EBMT

CORRESPONDENCE

The use of MSCs in steroid-refractory acute GvHD in Europe: a survey from the EBMT cellular therapy & immunobiology working party

Acute graft-versus-host disease (aGvHD) remains a significant complication of allogeneic hematopoietic cell transplantation, with 40% of patients failing to respond to high-dose steroids. Ruxolitinib has become the standard treatment for steroid-refractory aGvHD (SR-GvHD), but its failure in approximately one-third of cases highlights the need for alternative therapies. Mesenchymal stromal cells (MSCs), known for their immunomodulatory properties, are suggested as a treatment option, but their role in SR-GvHD remains unclear. To better understand MSC therapy outcomes, the EBMT Cellular Therapy & Immunobiology Working Party conducted a survey of centers treating >20 SR-GvHD patients with MSCs between 2007 and 2020. Data from 313 patients were analyzed, revealing a 44.5% overall response rate at day 28. Responders at day 7 had a higher likelihood of maintaining responses by day 28. Using a landmark analysis, the overall survival at 12 months, conditional on being alive at day 28, was 39.2%. Survival at 12 months was 48.6% for responders, compared to 24.4% for non-responders. Despite manufacturing variabilities, MSCs produced by academic pharma appear effective in SR-GvHD, offering a viable treatment alternative for heavily pretreated patients. These findings support further investigation of MSCs to establish standardized protocols and validate their efficacy as third-line therapy for SR-GvHD.

Bone Marrow Transplantation (2025) 60:708–714; https://doi.org/10.1038/s41409-025-02531-3

INTRODUCTION

Despite novel developments in conditioning regimens and graft engineering, acute graft-versus-host disease (aGvHD) remains a life-threatening complication of allogeneic hematopoietic cell transplantation. Around 40% of patients with aGvHD do not respond to high-dose steroid therapy [1]. Since the publication of the REACH-2 trial, ruxolitinib is the standard of care for patients with steroid-refractory aGvHD (SR-GvHD). Unfortunately, 32% of patients discontinued ruxolitinib due to lack of response or toxicity in the REACH-2 trial [2]. These patients have a dismal outcome and there is no standardized third line therapy for SR-GvHD [3]. The recent EBMT guidelines on aGvHD do not specify which treatment to offer these patients; instead, they recommend that centers follow their institutional guidelines [4]. Mesenchymal stromal cells (MSCs) are among the treatment options recommended by the EBMT, but their exact role in aGvHD therapy has yet to be determined.

MSCs represent a heterogeneous population of cells with potent immunomodulatory capacity, that can promote a shift from a pro-inflammatory to an anti-inflammatory environment [5]. Uniform evidence shows that this treatment is well-tolerated and safe. Response percentages vary between 47–93% in heavily pretreated patients, and suggest a survival benefit in responding patients [6]. The large variance in response rates is most likely due to differences in the type of MSCs, in the production processes, as well as in the number of administrations and MSC dose per administration [6]. Whereas most MSC are harvested from bone marrow [7–11], trials were also performed with induced pluripotent stem cells [12], MSCs derived from umbilical cord [13], placenta [14], and adipose tissue [15]. In addition, different academic centers use different production processes for MSC harvested from bone marrow. This lack of standardization hinders the implementation of MSCs as an established treatment for SR-GvHD. Another important factor is the scarcity of randomized controlled trials (RCTs). Recently two of very few RCTs in SR-GVHD were published. The first trial compared basiliximab with or without MSCs in patients with SR-GvHD, showing an improved complete response rate for patients receiving MSCs [16]. The second trial included 78 steroid-refractory patients who were treated with various regimes of second-line GvHD therapy, randomized 1:1 between the addition of MSCs or placebo. No significant differences concerning overall response rate and survival were found between the groups in the intention-to-treat analysis, but in the per-protocol analysis, overall response rate was significantly better in the group receiving MSCs [17]. Both trials were performed with umbilical cord-derived MSCs.

