, January/2008 to December 2011): patients of the more recent group were older than patients in the earlier group, but, on the contrary, they were more frequently allografted in earlier phases of the disease. URD were more frequently used and TBI-containing protocols less so, in this more recent population of patients (Table 1).

We also analyzed the differences in patient characteristics between URD allo-HSCT ($n = 43$) and HLA identical sibling ($n = 70$) (Table 2). URD were more frequently used in the more recent period of time (2008–2011) and TCD was also more frequently used.

Acute and chronic GVHD

The cumulative incidence of grades II-IV aGVHD was 47% (95% CI 37%–56%) at day 100, and cGVHD 35% (95%CI 25%–44%) at 1 year and 48% (95%CI 37%–57%) at 5 years.

Table 1 Demography and clinical characteristics of the whole series.

Clinical characteristics	Global series ($n = 113$)	Initial CTCL cohort ($n = 60$) (January/1997– December/2007)	Recent CTCL cohort ($n = 53$) (January/2008–December/2011)	p value
Gender				
Male/Female	71 (63%)/42 (37%)	37 (62%)/23 (38%)	34 (64%)/19 (36%)	NS
Histology				
Mycosis fungoides/Sezary syndrome	77 (68%)/36 (32%)	36 (60%)/24 (40%)	41 (77%)/12 (23%)	NS
EORTC-ISCL Stage at diagnosis				
I–III	29 (26%)	12 (20%)	17 (32%)	NS
IV	56 (50%)	34 (57%)	22 (42%)	
Missing	28 (24%)	14 (23%)	14 (26%)	
N. of treatment lines before allo-HSCT [median (range)]	3 (0–10)	3 (0–10)	3 (0–4)	NS
Interval diagnosis –allo-HSCT				
≤18 months/>18 months	30 (26%)/83 (74%)	18 (30%)/42 (70%)	12 (23%)/41 (77%)	NS
Disease status at allo-HSCT[a]				
Early-phase / Advanced-phase	49 (43%)/64 (57%)	20 (33%)/40 (67%)	29 (55%)/24 (45%)	0.04
Age at allo-HSCT, in years [median (range)]	48 (21–72)	46 (22–67)	53 (21–72)	<0.001
Performance status at allo-HSCT				
Karnosfky ≥80%/<80%	97 (87%)/15 (13%)	50 (85%)/9 (15%)	47 (89%)/6 (11%)	NS
Type of donor				
HLA identical sibling/URD	70 (62%)/43 (38%)	45 (75%)/15 (25%)	24 (45%)/29 (55%)	0.001
Stem cell source				
BM/PB	16 (14%)/95 (86%)	10 (17%)/50 (83%)	6 (12%)/45 (88%)	NS
Conditioning regimen				
RIC/MAC	85 (75%)/28 (25%)	43 (72%)/17 (28%)	42 (79%)/11 (21%)	NS
TBI-based conditioning regimen	45 (40%)	30 (50%)	15 (28%)	0.03
T-cell depletion (in-vivo or ex-vivo)	55 (50%)	24 (42%)	31 (60%)	NS
Follow up for the surviving patients, in months [median (range)(IQR)]	73 (range: 16–150) (IQR: 39–97)	95 (range 32–150) (IQR 76–114)	39 (range 16–72) (IQR 32–52)	<0.0001

Allo-HSCT allogeneic hematopoietic stem cell transplantation, *EORTC-ISCL* European Organization for Research and Treatment of Cancer – International Society for Cutaneous Lymphomas, *BM* bone marrow, *PB* peripheral blood, *TBI* Total body irradiation, *ATG* anti-thymoglobulin, *NS* not significant.

[a]Early-phase: complete response (CR)1, CR2, partial response (PR)1, PR2 or relapse/progression with <3 lines of therapy; advanced-phase: CR/PR > 3, primary refractory or relapse/progression with ≥3 lines of therapy or number of lines unknown.

Multivariate analysis showed that a more recent year of transplantation (2008–2011) was the only independent adverse prognostic factor for the development of aGVHD [hazard ratio (HR) 3.02 (95% confidence interval (CI) 1.65–5.53), $p < 0.001$]. Being diagnosed with MF as well as EORTC stage IV disease at the time of diagnosis were associated with a significant increase in the risk of cGVHD [HR 0.36 (95%CI 0.17–0.77), $p = 0.0085$ and HR 2.34 (95%CI 1.06–5.15), $p = 0.035$, respectively]. When introduced as a two time dependents covariate in a cause-specific Cox model, neither aGVHD nor cGVHD had an impact on relapse.

