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ARTICLE

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Hemophagocytic lymphohistiocytosis (HLH; hemophagocytic syndrome) is a rare syndrome of potentially fatal, uncontrolled hyperinflammation. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is indicated in primary, recurrent or progressive HLH, but information about its outcomes in the adult population is limited. We obtained data about 87 adult (≥18 years of age) patients retrospectively reported to the EBMT. The median survival time was 13.9 months. The three and five-year overall survival (OS) was 44% (95% CI 33–54%). Among 39 patients with a follow-up longer than 15 months, only three died. Relapse rate was 21% (95% CI 13–30%), while NRM reached 36% (95% CI 25–46%). Younger patients (<30 years of age) had better prognosis, with an OS of 59% (95% CI 45–73%) at three and five years vs 23% (95% CI 8–37%) for older ones. No difference in survival between reduced and myeloablative conditioning was found. To our knowledge, this is the largest report of adult HLH patients who underwent allo-HSCT. Patients who survive the first period after this procedure can expect a long disease-free survival. Both reduced intensity and myeloablative conditioning have therapeutic potential in adult HLH.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH; hemophagocytic syndrome) is a rare syndrome of potentially fatal, uncontrolled hyperinflammation [1, 2]. In some individuals, if an inflammatory reaction exceeds a certain threshold, it cannot be physiologically halted, but is fueled by pathologic positive feedback loops until it is stopped either by an effective treatment or a patient's death. In familial (primary) HLH this mechanism is attributed to a genetic defect in the cytotoxic granule pathway, while cytokine production remains intact, causing dysregulated interactions between cytotoxic and other immune cells. The more this cytotoxic function is diminished, the earlier and easier (at a lower threshold) HLH will occur – the proportion of genetic (primary) HLH lowers with an increasing age [3]. In adults the majority of patients do not have mutations in typical genes, but primary cases with late onset were observed [4, 5]. Secondary HLH occurs when inflammation triggered by infection, malignancy or autoimmune disease exceeds the threshold for HLH and starts this hyperinflammatory pathomechanism.

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Table 1. Patient and transplant characteristics.

Characteristics		N	%	Missing
Patient sex	Female	30	34.5	
	Male	57	65.5	
Patient age at HSCT [years]	Median (IQR)	28.1 (22–39.1)		
Patient age at diagnosis [years]	Median (IQR)	27.1 (19.3–37.6)		
Time from diagnosis to HSCT [months]	Median (IQR)	9.2 (5.6–18.9)		
HSCT source	BM	18	20.7	
	PB	68	78.2	
	CB	1	1.1	
Donor	Identical sibling	29	33.3	
	Matched other relative	2	2.3	
	Matched unrelated	6	6.9	
	Mismatched relative	6	6.9	
	Mismatched unrelated	3	3.4	
	Unrelated	41	47.1	
Conditioning intensity	MAC	52	61.2	2 (2.3%)
	RIC	33	38.8	
TBI used	Yes	14	16.1	
	No	73	83.9	
Conditioning regimen[a]	Flu-Bu-ATG	14	17.1	5 (5.7%)
	Flu-Mel-Alem	10	12.2	
	Ctx-ATG	6	7.3	
	Bu-Ctx-Etoposide	4	4.9	
	Flu-Melphalan	3	3.7	
	Ctx alone	3	3.7	
	Flu-Mel-ATG	3	3.7	
	Other	39	47.6	
GvHD prophylaxis[a]	CsA-Mtx	21	26.9	9(10.3%)
	CsA alone	14	17.9	
	CsA-MMF	11	14.1	
	MMF-Tacrolimus	4	5.1	
	CsA-Mtx-ATG	3	3.8	
	Other	25	32.1	
HLH type	Primary HLH	39	46.4	3 (3.4%)
	Reactive/viral HLH	45	53.6	
Remission status	CR	9	23.1	48 (55.2%)
	VGPR	1	2.6	
	PR	15	38.5	
	<PR	13	33.3	
	Upfront	1	2.6	
Patient CMV serostatus	Positive	62	77.5	7 (8%)
	Negative	18	22.5	
Donor CMV serostatus	Positive	44	55.7	8 (9.2%)
	Negative	35	44.3	