To better understand the administration and outcomes of academically produced MSCs in SR-GvHD, the EBMT Cellular Therapy & Immunobiology Working Party (CTIWP) conducted a survey among EBMT centers.

METHODS

An EBMT survey was created. Information on the MSC manufacturing process, the number of administrations and the outcomes was obtained from centers that had performed >20 MSC treatments for SR-GvHD treatment between 2007 and 2020. GvHD grade was scored at baseline, on day 7 and on day 14 after MSC infusion. The primary endpoint was the probability of overall response (OR), defined as either complete response (CR) or partial

Received: 9 November 2024 Revised: 27 January 2025 Accepted: 11 February 2025
Published online: 20 February 2025

Table 1. MSC manufacturing process per center.

Centers		A	B	C	D	E	F
Number of patients treated		107	30	59	48	42	27
Origin of MSC	Bone marrow	x	x	x	x	x	x
	Adipose Tissue			x			
Donor age range		2-33	18-52	21-46	20-38	21-46	18-35
Selection	Plastic adherence	x	x	x		x	x
	Filter-based separation device				x		
Culture medium	FCS		x				
	Human Platelet lysate	x		x	x	x	x
Purity markers	CD73+	x	x	x	x	x	x
	CD90+	x	x	x	x	x	x
	CD105+	x	x	x	x	x	x
	CD34-		x	x	x	x	x
	CD45-	x	x	x	x	x	x
	CD14-		x	x		x	x
	CD3-	x	x				
	CD19-						x
	HLA-DR		x	x		x	x
	CD166					x	
	additional markers	none	none	none	none	none	CD44 +, D49e +, CD13 +, CD29 +, HLA-ABC+
Quality test	Mycoplasm	x	x	x	x	x	
	Sterility	x	x	x	x	x	x
	Endotoxin	x	x	x	x		x
	Karyotype		x		x		x
	Differentiation assay			x		x	x
	Potency assay			x		x	x
	Population Doubling time	x	x			x	x
Dose of MSC, x10^6/kg		1 to 2	1 to 4	1	1	1	2
Number of infusions	responding patients	3	1	4	2 or 6	2	1 to 6
	non-responding patients	1 to 3	1	4	2, 3 or 6	2 to 3	1 to 6
Infusion days		1, 8, 22	1	1, 4, 11, 18	1, 8, 15, 22, 29, 36	1, 3, 5	unknown
Number of donors per infusion day		1	1	>1	1	>1	1
Maximum mitotic age		p3	p3	p3	p2	p2	p2

response (PR) of aGvHD, on day 28 after MSC administration. CR is defined as the return of aGvHD to overall grade 0, and PR is defined as improvement by at least one grade. Information on organ-specific involvement and response was not included due to a large amount of missing data. Death before day 28 was considered a competing event for OR. As a secondary endpoint, OR on day 7 was calculated.

Patient characteristics at time of first MSC infusion (MSC1) and the preceding HSCT were reported using the median and range for continuous variables, and frequencies and proportions for categorical variables. Data on some patients has been part of previous publications [7, 18]. Baseline was defined as time of MSC1. Death was considered a competing event when computing the proportion of patients having achieved overall response until days 7 and 28 after MSC1. GvHD grading was done according to the Glucksberg classification [19]. Overall survival was estimated using the Kaplan–Meier product limit estimation method, and differences in subgroups until 12 months were assessed by means of the Log-Rank test. The cumulative incidence of disease relapse was considered for patients with no prior relapse or progression between HCT and MSC1. Non-relapse mortality was considered a competing event in this analysis. Landmark analyses were used to assess the impact of MSC1 response at day 28 on overall survival [20].

Risk factors for the probability of MSC response at day 28 (conditional on being alive at day 7) were assessed using a multivariable logistic regression model, fit using Firth's bias reduction method [21]. Death at day 28 was considered as non-response for this analysis. Individuals with missing data on predictor variables and/or response were excluded from the multivariable model (complete-case analysis).

