ARTICLE

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Cytogenetic abnormalities predict survival after allogeneic hematopoietic stem cell transplantation for pediatric acute myeloid leukemia: a PDWP/EBMT study

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Poor-risk (PR) cytogenetic/molecular abnormalities generally direct pediatric patients with acute myeloid leukemia (AML) to allogeneic hematopoietic stem cell transplant (HSCT). We assessed the predictive value of cytogenetic risk classification at diagnosis with respect to post-HSCT outcomes in pediatric patients. Patients younger than 18 years at the time of their first allogeneic HSCT for AML in CR1 between 2005 and 2022 who were reported to the European Society for Blood and Marrow Transplantation registry were subgrouped into four categories. Of the 845 pediatric patients included in this study, 36% had an 11q23 abnormality, 24% had monosomy 7/del7q or monosomy 5/del5q, 24% had a complex or monosomal karyotype, and 16% had other PR cytogenetic abnormalities. In a multivariable model, 11q23 (hazard ratio [HR] = 0.66, $P = 0.03$) and other PR cytogenetic abnormalities (HR = 0.55, $P = 0.02$) were associated with significantly better overall survival when compared with monosomy 7/del7q or monosomy 5/del5q. Patients with other PR cytogenetic abnormalities had a lower risk of disease relapse after HSCT (HR = 0.49, $P = 0.01$) and, hence, better leukemia-free survival (HR = 0.55, $P = 0.01$). Therefore, we conclude that PR cytogenetic abnormalities at diagnosis predict overall survival after HSCT for AML in pediatric patients.

Bone Marrow Transplantation (2024) 59:451–458; https://doi.org/10.1038/s41409-024-02197-3

INTRODUCTION

Advances in risk stratification, therapy intensification, and supportive care have all contributed to improving the outcomes for children with acute myeloid leukemia (AML) [1]. Genetic/molecular features such as fusion genes and molecular aberrations of the leukemic cells, as well as the response to induction therapy, play a major role in determining which patients are at highest risk of relapse with conventional chemotherapy [2, 3]. Although the overall survival (OS) of children with AML has improved over the past few decades, only 70% of these children become long-term survivors [1]. For children with high-risk AML (HR-AML), defined by a combination of poor-risk (PR) cytogenetic/molecular abnormalities or an inadequate response to chemotherapy as assessed by measurable residual disease (MRD), outcomes are inferior, with an

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Received: 29 October 2023 Revised: 14 December 2023 Accepted: 2 January 2024
Published online: 15 January 2024

OS of less than 50% [4]. Although an allogeneic hematopoietic stem cell transplant (HSCT) is generally recommended for patients with HR-AML with PR cytogenetics/molecular abnormalities in first complete remission (CR1) [1], it is unknown whether these cytogenetic and molecular features retain their prognostic value after HSCT. The success of an allogeneic HSCT largely depends on the graft-versus-leukemia (GVL) effect mediated by the alloreactive immune system derived from the graft, which is distinct from the cytolytic and cytostatic effects of antileukemic drugs. Additionally, AML with PR cytogenetics is a heterogeneous category that includes several distinct cytogenetic abnormalities. As a group, patients with PR cytogenetics may not benefit from HSCT or, alternatively, specific subgroups may benefit and others may not [5–8]. In this study, we evaluated whether the specific cytogenetic abnormalities present at the diagnosis of AML were predictive of post-HSCT outcomes in pediatric patients with HR-AML.