HSCT Hematopoietic Stem Cell Transplantation, *BM* Bone Marrow, *PB* Peripheral Blood, *MAC* Myeloablative Conditioning, *RIC* Reduced Intensity Conditioning, *TBI* Total Body Irradiation, *Flu* Fludarabine, *Bu* Busulfan, *ATG* Anti-thymocyte globulin, *Alem* Alemtuzumab, *Ctx* Cyclophosphamide, *CsA* Cyclosporin A, *Mtx* Methotrexate, *MMF* Mycophenolate mofetil, *HLH* Hemophagocytic Lymphohistiocytosis, *CR* Complete Remission, *VGPR* Very Good Partial Remission, *PR* Partial Remission, *CMV* Cytomegalovirus.
[a]regimens received by more than two patients are listed.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) provides cure for HLH. After the first procedure in 1984 [6], it became indicated for children in the HLH-94 [7] and HLH-2004 [8] protocols (after the initial treatment based on etoposide, dexamethasone and cyclosporine A). Mortality was mostly attributed to the toxicity of myeloablative conditioning: 66% of deaths (28/42) in HLH-94 [9] and 48% (31/64) in HLH-2004 [10] (54% including five after the second transplant [11]) were described as treatment-related. Better survival results initially achieved with reduced intensity conditioning (three-year survival of 92% after RIC vs 43% after myeloablative conditioning—MAC) [12], raised interest in this method, but problems with engraftment and mixed chimerism cause a need for its optimization [11, 13–18]. MAC approach can be more beneficial in terms of EFS (event-free survival) [19].

In adults with HLH, allo-HSCT is recommended, including the current international expert consensus [20], in primary or relapsed/refractory disease [21–23]. Published data for this patient group are scarce with information based on single groups from Asia [24–26] and USA [27], case reports and single patients transplanted in adult patient series [28–31] or included in pediatric transplant groups [12, 13, 18, 32–34]. There is a strong need to assist difficult clinical transplant decisions by providing representative data of adult patients.

The aim of this study was to analyze the information from the EBMT databases about adult HLH patients who underwent allogeneic hematopoietic stem cell transplantation as a joint effort of Chronic Malignancies and Inborn Errors Working Parties (CMWP and IEWP) of the EBMT (European Society for Blood and Marrow Transplantation).

SUBJECTS AND METHODS

We obtained data from 87 adult (≥18 years of age) patients reported to the EBMT databases after allo-HSCT due to HLH between 1995 and 2018. HLH subtypes were reported by the centers as familial (primary) or reactive/viral HLH. In this cohort malignancy played a marginal role: only one patient had HLH triggered by lymphoma, another one by influenza virus while he was undergoing Hodgkin lymphoma therapy and in one case T-cell lymphoma was assumed retrospectively in a patient transplanted for EBV-triggered HLH. Three and five-year measures of survival were applied.

All main analyses of this manuscript were performed using information extracted from standard EBMT reports (including, among others, parameters presented in Tables 1, 2). These reports do not contain HLH-specific information like initial therapy, ferritin concentrations or genetic testing. In order to obtain these data an additional questionnaire was created. After contacting all of the centers, which had reported adult HLH patients, responses were received for 33 patients. Some of the data were reported for a lower number of patients (e.g. genetic testing), as indicated in the results section.

Statistical analysis

The primary goal of the analysis was to describe the characteristics of patients transplanted with HLH and report post-transplant outcomes until five years after allo-HSCT (3-years for stratified outcomes).

Table 2. Three-year outcome estimates stratified by patient and transplant characteristics.