For the time-to-event outcomes, artificial censoring was applied at 12 months after the first MSC infusion. In this period, only 6 patients were censored. All statistical tests were two-sided, at a

significance level of 0.05. All analyses were performed in R version 4.4.1, using packages "survival", "cmprsk", "prodlim", and "brglm2".

RESULTS

Responses were obtained from 6 participating EBMT centers across 6 different countries. Detailed information on the manufacturing process at each center is provided in Table 1. The MSC source was bone marrow in all centers, although 1 center also included patients treated with adipose tissue-derived MSCs. MSC donors were adults up to 52 years old in all centers, except for one, which also included pediatric donors. Five of the six centers used plastic adherence for MSC selection, whereas one center utilized a filter-based separation method. Most MSCs were cultured in human platelet lysate, with only 1 center using fetal calf serum (FCS). Pooled MSC batches were used in only one center. The mitotic age was between 2 and 3 passages. Purity markers and quality controls are depicted in Table 1. Regarding MSC administration, all products were frozen, and the administered dose was at least 1×10^6 MSCs per kilogram per infusion. Interestingly, there was quite a large difference in the number of infusions, varying between 1 and 6.

Results were obtained form 313 patients (Table 2). Median patient age was 55 years old at MSC infusion (range 17.6–74.5). Patients had different hematological diseases, the majority being acute myeloid leukemia (33.5%) and myelodysplastic syndrome (14.4%). Most transplants were performed with unrelated donors (75.1%). 44.9% of patients received myeloablative conditioning, while 55.1% received reduced intensity conditioning. ATG was used in 50.2% of cases, and PTCy was used in only 3.2% of cases. This is illustrative of GvHD prophylaxis in the period of inclusion (2007 to 2020), which also explains why only 9.3% of patients received ruxolitinib before MSC administration. The median number of aGvHD treatments before administration of MSCs was 3 (range 1–7).

At the start of MSC infusion, aGvHD grade was scored: grade 1: 3%, grade 2: 14%, grade 3: 56% and grade 4: 27% (Fig. 1a). GvHD grade on day 7 and 28 are depicted in Fig. 1a, b. With these data the primary and secondary endpoints were calculated: On day 7, the overall response rate was 26.5%. At day 28, 44.5% of patients showed an overall response to MSCs. (Fig. 1c).

Overall survival in this cohort was 30.7% (95% confidence interval (CI): 25.6–35.9%) at 12 months after MSC infusion (Fig. 2a). Using a landmark analysis, the overall survival at 12 months, conditional on being alive at day 28, was 39.2% (95% CI: 33.1–45.4%) (Fig. 2b). The overall survival in responding patients was 48.6% (95% CI: 39.4–57.7%) at 12 months, compared to 24.4% (95% CI: 14.8–33.9%) in non-responders alive at day 28, which was a statistically significant difference ($p.$ <0.001) (Fig. 2c). The cumulative incidence of relapse of the underlying hematological malignancy at 12 months after MSC administration, given no prior relapse between HCT and MSC1, was 9.5% (95% CI: 6–12.9%) (Fig. 3a), while non-relapse mortality (NRM) (Fig. 3b) and relapse-free survival at 12 months were 58.8% (95% CI: 53–64.7%) and 31.7% (95% CI: 26.2–37.2%) respectively (Fig. 3c).

A previous study has shown that response to MSC therapy at day 7 predicts the response on day 28 [22]. Our study confirms this: the majority of responders (84.8%) at day 7 maintained the response at day 28. However, among non-responders alive at day 7, still 35.1% achieved a response by day 28. (Table 3A). The average number of MSC infusions was 4 (range 1–9) in responders and 3 (range 1–7) in non-responders alive at day 28. Multivariable logistic regression on predictors of MSC outcome on day 28 showed that being a responder at day 7 was significantly associated with response on day 28 ($p < 0.001$). The conditioning regimen, the interval from onset of GvHD to MSC administration, patient age, MSC dose and GvHD grade at first MSC administration were not significantly associated with response on day 28 (Table 3B).