METHODS

Study design and patients

This retrospective study was conducted using the data reported to the Pediatric Diseases Working Party (PDWP) of the European Society for Blood and Marrow Transplantation (EBMT) registry by 150 participating centers in 38 countries. The EBMT is a nonprofit medical and scientific organization representing more than 600 transplant centers, mainly located in Europe. Centers commit to reporting all consecutive HSCTs and follow-up data once a year. Data are entered, managed, and maintained in a central database and are validated by verification of the computer printout of the entered data. All patients gave informed consent to the use of their personal information for research purposes. This study was approved by the PDWP of the EBMT institutional review board and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Eligible patients were younger than 18 years at the time of HSCT for AML, had received their first allogeneic HSCT in CR1 between January 1, 2005, and December 31, 2022, and had a recorded cytogenetic assessment at diagnosis. Cytogenetic abnormalities considered as PR were monosomy 7, del(7q), monosomy 5, del(5q), 11q23 abnormalities excluding t(9;11), t(8;16), 12p13 abnormalities, del(12p), t(9;22), t(6;9), inv(3), t(3;5), t(16;21), and 11p15 abnormalities [5, 9–13]. Patients characterized by t(9;11), t(8;21), t(15;17), inv(16), or t(16;16) were excluded from this analysis as they were considered to have intermediate-risk or favorable-risk cytogenetic abnormalities.

Assignment to risk groups

Patients were assigned to one of the following subgroups according to their cytogenetic assessment at diagnosis: (a) patients with monosomy 7/del7q or monosomy 5/del5q, irrespective of the presence of any other cytogenetic abnormality; (b) patients with 11q23 abnormalities; (c) patients with a complex or monosomal karyotype; and (d) patients with other PR cytogenetic abnormalities. A complex karyotype was defined as one with three or more structural abnormalities. A monosomal karyotype was defined as a monosomy with one or more structural abnormalities or two or more autosomal monosomies. The subgroup for patients with other PR cytogenetic abnormalities included those with t(6;9), t(3;5), t(9;22), t(8;16), inv(3) or t(3;3), t(16;21), abn(11p15), or del(12p) or abn(12p13).

Statistical analysis

Qualitative variables are reported as frequencies and percentages. Quantitative variables are reported as the median, quartile 1 and quartile 3, or minimum and maximum values. The difference in the distribution of qualitative or quantitative variables among the cytogenetic groups was evaluated with chi-square tests or Fisher exact tests and with Kruskal–Wallis tests, respectively.

The primary endpoint of the study was OS, defined as the time from HSCT to death. Secondary endpoints were the leukemia-free survival (LFS), defined as the time from HSCT to relapse or death, whichever occurred first, and the relapse incidence and non-relapse mortality (NRM), defined, respectively, as the time from HSCT to relapse and the time from HSCT to death without relapse. Other secondary endpoints were the incidence of grade II–IV and grade III or IV acute graft-versus-host disease (GVHD) and the incidence of chronic GVHD. Finally, the GVHD-free relapse-free survival (GRFS) was estimated, defined as the time from HSCT to the first occurrence of grade III or IV acute GVHD, extensive chronic GVHD, relapse, or death. All of the outcomes were censored at last follow-up. OS, LFS, and GRFS curves were estimated by the Kaplan–Meier method. The cumulative incidence function was used to estimate outcomes with competing events. NRM and relapse were mutually competing events. Relapse and death were competing events for acute and chronic GVHD. Median follow-up was estimated using the reverse Kaplan–Meier method. Because of the shorter median follow-up time in one group, outcomes were censored at 3 years. Multivariable analyses were performed by fitting Cox regression models, and they included clinically relevant variables, including cytogenetic subgroup, age at HSCT, donor type, whether the HSCT was from a female donor to a male recipient, patient/donor CMV status, time from AML diagnosis to HSCT, and year of HSCT. Center effect was taken into account as frailty. Point estimates of the outcomes and hazard ratio (HR) are given with their 95% confidence intervals (CIs). Two-sided P values less than 0.05 were considered to indicate statistical significance. Analyses were performed using R software version 4.0.2.