Non-relapse mortality

Thirty-one (27%) patients died without disease relapse or progression. NRM was 26% (95%CI, 18%–34%) at 1 year and 28% (95% CI, 20%–37%) at 3 years and thereafter (Fig. 2a). Causes of death were the following: 17 patients died of infections (5 viral, 4 Bacterial, 1 fungal and 7 not specified), 4 of multiorgan failure, 7 of GVHD and 3 of pulmonary toxicity. Advanced-phase of the disease, poor performance status at the time of transplant and being allografted in more recent years were independent adverse prognostic factors for NRM in the multivariate analysis. TCD significantly decreased NRM (Table 3).

Relapse

Fifty patients (44%) relapsed/progressed after transplant; the median time to relapse was 3.5 months (interquartile range 2.5–6.3). Disease relapse was the main cause of treatment failure, with a cumulative incidence of 40% (95% CI 31–49%) at 1 year and 45% (95%CI 35–54%) at 5 years (Fig. 2a), and a mortality rate after relapse of 70% (35/50). Multivariate analysis showed that advanced-phase disease at the time of transplant significantly increased the incidence of relapse. On the contrary, a time interval between diagnosis and transplant longer than 18 months as well as the use of TBI in the conditioning regimen were associated with a lower incidence of relapse (Table 3).

Table 2 Demography and clinical characteristics of HLA identical sibling (ID SIB) and Matched Unrelated donors (MUD).

Clinical characteristics	HLA-id sib	URD	*p* value
Gender			
Male/Female	44 (63%)/26 (37%)	27 (63%)/16 (37%)	NS
Histology			
Mycosis fungoides/Sézary syndrome	47 (67%)/23 (33%)	30 (70%)/13 (30%)	NS
Year of SCT			
1997–2003	16 (23%)	3 (7%)	0.0028
2004–2007	28 (40%)	10 (23%)	
2008–2011	26 (37%)	30 (70%)	
EORTC-ISCL Stage at diagnosis			
I–III	17 (24%)	12 (28%)	
IV	38 (54%)	18 (42%)	NS
Missing	15 (22%)	13 (30%)	
N. of treatment lines before allo-HSCT [median (range)]	3 (0–10)	3 (0–8)	NS
Interval diagnosis –allo-HSCT			
≤18 months/>18 months	20 (29%)/50 (71%)	10 (23%)/33 (77%)	NS
Disease status at allo-HSCT[a]			
Early-phase/Advanced-phase	27 (39%)/43 (61%)	22 (51%)/21 (49%)	NS
Age at allo-HSCT, in years [median (range)]	47 (22–72)	53 (21–70)	NS
Performance status at allo-HSCT			
Karnosfky ≥80%/<80%	61 (88%)/8 (12%)	36 (84%)/7 (16%)	NS
Stem cell source			
BM/PB	9 (13%)/61 (87%)	7 (17%)/34 (83%)	NS
Conditioning regimen			
RIC / MAC	53 (76%)/17 (24%)	32 (74%)/11 (26%)	NS
TBI-based conditioning regimen	31 (44%)	14 (33%)	NS
T-cell depletion (in-vivo or ex-vivo)	22 (32%)	33 (81%)	<0.0001
Main cause of death			
Relapse / Progression	14 (40%)	15 (44%)	
HSCT related	21 (60%)	18 (53%)	NS
Other	0	1 (3%)	

HLA-id sib HLA identical sibling, *URD* Unrelated donor, *Allo-HSCT* allogeneic hematopoietic stem cell transplantation, *EORTC-ISCL* European Organization for Research and Treatment of Cancer – International Society for Cutaneous Lymphomas, *BM* bone marrow, *PB* peripheral blood, *RIC* Reduced-intensity conditioning regimen, *MAC* Myeloablative protocols, *TBI* Total body irradiation, *HSCT* stem cell transplant, *NS* not significant.