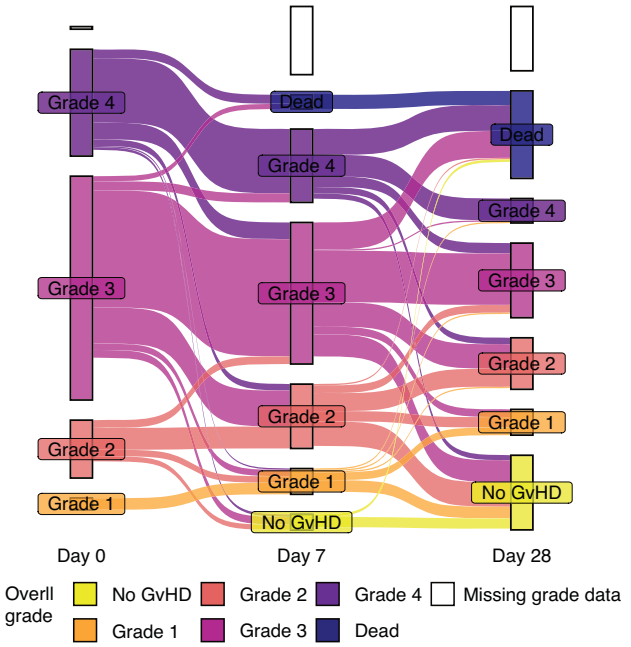
Table 2. Baseline characteristics of patients treated with MSCs.

Variable	Level	Overall, $N = 313$
Patient sex	Male	202 (64.5%)
	Female	111 (35.5%)
Diagnosis (grouped)	AML	105 (33.5%)
	MDS	45 (14.4%)
	NHL	35 (11.2%)
	ALL	28 (8.9%)
	MPN	24 (7.7%)
	MM and PCL	17 (5.4%)
	Other	15 (4.8%)
	CML	11 (3.5%)
	CLL	11 (3.5%)
	Other AL	10 (3.2%)
	MDS/MPS overlap	7 (2.2%)
	Hodgkin lymphoma	5 (1.6%)
Age at msc1 (in years)		55.0 [17.6, 74.5]
Number of last allo-HSCT before MSC infusion	First	294 (93.9%)
	Second	19 (6.1%)
Conditioning regimen	Standard	136 (44.9%)
	Reduced	167 (55.1%)
	(Missing)	10
Donor type	Identical sibling	64 (20.5%)
	Matched other relative	1 (0.3%)
	Mismatched relative	12 (3.8%)
	Unrelated	235 (75.3%)
	(Missing)	1
Stem cell sources	BM	16 (5.1%)
	PB	284 (90.7%)
	CB	12 (3.8%)
	PB + CB	1 (0.3%)
PTCy given as GvHD prophylaxis	No	271 (96.8%)
	Yes	9 (3.2%)
	(Missing)	33
ATG given (for any reason)	No	155 (49.8%)
	Yes	156 (50.2%)
	(Missing)	2
Ex-vivo T-cell depletion	No	285 (93.8%)
	Yes	19 (6.3%)
	(Missing)	9
Number of GvHD treatments before MSC1	1	41 (25.3%)
	2	39 (24.1%)
	3	46 (28.4%)
	4 or more	36 (22.2%)
	(Missing)	151
Ruxolitinib as GVHD therapy pre-MSC1	No	147 (90.7%)
	Yes	15 (9.3%)
	(Missing)	151
Interval GvHD onset to msc1 (months)		0.46 [0.03, 10.81]

a

Overall grade	Day 0, *N* = 313	Day 7, *N* = 313	Day 28, *N* = 313
No GvHD	0 (0%)	12 (4.6%)	58 (22%)
Grade 1	9 (2.9%)	20 (7.7%)	20 (7.6%)
Grade 2	45 (14%)	50 (19%)	40 (15%)
Grade 3	174 (56%)	110 (42%)	58 (22%)
Grade 4	83 (27%)	57 (22%)	19 (7.2%)
Dead	0 (0%)	11 (4.2%)	68 (26%)
(Missing)	2	53	50

b



c

Timepoint	Response	Overall, *N* = 313
Response day7	Non-responder	180 (69.2%)
	Responder	69 (26.5%)
	Dead	11 (4.2%)
	(Missing grade)	53
Response day 28	Non-responder	78 (29.7%)
	Responder	117 (44.5%)
	Dead	68 (25.9%)
	(Missing grade)	50