RESULTS

Patient characteristics

We included 845 pediatric patients from 150 participating centers in this study. Three hundred and sixty (42.7%) of the HSCT recipients were female. The median age at HSCT was 8.6 years (inter-quartile range [IQR]: 2.5–13.8 years), and the median follow-up after HSCT was 4.1 years (95% confidence interval [CI]: 3.7–4.5). Three hundred and four patients (36.0%) had 11q23 abnormalities, 199 (23.6%) had monosomy 7/del7q or monosomy 5/del5q, 207 (24.5%) had a complex or monosomal karyotype, and 135 (16.0%) had other PR cytogenetic abnormalities. Only 62 patients (7.3%) had secondary AML. Table 1 and the Supplemental Tables present the clinical characteristics of these 845 patients, stratified by the different subgroups. Pre-HSCT MRD data were available for 413 patients (48.9% of the total), 352 (85.2%) of whom were MRD negative at the time of HSCT. Patients received grafts from a matched related donor ($n = 222$, 26.3%), a mismatched related donor ($n = 102$, 12.1%), an unrelated donor ($n = 385$, 45.6%), or an unrelated cord blood donor ($n = 136$, 16.1%). Four hundred and sixty patients (54.4%) received bone marrow, 249 (29.5%) received peripheral blood–derived stem cells, and the rest ($n = 136$, 16.1%) received cord blood as the stem cell source. Myeloablative conditioning was used in 820 patients (97.0%). Any regimens containing intravenous Busulfan greater than 9.6 mg/kg or oral Busulfan greater than 12 mg/kg, total body irradiation greater than 8 Gy, or any Treosulfan containing regimens were considered as myeloablative.

Survival and GVHD

The 2-year OS and LFS for the entire cohort were 75.3% (95% CI: 72–78.3%) and 67.9% (95% CI: 64.4–71.1%), respectively (Table 2). The cumulative incidence of relapse was 23.5% (95% CI: 20.5–26.7%) and the incidence of NRM was 8.6% (95% CI: 6.7–10.7%) at 2 years after HSCT. In this cohort, 9.5% of the patients (95% CI: 7.6–11.7%) experienced grade III or IV acute GVHD within the first 100 days after HSCT and 6.7% (95% CI: 5–8.7%) experienced extensive chronic GVHD within the first 2 years after HSCT. The 2-year GVHD-free relapse-free survival (GRFS) was 57.3% (95% CI: 53.6–60.8%). Kaplan–Meier survival curves describing the OS and LFS and cumulative incidence curves showing the relapse incidence and NRM are shown in Fig. 1.

Effect of cytogenetic risk on post-transplant outcomes

In a multivariable model (Table 3), 11q23 (HR = 0.66 [95% CI: 0.44–0.97], $P = 0.03$) and other PR cytogenetic abnormalities (HR = 0.55 [95% CI: 0.33–0.91], $P = 0.02$) were associated with significantly better OS when compared with monosomy 7/del7q and monosomy 5/del5q. OS was not significantly different for the complex/monosomal karyotype group (HR = 0.98 [95% CI: 0.66–1.46], $P = 0.94$). There were no significant differences in NRM among the four subgroups (HR = 0.86 [95% CI: 0.45–1.66], $P = 0.66$; HR = 0.96

Table 1. Demographics and patient characteristics.