Characteristics	Strata	*N*	OS	*p*	PFS	*p*	Relapse	*p*	NRM	*p*
HLH type	Familial HLH	39	58% (42–74%)	0.06	58% (42–74%)	0.028	8% (0–16%)	0.011	34% (19–49%)	0.8
	Reactive/viral HLH	45	33% (18–47%)		31% (17–45%)		32% (18–45%)		37% (22–52%)	
Conditioning	Standard	52	48% (34–62%)	0.8	46% (32–60%)	0.7	14% (4–24%)	0.08	40% (26–53%)	0.3
	Reduced	33	40% (23–58%)		41% (24–58%)		30% (15–46%)		29% (13–44%)	
Patient CMV	Negative	18	71% (50–93%)	0.016	67% (45–88%)	0.05	28% (7–48%)	0.5	6% (0–16%)	0.007
	Positive	62	39% (27–52%)		39% (27–52%)		18% (8–28%)		42% (30–55%)	
Donor CMV	Negative	35	61% (44–78%)	0.07	59% (42–76%)	0.14	21% (7–35%)	0.8	20% (7–34%)	0.13
	Positive	44	39% (24–54%)		39% (24–54%)		23% (11–36%)		38% (23–52%)	
Age at HSCT	Age <30	50	59% (45–73%)	0.004	59% (46–73%)	0.001	14% (4–24%)	0.07	26% (14–39%)	0.06
	Age ≥30	37	23% (8–37%)		20% (7–34%)		31% (16–47%)		48% (31–65%)	
Donor	Related	37	46% (29–63%)	0.7	43% (27–60%)	0.8	20% (7–33%)	0.7	37% (21–53%)	0.9
	Unrelated	50	43% (29–57%)		43% (29–57%)		22% (11–34%)		35% (21–48%)	
Stem cell source	BM	18	61% (39–84%)	0.2	61% (39–84%)	0.2	22% (3–41%)	0.9	17% (0–34%)	0.11
	PB	68	40% (27–52%)		39% (26–51%)		21% (11–32%)		40% (28–52%)	
HSCT year	<2014	47	47% (33–62%)	0.5	47% (33–62%)	0.4	15% (5–26%)	0.15	37% (23–51%)	0.8
	2014-2018	40	39% (23–56%)		38% (23–54%)		29% (14–43%)		33% (18–48%)	
Interval diagnosis-HSCT	≤12 m	53	42% (28–56%)	0.9	41% (27–55%)	0.8	26% (13–38%)	0.3	34% (20–47%)	0.5
	>12 m	34	46% (29–63%)		46% (29–63%)		15% (3–27%)		39% (22–55%)	
Patient sex	Male	57	43% (30–57%)	0.8	42% (28–55%)	0.9	16% (7–26%)	0.11	42% (29–55%)	0.12
	Female	30	45% (27–64%)		46% (28–64%)		31% (14–47%)		24% (8–39%)	

HLH Hemophagocytic lymphohistiocytosis, *CMV* Cytomegalovirus, *HSCT* Hematopoietic stem cell transplantation, *BM* Bone marrow, *PB* Peripheral blood;

The relationship between conditioning intensity and outcomes was of special interest. The main outcomes analyzed in the study were overall survival (OS), progression-free survival (PFS), relapse incidence, and non-relapse mortality (NRM). OS was defined as the time from transplantation to death from any cause. PFS was defined as the time from transplantation to relapse, disease progression, or death from any cause (whatever occurred first). NRM was defined as death before any evidence of relapse or progression. Neutrophil engraftment was defined as achieving an absolute neutrophil count $\geq 0.5 \times 10^9$/L for three consecutive days. Median follow-up was determined using the reverse Kaplan-Meier method. OS and PFS were estimated using the Kaplan-Meier product limit estimation method, and differences in subgroups were assessed by the Log-Rank test.

Cumulative incidences of relapse (CIR) and NRM were analyzed together in a competing risks framework. Competing risks analyses were also applied to estimate incidences of primary and secondary graft failure, with the competing event death, neutrophil engraftment by 28 days with the competing event death, limited and extensive chronic GvHD (cGvHD) with competing event death and acute GvHD grade II-IV (aGvHD) with the competing event death, by 100 days. Missing intervals allo-HSCT–aGvHD II-IV were imputed at 2 weeks post-transplant. Subgroup differences in cumulative incidences were assessed using Gray's test. The linear effect of continuous risk factors age at HSCT and year of HSCT on outcomes was investigated by means of univariate Cause Specific Hazards models.