Fig. 1 GvHD grade per timepoint, and proportion of response on day 7 and day 28. a GvHD grade per time point – Table **b** GvHD grade per time point – Sankey diagram. **c** Proportion of response was calculated for all patients on day 7 and day 28, with response defined as either complete response (CR) or partial response (PR) of aGVHD. Non-response is defined as patients alive without a PR or CR.

DISCUSSION

This is the first comprehensive survey of MSC use in SR-GvHD in Europe, highlighting a survival benefit for responding patients. We show that almost half of the patients with aGvHD in this cohort respond to MSCs on day 28, which was associated with significantly better survival. These results emphasize the effectiveness of MSCs in heavily pretreated patients, indicating that academically produced MSCs are a viable option for refractory aGvHD.

The advantages of MSCs include their off-the-shelf availability, established safety profile, and the limited number of infusions. However, a significant disadvantage is the absence of standardized manufacturing processes, leading to variability in MSC products across different centers. Not all MSCs are equal in potency. When comparing the MSC manufacturing processes across the centers in this survey, we identified notable consistencies in terms of MSC origin, selection methods, culture media used and MSC dose per infusion. Nonetheless, the number of administrations varied, ranging from a single administration to up to six infusions per patient, which constitutes a limitation of this survey. Other limitations include its retrospective design, the fact that most patients were treated prior to the approval of ruxolitinib, and the lack of information on aGvHD organ involvement. MSC production is confined to a limited number of centers, and consequently, only a small number of centers have participated in our survey. Notably, most reference centers treat patients from multiple institutions within their respective countries.

Recently, commercial MSC products have also been developed. Remestemcel-L/Ryoncil©, which underwent culturing for many passages, did not meet the primary endpoint in SR aGvHD in a phase III trial [23]. MSC-FFM/Obnitix© is derived from a pooled