[a]Early-phase: complete response (CR)1, CR2, partial response (PR)1, PR2 or relapse/progression with <3 lines of therapy; advanced-phase: CR/PR >3, primary refractory or relapse/progression with ≥3 lines of therapy or number of lines unknown.

Progression-free survival

Allo-HSCT for MF/SS resulted in an estimated PFS of 34% (95%CI 26%–44%) and 26% (95%CI 19%–36%) at 1 and 5 years, respectively (Fig. 2b). Multivariate analysis demonstrated that advanced-phase disease (Fig. 3a) was an independent adverse prognostic factor for PFS, while a time interval longer than 18 months between diagnosis and transplant significantly improved PFS (Table 3). Of note, the use of URD was associated with a lower PFS but did not retain predictive value as an independent prognostic factor in the multivariate analysis (Fig. 4a).

Overall survival

Forty-three (38%) of 113 patients were alive at last follow-up, with a median observation time for surviving patients of 73 months (interquartile range: 39–97). Estimated OS was 56% (95%CI 48%–66%) at 1 year, and 38% (95%CI 30%–49%) at 5 years (Fig. 2c). Advanced-phase disease at the time of allo-HSCT (Fig. 3b) and the use of URD (Fig. 4b) were independent adverse prognostic factors for OS in the multivariate analysis (Table 3).

Discussion

This updated report on the results of allo-HSCT in patients with advanced-stage MF/SS, despite the inherent caveats associated to all registry-based retrospective analyses, represents one of the largest studies in this field and has the longest follow-up for surviving patients published to date. Our data contributes to the knowledge of what the scientific community can expect from this treatment strategy in this group of patients in terms of long-term efficacy and toxicity.

In our series, allo-HSCT provides an estimated PFS of around 25% after 5 years in a very heavily pretreated population of MF/SS patients with an OS of 38% at the same time point. Lechowitz et al., on behalf of the Center for the International Blood and Marrow Transplant (CIBMTR), reported a 5-year PFS of 17% and an OS of 32% in 129 patients with relapsed/refractory MF/SS, albeit with a median follow up of only 30 (4–206) months [9]. The French Society of Bone Marrow Transplantation together with the French Study Group of Cutaneous Lymphomas recently reported a PFS of 31% and OS of 57% at 2 years in a small group of 37 heavily pretreated patients [17]. Results might seem more favorable in a group of 19 heavily pretreated patients from a single institution reported in 2010 by Duvic in whom total skin electron beam was included as part of the allotransplant strategy; 2-year PFS and OS were of 59% and 73%, respectively [14]. A recent update in 2015 from the same institution with 47 patients including the previous series showed a 4-year PFS and OS of 26% and 51%, respectively [15]. More recently, the Japanese Society for Hematopoietic Cell Transplantation has published a series of 48 patients, with a 3-year OS and PFS of 30% and 19%, respectively [19], being disease status before HSCT and PS the two variables impacting in survival.

Understandably, advanced-phase at the time of transplant was by far the most important negative predictive factor for