Continuous variables are presented by median (interquartile range or range) and categorical variables by percentage (frequency / evaluable total) within the group of patients with available data. All estimates are reported with corresponding 95% confidence intervals. All p-values were two-sided and $p < 0.05$ was considered significant. Statistical analyses were performed in R version 3.3.2 (R Development Core Team, Vienna, Austria), using packages 'survival', 'prodlim' and 'cmprsk'.

RESULTS

Patient and HSCT characteristics

Age distribution was right-skewed with a median at transplantation of 28 years (interquartile range: 22–39; range: 18–65) and a slight male predominance (66%; 57/87). Similar proportion of patients had primary (46%; 39/84) and secondary HLH (54%; 45/84)–as reported by the centers. Detailed patient and transplant characteristics are summarized in Table 1.

Myeloablative conditioning (MAC) was used in 61% (52/85) of patients, while 39% (33/85) received reduced intensity conditioning (RIC) – as reported by the centers. The first reported MAC transplantation was in 1995, while the first RIC took place in 2004. Until 2007 only 13 transplants were performed. There were four haploidentical transplants reported, with results comparable to the rest of procedures.

Outcomes

The median survival time was 13.9 months (Fig. 1a). Both three and five-year OS were 44% (33–54%), with the same results for PFS. All relapses were fatal – which is reflected in similarity of the PFS and OS estimates and curves. The median time between relapse and death was one month (IQR 0.5–1.4 m). Among 39 patients with observation times longer than 15 months only three patients died. After 23 months, no more HLH relapses were observed (Fig. 1b) – the cumulative incidence of relapse reached 21% (13–30%). The non-relapse mortality was 36% (25–46%).

The cumulative incidence of neutrophil engraftment by day 28 was 84% (76–92%). The incidences of primary and secondary graft failure by 60 months after transplantation were 9% (3–15%) and 4% (0–9%) respectively. No differences among sub-groups were found, including conditioning intensity, CMV serostatus, sex and age. The cumulative incidence of grade II-IV acute graft versus host disease (aGvHD) by 100 days was 32% (22–42%), with the following grades: II 18% (9–26%), III 8% (2–14%), IV 6% (1–12%) of the reported patients. The cumulative incidence of grade I aGvHD was 13% (5–20%). The cumulative incidence of chronic GvHD by one year after allo-HSCT was 12% (5–19%), increased to 22% (13–32%) by three years and remained unchanged until 5 years.

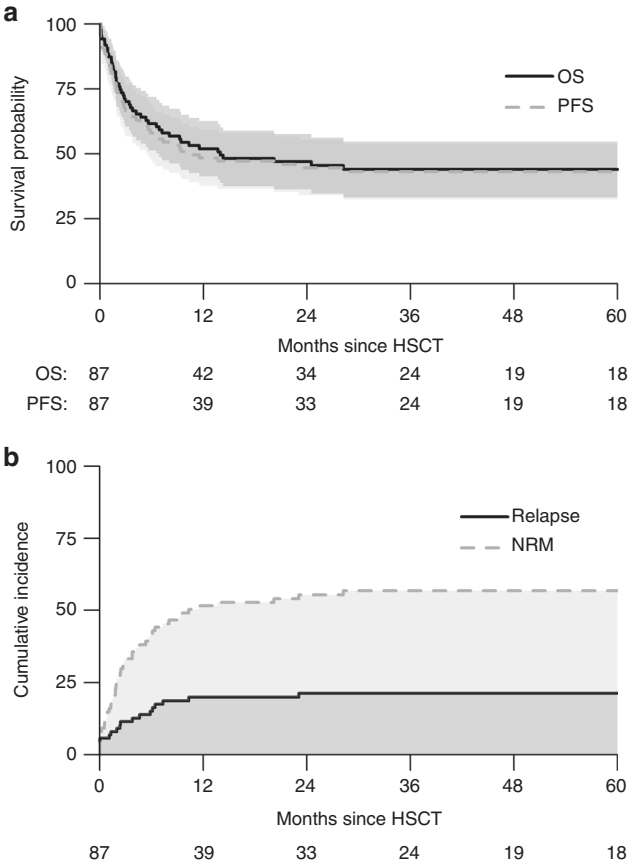

Fig. 1 Outcomes of allogeneic hematopoietic stem cell transplantation in 87 adult HLH patients. a Overall Survival (OS) and Progression-Free Survival (PFS). **b** Relapse rate and Non-Relapse Mortality.