Variable	Modality	No. of patients ($N = 845$)	del(7/7q) and/or del(5/5q) ($N = 199$)	Complex/ monosomal ($N = 207$)	Abn 11q23 excluding t(9;11) and without del(7/7q) or del(5/5q) ($N = 304$)	Other poor-risk abnormalities ($N = 135$)	*P*
Age at diagnosis (years)	Median [IQR]	8.2 [2.1–13.4]	10 [5.1–14.2]	6.6 [2–13.1]	4.6 [1–12.7]	11.1 [6.2–14.2]	<0.001
Patient sex	Female	360 (42.7%)	83 (41.7%)	86 (41.7%)	126 (41.4%)	65 (48.1%)	0.57
	Male	484 (57.3%)	116 (58.3%)	120 (58.3%)	178 (58.6%)	70 (51.9%)	
Time from diagnosis to HSCT (months)	Median [IQR]	4.6 [3.8–5.6]	4.5 [3.7–5.3]	4.9 [3.9–6]	4.5 [3.8–5.5]	4.7 [3.9–5.5]	0.07
Age at HSCT (years)	Median [IQR]	8.6 [2.5–13.8]	10.4 [5.6–14.5]	7.3 [2.4–13.6]	5 [1.4–13.1]	11.5 [6.7–14.6]	<0.001
Age at HSCT (categorical)	0–4 years	285 (33.7%)	42 (21.1%)	77 (37.2%)	143 (47%)	23 (17%)	<0.001
	4–12 years	258 (30.5%)	74 (37.2%)	62 (30%)	74 (24.3%)	48 (35.6%)	
	12–18 years	302 (35.7%)	83 (41.7%)	68 (32.9%)	87 (28.6%)	64 (47.4%)	
Lansky performance score	<90	128 (16.6%)	32 (18.4%)	31 (16.5%)	42 (14.9%)	23 (18.4%)	0.73
	≥90	641 (83.4%)	142 (81.6%)	157 (83.5%)	240 (85.1%)	102 (81.6%)	
	Missing	76	25	19	22	10	
Molecular remission at HSCT	No	61 (14.8%)	12 (17.4%)	11 (11.2%)	19 (11.3%)	19 (24.4%)	0.03
	Yes	352 (85.2%)	57 (82.6%)	87 (88.8%)	149 (88.7%)	59 (75.6%)	
	Missing	432	130	109	136	57	
Donor type	Matched related donor	222 (26.3%)	45 (22.6%)	59 (28.5%)	86 (28.3%)	32 (23.7%)	0.12
	Mismatched relative	102 (12.1%)	30 (15.1%)	28 (13.5%)	31 (10.2%)	13 (9.6%)	
	Unrelated donor	385 (45.6%)	101 (50.8%)	91 (44%)	127 (41.8%)	66 (48.9%)	
	UCB	136 (16.1%)	23 (11.6%)	29 (14%)	60 (19.7%)	24 (17.8%)	
Donor sex	Female	328 (40%)	76 (39.4%)	81 (40.1%)	122 (41.1%)	49 (38%)	0.94
	Male	493 (60%)	117 (60.6%)	121 (59.9%)	175 (58.9%)	80 (62%)	
	Missing	24	6	5	7	6	
Graft source	Bone marrow	460 (54.4%)	103 (51.8%)	116 (56%)	168 (55.3%)	73 (54.1%)	Not tested
	Peripheral blood	249 (29.5%)	73 (36.7%)	62 (30%)	76 (25%)	38 (28.1%)	
	Cord blood	118 (14%)	20 (10.1%)	28 (13.5%)	50 (16.4%)	20 (14.8%)	
	Double cord blood units	18 (2.1%)	3 (1.5%)	1 (0.5%)	10 (3.3%)	4 (3%)	
Female donor to male recipient	No	644 (77.5%)	150 (76.9%)	160 (78.4%)	228 (76.3%)	106 (79.7%)	0.86
	Yes	187 (22.5%)	45 (23.1%)	44 (21.6%)	71 (23.7%)	27 (20.3%)	
	Missing	14	4	3	5	2	
Patient CMV serostatus	Negative	319 (38.9%)	70 (36.8%)	68 (33.8%)	119 (39.8%)	62 (47.3%)	0.09
	Positive	502 (61.1%)	120 (63.2%)	133 (66.2%)	180 (60.2%)	69 (52.7%)	
	Missing	24	9	6	5	4	
Donor CMV serostatus	Negative	402 (50.1%)	93 (48.7%)	84 (42.6%)	154 (53.3%)	71 (56.3%)	0.053
	Positive	401 (49.9%)	98 (51.3%)	113 (57.4%)	135 (46.7%)	55 (43.7%)	
	Missing	42	8	10	15	9	
CMV serostatus (donor to patient)	Negative to negative	215 (27.3%)	47 (25.4%)	41 (21%)	84 (29.6%)	43 (34.7%)	0.24
	Negative to positive	177 (22.5%)	41 (22.2%)	42 (21.5%)	67 (23.6%)	27 (21.8%)	
	Positive to negative	88 (11.2%)	20 (10.8%)	23 (11.8%)	30 (10.6%)	15 (12.1%)	
	Positive to positive	308 (39.1%)	77 (41.6%)	89 (45.6%)	103 (36.3%)	39 (31.5%)	
	Missing	57	14	12	20	11	
Conditioning intensity	Reduced intensity	24 (2.8%)	9 (4.5%)	3 (1.4%)	11 (3.6%)	1 (0.7%)	0.1
	Myeloablative conditioning	820 (97.2%)	190 (95.5%)	204 (98.6%)	293 (96.4%)	133 (99.3%)	
	Missing	1	0	0	0	1	