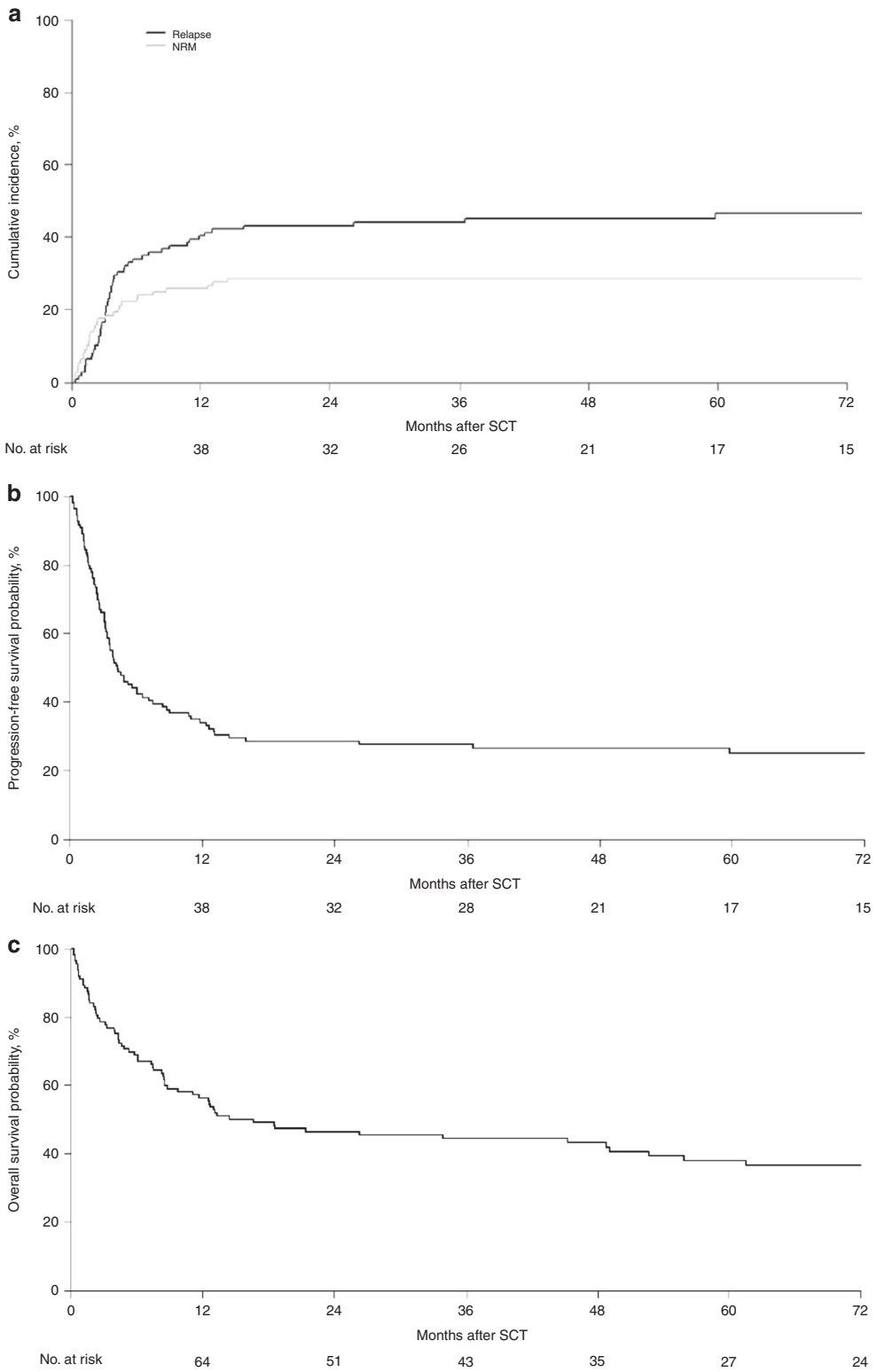

Fig. 2 Long term outcomes of the global series. a Non-relapse mortality and disease relapse. **b** Progression-free survival. **c** Overall survival.

both PFS and OS in all the above-mentioned analyses. The rarity of these disorders, the existence of an extensive number of topical and non-topical available therapies and the somewhat complicated referring pathway between dermatologists and clinical hematologists are some of the reasons that account for the late referral of these patients to

Table 3 Multivariate analysis.

	Non-relapse mortality HR (95%CI), *p* value	Incidence of relapse HR (95%CI), *p* value	Progression-free survival HR (95% CI), *p* value	Overall survival HR (95%CI), *p* value
Karnofsky PS (poor *vs* good)	2.84 (1.16–6.93), $p = 0.0221$	NS	NS	NS
Type of donor (URD *vs* HLA identical sibling)	NS	NS	NS	2.23 (1.3–3.85), $p = 0.0038$
Disease status at HSCT (advanced *vs* early)	2.38 (1.07–5.31), $p = 0.0345$	3.38 (1.61–7.08), $p = 0.0013$	3.23 (1.81–5.76), $p < 0.001$	2.42 (1.39–4.2), $p = 0.0017$
T-Cell depletion (yes vs no)	0.39 (0.16–0.95), $p = 0.0385$	1.82 (0.96–3.47), $p = 0.0682$	NS	NS
Time from dx to allo-HSCT (>18 mo vs ≤18 mo)	NS	0.27 (0.12–0.6), $p = 0.0012$	0.38 (0.2–0.71), $p = 0.0024$	NS
Use of TBI in the conditioning regimen (yes vs no)	NS	0.48 (0.24–0.96), $p = 0.0389$	NS	NS
Allo-HSCT Period 2008–2011 vs 1997–2003	2.58 (1.12–5.95), $p = 0.0262$		1.63 (1–2.65), $p = 0.05$	NS
EORTC missing vs stage I–III	NS	2.24 (1.03–4.87), $p = 0.0428$	NS	NS
stage IV vs stage I–III	NS	NS	NS	NS
Myeloablative conditioning (yes vs no)	NS	NS	NS	NS