By 3 years 14% (6–22%) patients suffered from limited and 8% (2–14%) from extensive GvHD. There was no difference in terms of GvHD between related and unrelated donors.

Main causes of death within a five-year follow-up period were: relapse/progression (32%; 15/47), infection (30%; 14/47, including five fungal), and GvHD (15%; 7/47). Other causes (21%; 10/47) included: four cases of multiorgan failure, three of secondary malignancy (including post-transplant lymphoproliferative disorder), and three of non-specified treatment-related mortality. In six patients (14%) with another primary cause of death, a hemorrhage was also reported.

Younger patients had better allo-HSCT outcomes. Figure 2a shows a superior three and five-year overall survival below the age of 30 years: 59% (45–73%) vs 23% (8–37%) for older patients ($p = 0.004$). This effect appears to be continuous with a HR = 1.41 (1.15–1.74) per decade, $p = 0.001$. Younger patients also had improved PFS of 59% (46–73%) vs 20% (7–34%), $p = 0.001$, HR = 1.4 (1.15–1.71), $p = 0.001$; lower relapse rate of 14% (4–24%) vs 31% (16–47%), $p = 0.07$, HR = 1.48 (1.07–2.06); $p = 0.018$; and lower NRM of 26% (14–39%) vs 48% (31–65%), HR = 1.34 (1.04–1.74), $p = 0.026$.

Patients with primary HLH had a better PFS of 58% (42–74%) vs 31% (17–45%) at 36 months––$p = 0.028$, with a trend for better OS: 58% (42–74%) vs 33% (18–47%), $p = 0.06$ (Fig. 2b). They were also younger (median 25 vs 29 years, $p = 0.035$), were transplanted earlier (2011 vs 2014, $p = 0.006$), more often with MAC (76 vs 49%; $p = 0.025$) and from CMV negative donor (60 vs 29%; $p = 0.014$). Remission status prior to allo-HSCT was reported for only 45% of patients. Half (50%) of primary HLH patients were transplanted in partial remission (or less), whereas in secondary HLH it was 85% ($p = 0.03$).

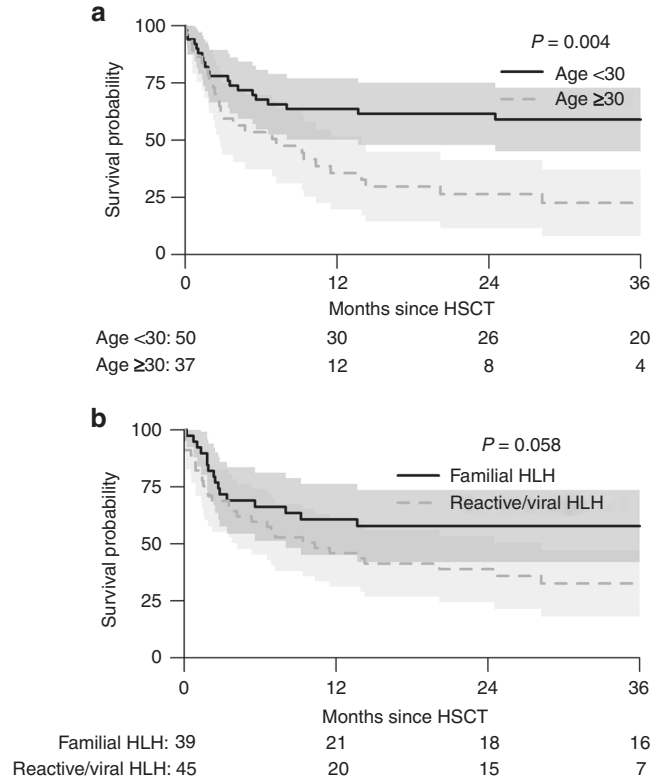

Fig. 2 Overall survival of adult HLH patietns undergoing allogeneic hematopoietic stem cell transplantation. a Patients above and below the median age. **b** Patients with familial or reactive/viral HLH.