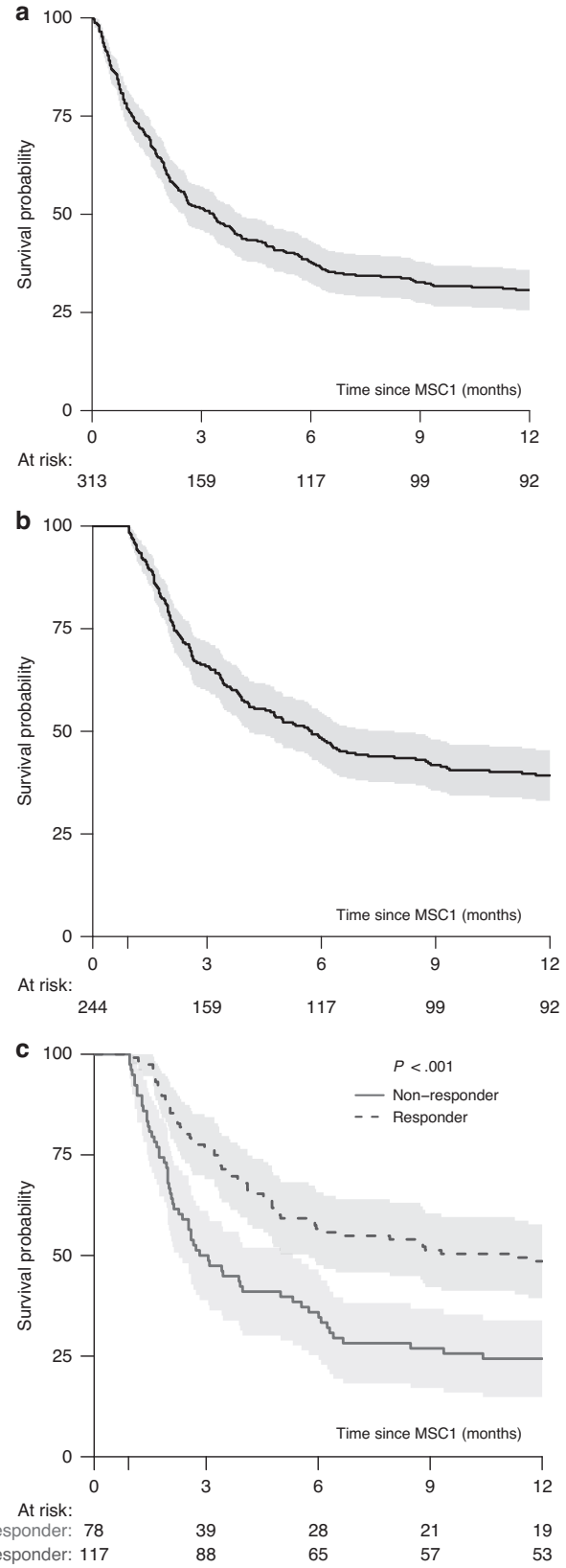


Fig. 2 Overall survival. a Overall survival of the whole cohort **b** Landmark analysis of the whole cohort: Overall survival given that a patient is still alive at day 28 after MSC administration. **c** Landmark analysis by response : Overall survival given that a patient is still alive at day 28 after MSC administration, separated by response (CR or PR) or non-response (all other patients).