HR hazard ratio, *95% CI* 95% confidence interval, *PS* performance status, *URD* unrelated donor, *HSCT* hematopoietic stem cell transplantation, *dx* diagnosis, *mo* months, *TBI* total body irradiation, *NS* not significant.

a transplantation program. Of note, the proportion of patients referred to HSCT with advanced-phase has decreased in the more recent cohort, which suggests an increased awareness of the role of HSCT in this population. The increasing use of URD in this setting might have contributed to transplanting patients in less advanced-phase, but this, in turn, has increased the complexity of the HSCT with more TCD in recent years. In spite of the higher experience in the use of URD allo-HSCT in these histologies, URD came out as an adverse prognostic factor for OS in this extended report; in light of these results, one may argue that haploidentical transplants using the post-cyclophosphamide platform as GVHD prophylaxis could eventually be a better option for those patients that do not have a matched sibling donor available. The use of haploidentical donors has significantly increased over the last few years and, in the absence of well-designed prospective clinical trials, long term outcomes are not different from those of URD and matched sibling transplants [24].

Investigators of the MD Anderson Cancer Center [16] indicated in their prospective single center analysis of allo-HSCT in both MF and SS patients, that SS patients had a better long term outcome than MF patients. This histological distinction did not impact in the long term outcome of our series; a similar pattern was also described by the retrospective analysis of the CIBMTR [9]. Differences in clinical characteristics of the series, CIBMTR and ours being a retrospective multicenter registry analysis and the one from the MD Anderson being a single center prospective one, could eventually account for these differences.

Disease relapse or progression represents by far the most frequent cause of treatment failure; 45% of the patients had relapsed/progressed at 5 years after allo-HSCT. A high relapse rate has also been seen in prior analyses; the risk of disease progression was 50% at 1 year and 61% at 5 years in the CIBMTR retrospective analysis [9], it was 56% at 2 years in the French study [17], and 50% in the series from the MD Anderson Cancer Center [14, 15]. Clinical factors that contribute to disease relapse are number of lines of therapy before the allo-HSCT, disease burden at the time of transplant and, the use of TCD [8, 10, 17, 19]. In the present series, advanced-phase disease at the time of transplant was associated with a higher relapse rate; TCD methods marginally increased the rate of relapse, too. Interestingly, TBI-containing protocols had a lower relapse rate after transplant; this finding is not easy to explain as the use of low dose TBI in the setting of RIC protocols is associated with a higher rate of relapse in other lymphoma histologies [25]. In this scenario, there is a clear need for new and more effective salvage strategies. Brentuximab vedotin has demonstrated superiority to either methotrexate or bexarotene as rescue strategy in patients with SS and primary cutaneous anaplastic large cell lymphoma as