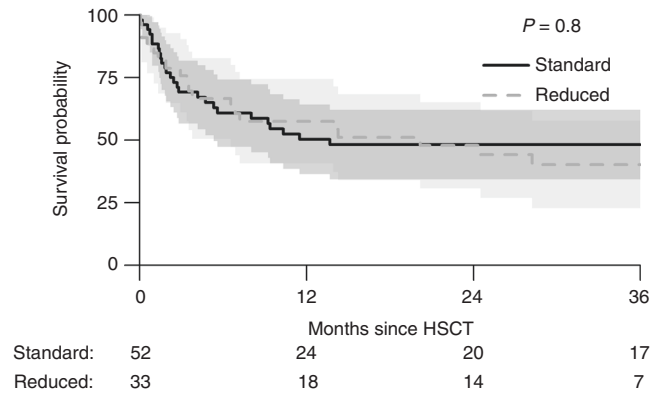

Fig. 3 Overall survival of patients by the conditioning intensity. Patients were undergoing myeloablative (MAC; standard) or reduced intensity (RIC) conditioning.

Negative patient (not donor) CMV serostatus was associated with a better prognosis: OS of 71% (50–93%) vs 39% (27–52%; $p = 0.016$) by 36 months, which is reflected in a lower NRM: 6% (0–16%) vs 42% (30–55%; $p = 0.007$), while the relapse rate was similar. The choice of donor––matched related or matched unrelated––did not significantly affect survival. Stem cell source, year of transplant and diagnosis-transplant interval did not affect any of the analyzed outcomes. Detailed information is presented in Table 2.

RIC vs MAC

Reduced intensity conditioning (RIC) was associated with an identical prognosis as myeloablative regimens (MAC) (Fig. 3). In order to verify if this finding may be attributed to the differences in baseline characteristics between the two groups, a comparison of all parameters included in Table 2 was performed. It revealed only the difference in HLH type (RIC in 24% of familial HLH and 15% of reactive/viral HLH; $p = 0.025$). Additionally, a non-significant higher NRM in MAC 40% (26–53%) vs 29% (13–44%; $p = 0.3$) was accompanied by a trend for a higher relapse rate in RIC: 30% (15–46%) vs 14% in MAC (4–24%; $p = 0.078$). No important differences could be found in all other potentially relevant variables, including: age, sex, CMV status, stem cell source, use of TBI or etoposide.

Questionnaires

All main findings described above are based on the general transplant data from standard EBMT databases. Additionally, for 33 patients results of an HLH-oriented questionnaire were obtained. Comparison between patients with and without questionnaire data did not reveal any important differences (Supplementary Table 1). Questionnaire data confirmed a clinical picture typical for HLH at the diagnosis: fever in 97% (31/32), splenomegaly in 97% (28/29), hemophagocytosis in 87% (26/30) and hyperferritinemia in 90% (28/31) of the patients. The median ferritin concentration reached 6,100 ng/ml (range: 63-260,160). In the induction therapy most frequently used were steroids (84%; 27/32) and etoposide (78%; 25/32).

Ferritin concentration was fluctuating due to the transplant procedure: 1,160 ng/ml (13–105,000; $n = 29$) before conditioning, 4,020 at day 28 (270–15,170; $n = 18$) and finally at day 100 it lowered to 1,900 (195–406,140; $n = 20$). The percentage of patients with hemophagocytosis was gradually diminishing: 55% before conditioning (12/22), 16% (3/19) in the first biopsy after allo-HSCT and finally it was not found in any reported patient with a second bone marrow biopsy (0/10).