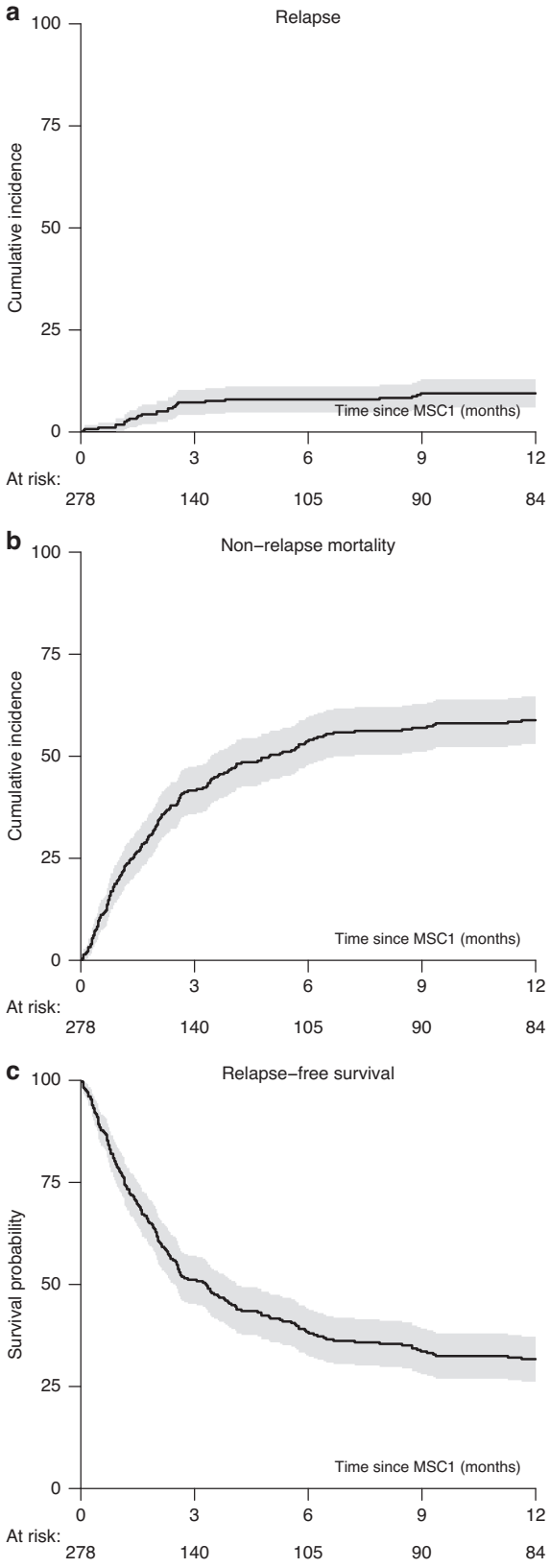


Fig. 3 Relapse, non-relapse mortality and relapse-free survival. a Cumulative incidence of relapse of the underlying hematological malignancy after MSC administration (among patients with no prior relapse between HCT and first MSC administration) **b** Cumulative incidence of non-relapse mortality after MSC administration **c** Relapse-free survival after MSC administration.

Table 3. Response at day 27 predicts response on day 28.

A

		Response day 28			
		Non-responder	**Responder**	**Dead**	**Total**
Response day 7	**Non-responder**	70 (41.7%)	59 (35.1%)	39 (23.2%)	168 (100%)
	Responder	5 (7.6%)	56 (84.8%)	5 (7.6%)	66 (100%)
	Total	75 (32.1%)	115 (49.1%)	44 (18.8%)	234 (100%)

B

Characteristic	**Level**	**OR**	**95% CI**	***p*-value**
Response at day 7 after MSC1	Non-responder			
	Responder	11.2	5.12, 24.4	<0.001
GvHD grade at MSC1	1			
	2	0.57	0.09, 3.69	0.6
	3	0.54	0.10, 2.98	0.5
	4	0.41	0.07, 2.42	0.3
Conditioning regimen at last alloHCT before MSC1	standard			
	reduced	0.60	0.31, 1.18	0.14
Interval onset GvHD-MSC1 (months)		0.86	0.66, 1.11	0.2
Age at msc1 (in years)		1.00	0.98, 1.03	>0.9
Dose MSC1 (1×10^6/kg)		0.69	0.42, 1.12	0.13

3A: Cross-table day 7 and day 28 response: For the patients included in the landmark dataset on day 7, response at day 7 was cross-tabulated with response at day 28 (including death) for those with available data on both days. On the vertical axis responses at day 7 are shown, while on the horizontal axis the corresponding responses on day 28 are shown.
3B: All patients alive at day 7 after MSC1 (landmark dataset) with complete GvHD grading for both day 7 and 28 and complete information for the other predictors of this multivariable model were used for this analyses. This led to a total of 222 patients. The outcome is MSC response at day 28 (death treated as non-responder). This is a logistic regression model, fit using Firth's bias reduction method. *OR* odds ratio.

donor bank, without the need of many passages in vitro. Encouraging results were shown in a single arm trial and in real world data: a 46% overall response rate at day 28 in ruxolitinib-resistant patients, with an overall survival of 35% after 1 year [24]. Interestingly, the overall survival shown here for various academic products is comparable to MSC-FFM: OS after 1 year is 30.7% for academic products in the current survey vs. 35% for MSC-FFM in real world data [24]. This encourages more ATMP trials in academia, and supports the ongoing use of hospital exemption programs for MSCs around Europe. Including all patients treated with academic MSCs in the EBMT registry would enhance knowledge on outcomes, while at the same time providing the opportunity to use these data as a control arm in future studies.

Concluding, MSCs might be a non-toxic option for aGVHD, used in third line after steroids and ruxolitinib. Future studies, preferably RCTs, are needed to provide final proof of action for these academic products.

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AUTHOR CONTRIBUTIONS

LGMD and JK performed analyses, created tables and wrote the manuscript. LEvdW, LLC, AB, MB, YB and MIR were responsible physicians at the hospitals where the patients were treated. They provided the data for the report. FD created the questionnaires. JDH performed data management. EFB performed data analysis, statistical analyses and created the figures. LCdW supervised the statical analyses. FM, CC, FD and AR provided feedback on the report.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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