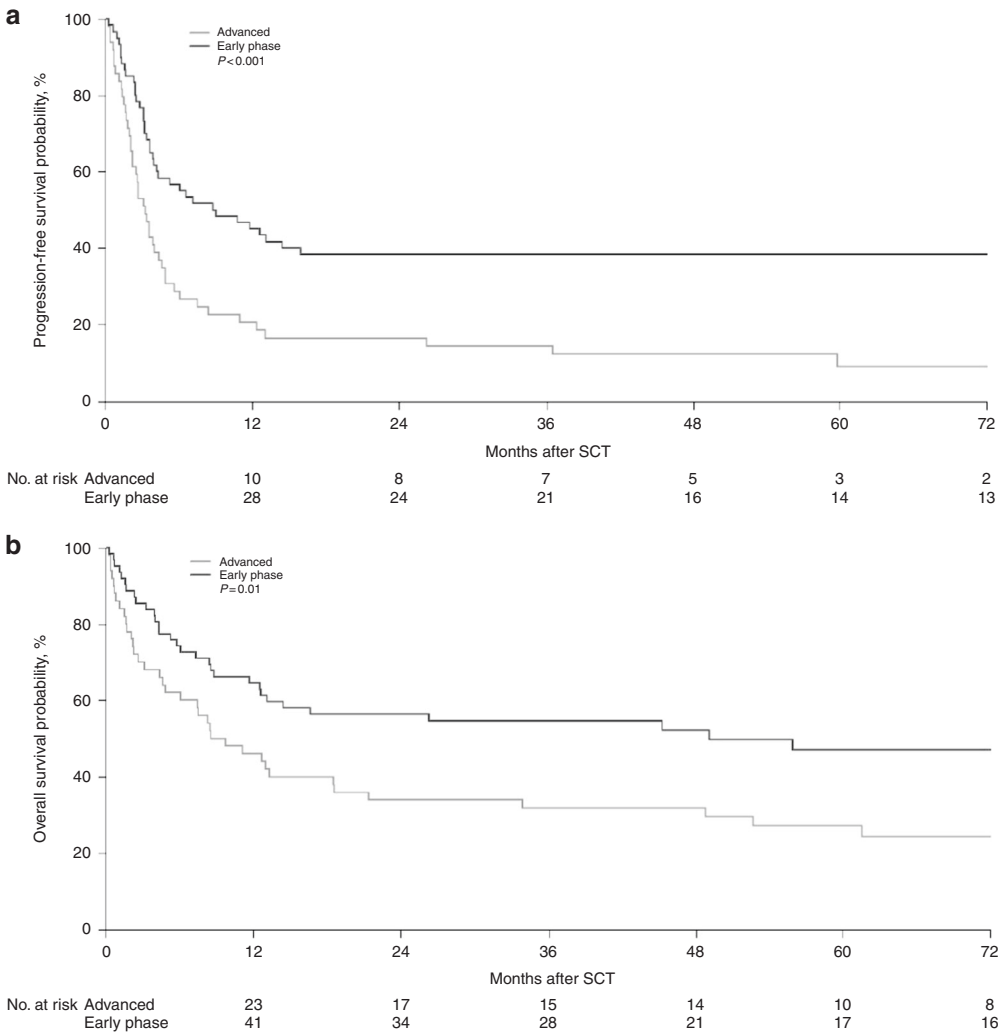

Fig. 3 Impact of the disease phase at the time of allo-HSCT in progression-free survival and overall survival. a Progression-free survival. **b** Overall survival.

indicated by the recently published ALCANZA trial [26]. Overall response rate lasting more than 4 months and PFS were significantly improved with the use of brentuximab single drug and these results have recently granted approval of this drug by the Food and Drug Administration. Mogamulizumab, a novel monoclonal antibody directed against C-C chemokine receptor 4, has also demonstrated an increase of PFS when compared to other strategies in these patients (median PFS 7.7 months with mogamulizumab vs 3.1 months with vorinostat) [27], with an ORR of 36.8% [28]. Check-point inhibitors have also demonstrated significant activity in patients with relapsed/refractory MF/SS with a 38% ORR [29]. All these new drugs are rarely curative and due to their mild toxicity profile they could eventually be used as bridge to allo-HSCT allowing patients to go into the transplantation procedure in better conditions both in terms of PS and disease control as shown in other settings [30–33]. The inclusion period in our analysis has not allowed us to evaluate this aspect as new drugs were not available outside prospective clinical trials.

This follow-up study of the EBMT experience has also allowed us to further analyze unique features of the EBMT transplantation activity in this disease and to highlight significant changes overtime. As mentioned previously, the complexity of the HSCT has increased, transplanting older patients and using more URD and TCD. This might explain the higher NRM in the most recent cohort. In addition, there might be other factors that cannot be captured by the EBMT registry, such as the specific type of therapies used prior to HSCT. We have, nevertheless, ruled out that the increasing number of centers performing allogeneic transplantation in MF/SS in recent years may have had a potential center effect on outcomes (data not shown).