The most frequently mutated gene was *STXBP2*: in six out of 15 patients with test results available. Two patients had mutations in the *UNC13D* (2/15) and another two in *RAB27A* (2/9). One patient was transplanted due to the XLP2 syndrome. No mutations in the perforin gene (*PRF1*) were found (0/15).

DISCUSSION

We report data of the largest to date cohort of 87 adult patients who underwent allogeneic hematopoietic stem cell transplantation due to HLH. We confirm that allo-HSCT can provide a durable cure in this group (no relapses after 23 months from the procedure). The median survival of 13.9 months, three and five-year probability of survival of 44% are less encouraging than a 66% five-year probability of survival of transplant patients in both of the largest pediatric studies: HLH-94 [9] and HLH-2004 [10, 11]. Nevertheless, among 39 patients who survived at least 15 months–only three died. All relapses were fatal, with a 21% relapse rate. NRM of 36% was relatively high.

Age is the most important prognostic factor in allo-HSCT in HLH––in our cohort difference was found between the younger and older adults, in other studies children generally have better outcomes than adults. This effect was also present in a comparison of young adults and adolescents with children [35]. Interestingly, in that small group all 11 deaths were NRM. Furthermore, the largest pediatric studies HLH-94 [9] and HLH-2004 [10] also report a high proportion of treatment-related mortalities among causes of death: 66% and 48%, respectively. When second transplants were included in HLH-2004 data analysis, this rate rose to 54% [11].

Relatively high NRM in the analyzed group can be attributed to several factors. The time range of this analysis (since 1995) contributed to this result, as in recent decades NRM was reduced in all transplant recipients [36, 37]. The time of the analysis is also an important factor in pediatric HLH cohorts: a more recent pediatric report from Italy shows a 71% [38] 5-year probability of

survival (years 2000–2014), while in the CIBMTR data from 1989 to 2005 it was only 45% after three years [39]. Positive CMV serostatus is an example of an NRM cause, which generally decreased over the past years in transplant recipients, but still has a negative effect on survival [40, 41]. In our cohort, this effect was also observed for recipient (but not for donor) positive serostatus. Although CMV reactivation may potentially lead to have a potential towards HLH recurrence, CMV status did not affect relapse rate.

No difference observed between the reduced intensity (RIC) and myeloablative conditioning (MAC) outcomes is the most striking result of our analysis with important clinical implications. Based on initial pediatric results, RIC was considered a more promising approach, but our data confirm that MAC has therapeutic potential in adult HLH patients as well.

Unfortunately, this similar outcome is generally worse than results reported in children. The most visible difference is in RIC transplants, but we were not able to find a simple explanation for this finding. A trend for a higher relapse rate may have some contribution, as all relapses were fatal. On the other hand more patients with familial HLH, which had better prognosis, underwent RIC conditioning. A higher relapse risk in RIC (due to mixed chimerism) in children may be associated with a lower NRM than in MAC [13, 17]. Additionally, in children only 20–30% of donor chimerism was protective against HLH relapse [42]. Outcomes of the presented cohort (even though there was not enough chimerism data for analysis) show that abovementioned observations of pediatric RIC transplants do not transfer to adult patients to a degree that would visibly affect OS.

A report on 16 RIC (FluMel100) adult patients provided comparable outcomes: 49% survival at five years [25]. The higher median age in that group (42 years) is strongly counterbalanced by a short time to transplant from the diagnosis––the median of only 2.7 months. A group of 30 younger (adults and adolescents) MAC patients achieved a 63% two-year survival [24]. The same group of Prof. Zhao Wang reported results of 30 haploidentical transplant patients (MAC) with a three-year survival of 63% [26] in HLH triggered by EBV (the median age 32 years). CIBMTR retrospective data (2001–2012) of adult transplants in histiocytic conditions (37 HLH out of 47 patients) reports survival rate of 60% at one year (95% CI, 45–75) and 57% at two years (95% CI, 40–72) [27]. This very slight decrease between one and two-year survival probably reflects plateau in survival curve which was observed in Fig. 1 and supports observation that adult HLH patients can be cured with allo-HSCT.