Table 2. Overall survival, non-relapse mortality, relapse incidence, leukemia-free survival, GVHD-free relapse-free survival, and acute and chronic GVHD incidence for the entire cohort and various subgroups.

Outcomes	All patients	del(7/7q) and/or del(5/5q)	Complex/monosomal	Abn 11q23 excluding t(9;11) and without del(7/7q) or del(5/5q)	Other poor-risk abnormalities
Median follow-up (in years)	4.1 (3.7–4.5)	4.1 (3–4.7)	3.5 (3–4.3)	4.5 (4–4.9)	4.7 (3.3–5.1)
Overall survival (at 2 years)	75.3 (72–78.3)	67.9 (60.1–74.6)	72.5 (65.2–78.4)	79.2 (73.8–83.7)	81.5 (72.9–87.6)
Non-relapse mortality (at 2 years)	8.6 (6.7–10.7)	10.3 (6.3–15.4)	8.9 (5.3–13.4)	7.6 (4.9–11)	8.2 (4.2–14)
Relapse incidence (at 2 years)	23.5 (20.5–26.7)	27.8 (21.3–34.7)	23.6 (17.7–30)	23.3 (18.4–28.5)	17.6 (11.2–25.2)
Leukemia-free survival (at 2 years)	67.9 (64.4–71.1)	61.9 (54.1–68.8)	67.6 (60.3–73.8)	69.2 (63.3–74.3)	74.2 (65.1–81.3)
GVHD-free relapse-free survival (at 2 years)	57.3 (53.6–60.8)	49.3 (41.4–56.7)	56.8 (49.2–63.6)	61.2 (55–66.8)	61.2 (51.7–69.5)
Acute GVHD grade II–IV (by 100 days)	28.4 (25.4–31.6)	31.9 (25.4–38.6)	32.7 (26.2–39.2)	24.8 (20–29.8)	25.2 (18.1–32.9)
Acute GVHD grade III or IV (by 100 days)	9.5 (7.6–11.7)	11 (7.1–15.9)	13.1 (8.8–18.2)	5 (2.9–7.9)	12.2 (7.3–18.5)
Chronic GVHD (by 2 years)	16.3 (13.6–19.1)	21.8 (15.7–28.6)	14 (9.3–19.7)	12.7 (8.9–17.1)	20 (13–28)
Extensive chronic GVHD (by 2 years)	6.7 (5–8.7)	8.2 (4.6–13.1)	4.7 (2.2–8.6)	6.4 (3.8–9.8)	8.1 (3.9–14.1)

All values except for follow-up time are percentages. Ranges are shown in parentheses.