Although registry-based analyses are associated with well-known caveats (the most important one being the difficulty in comparing outcomes after HCT with those in

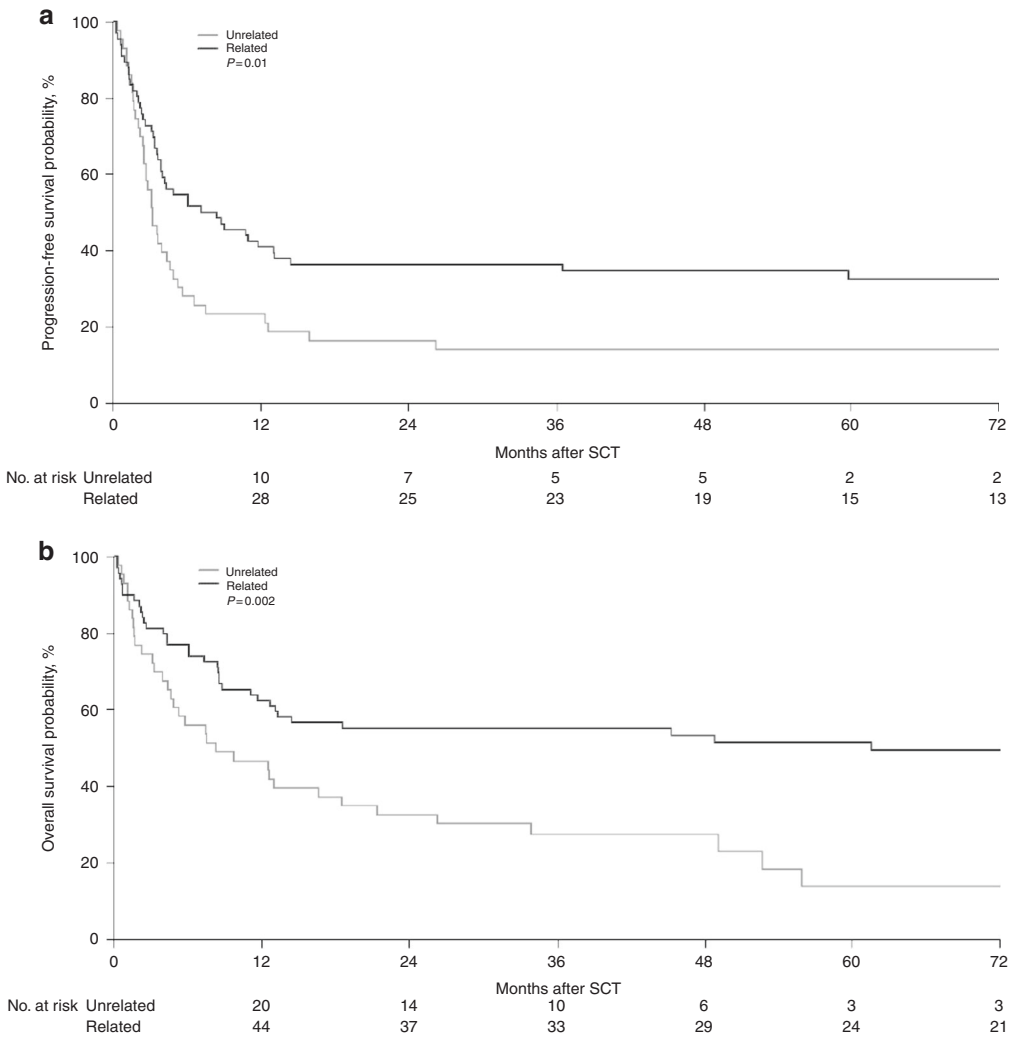

Fig. 4 Impact of the type of donor in progression-free survival and overall survival. a Progression-free survival. **b** Overall survival.

non-transplanted patients as they are not registered in the transplant data bases but also the existence of missing data, heterogeneity of the patients and inherent biasesrelated to the individual therapeutic decisions taken by the treating physician), they have the advantage of providing information on large number of patients. In this sense, relevant information that could set the basis for prospective trials or additional studies can be retrieved.

In conclusion, our data indicate that allo-HSCT is able to effectively rescue around one third of the population of patients with advanced-stage MF/SS that undergo the procedure. Survival curves show a flattening suggesting the potential existence of a beneficial GVL effect in patients that have failed other treatment strategies. Unfortunately, the still high relapse rate after transplant and the negative impact of URD are still a matter of concern. New strategies such as the introduction of new drugs as salvage treatments before allo-HSCT should be further evaluated in this setting.

Acknowledgements The authors acknowledge all collaborating EBMT Investigators and Institutions that contributed cases to this study.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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