On the other hand, the advantage of RIC outcomes in the pediatric population is not always present. Ness et al. report pediatric cohort from Israel with 86% OS at five years. There was no difference in survival, but MAC provided much better EFS (100% vs 72%, $p = 0.018$). Messina et al. [38] in an Italian cohort of over a hundred children described a tendency for a superior outcome of treosulfan-based MAC (initially described by Lehmberg et al. [33]) with 86% OS, while RIC resulted in only 62% survival. In our study, all patients who received treosulfan in conditioning survived. Yet, this is not a plausible explanation of the lack of difference between MAC and RIC, because this drug was used only on five patients (four MAC, one RIC).

RIC outcomes in the pediatric population are constantly optimized. RICHI approach (conditioning using fludarabine, melphalan and alemtuzumab) [13] was modified with addition of thiotepa what results in improving long-term stable engraftment [34]. Use of targeted busulfan (with fludarabine and alemtuzumab/ATG) is very promising with a 100% three-year overall and event free survival in 25 patients [18].

Data from the questionnaires confirmed a typical clinical picture of the analyzed HLH patients, and further strengthens the findings of this manuscript. Observations concerning diminishing percentage of hemophagocytosis and ferritinemia fluctuation are, to our best knowledge, shown for the first time in a large group of transplanted adult HLH patients. The increase in the ferritin concentration after allo-HSCT may be attributed to multiple transfusions. Additionally, around day 28 it is further raised by an acute phase response associated with infections, graft versus host disease and the engraftment syndrome. On day 100, these reactions are much more controlled, what lowers the hyperferritinemia.

In our adult patient cohort the most frequently reported mutations affected *STXBP2* gene (causing FHL 5). FHL 5 in some patients is associated with a milder phenotype [43], what supports our findings, as it enables its bearers to survive long enough to be transplanted as adults. Conversely, no mutations were found in the perforin gene (*PRF*), as an important impairment in its function would result in HLH presenting at a much earlier age.

The primary HLH was generally associated with a better survival, which is to some extent associated with a younger age, but also may be attributed to transplant indications. Many primary HLH patients had allo-HSCT performed in remission due to the genetic diagnosis. Patients with an equally good clinical outcome but without confirmed mutation would not be transplanted. This causes a higher proportion of patients in a worse clinical state (e.g. rescue transplant in no remission) outside the primary HLH group. Furthermore, a trend for a better prognosis of patients with confirmed (vs non-verified) familial HLH was also observed in the long term outcome analysis of the HLH-2004 study [10, 11].

Although the present study is the largest described group of adult patients undergoing allogeneic hematopoietic stem cell transplantation, our analysis has some intrinsic limitations due to its retrospective character. Analyses had to rely on facts reported by the centers (e.g. primary vs secondary HLH, remission status), without original data for verification. Reported chimerism data was very limited, preventing from analyzing this aspect. Genetic data was available only for 15 patients.

Conclusions from other, ideally prospective, studies are still needed to improve adult patients' prognosis––but provided low number of allo-HSCT in adult HLH this data has a high validity. Some of the pediatric data show very good results of RIC, but so far this approach did not show its full potential in adults. In turn, our study shows similar MAC outcomes in this group and gives an impulse for further development and optimization of both methods (e.g. use of treosulfan in MAC, low-dose busulfan in RIC).

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AUTHOR CONTRIBUTIONS

RM conceived and designed the study, analyzed and interpreted data, designed the questionnaire and drafted the manuscript, NK designed the study, analyzed and interpreted data and edited the manuscript, FS designed the questionnaire, provided clinical data and edited the manuscript, WWJ assisted with the study design and data interpretation and edited the manuscript, DJE and LdW performed statistical analyses and edited the manuscript, HJB performed data collection and edited the manuscript, CI, HE, XP, SvD, EN, JEJ, GK, MZ, RA, AG, JF, JLDM, FB, GMQ, SL, PSR, MT, PL, MC, MA, GE, KC, KH, KL, SS provided clinical data and edited the manuscript, AL, AG and IYA assisted with the study design and data interpretation and edited the manuscript.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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