[95% CI: 0.48–1.94], $P = 0.92$; and HR = 0.73 [95% CI: 0.33–1.65], $P = 0.46$, for the 11q23, complex/monosomal, and other PR cytogenetics subgroups, respectively) when compared with the monosomy 7/del7q or monosomy 5/del5q subgroup. Other PR cytogenetic abnormalities were associated with a lower risk of disease relapse after HSCT (HR = 0.49 [95% CI: 0.28–0.86], $P = 0.01$), whereas the risk of disease relapse was not significantly different for the other groups when compared with the monosomy 7/del7q or monosomy 5/del5q subgroup (HR = 0.78 [95% CI: 0.52–1.16], $P = 0.22$, and HR = 1.0 [95% CI: 0.65–1.53], $P = 1.0$, for the 11q23 abnormality group and the complex/monosomal karyotype group, respectively). Accordingly, LFS was significantly better for the other PR cytogenetic risk group (HR = 0.55 [95% CI: 0.35–0.87], $P = 0.01$) but not significantly different for the two other groups when compared with the monosomy 7/del7q or monosomy 5/del5q subgroup (HR = 0.79 [95% CI: 0.56–1.12], $P = 0.19$, and HR = 0.97 [95% CI: 0.67–1.39], $P = 0.86$, for the 11q23 and complex/monosomal subgroups, respectively).

Receiving an HSCT from an unrelated donor, as opposed to a matched related donor, was associated with lower relapse incidence (HR = 0.66 [95% CI: 0.45–0.98], $P = 0.04$), whereas this was not significantly different for the two other groups (HR = 0.86 [95% CI: 0.51–1.46], $P = 0.58$, and HR = 1.10 [95% CI: 0.68–1.79], $P = 0.7$, for mismatched related and cord blood recipients, respectively). Lastly, older age at HSCT (12–18 years) was associated with the highest risk of NRM (HR = 2.23 [95% CI: 1.16–4.30], $P = 0.02$) and with worse OS (HR = 1.63 [95% CI: 1.14–2.35], $P < 0.01$) as compared to that of younger patients (aged 4–12 years). NRM and OS were not significantly different when very young patients (aged 0–4 years) were compared with the group aged 4–12 years (HR = 1.46 [95% CI: 0.71–3.00], $P = 0.30$, and HR = 1.10 [95% CI: 0.73–1.65], $P = 0.66$, respectively).

DISCUSSION

Allogeneic HSCT is the cornerstone of therapy for pediatric patients with AML who have adverse cytogenetic abnormalities, and it offers the best chance of long-term survival. However, the current literature lacks detail on the impact of cytogenetic abnormalities on post-HSCT outcomes in this population. Cytogenetic abnormalities remain the strongest predictors of outcomes for patients with newly diagnosed AML, but the literature on whether these abnormalities predict survival and relapse after HSCT is contradictory. Whereas some studies suggest that cytogenetic features continue to predict outcomes for adult patients with AML after HSCT [14–18], others have inferred that these abnormalities have no prognostic significance after HSCT [19, 20]. In this large cohort of pediatric HSCT recipients, we found that cytogenetic abnormalities remained highly predictive of outcomes even after HSCT for AML in CR1. Whereas monosomy 7/del7q or monosomy 5/del5q conferred a poor prognosis even after HSCT, 11q23 abnormalities and other PR cytogenetic abnormalities predicted a more favorable outcome. Patients with other PR cytogenetic abnormalities had a decreased incidence of relapse, leading to improved survival after HSCT.

Even though the relapse incidence was not significantly different to that of the monosomy 7/del7q or monosomy 5/del5q and complex or monosomal karyotype risk groups for patients with 11q23 abnormalities, OS was better for the latter group. This finding suggests that AML with 11q23 abnormalities is a heterogeneous disease, with some fusions and abnormalities being associated with a more favorable prognosis than others, such that the overall effect appears variable [5, 8]. Although HSCT continues to be recommended for patients with HR-AML and is often attempted for patients whose disease does not respond to traditional chemotherapy, the GVL effect of allogeneic HSCT might be insufficient to overcome the chemoresistance of the myeloblasts. Given the risk of NRM, short-term morbidity, and late

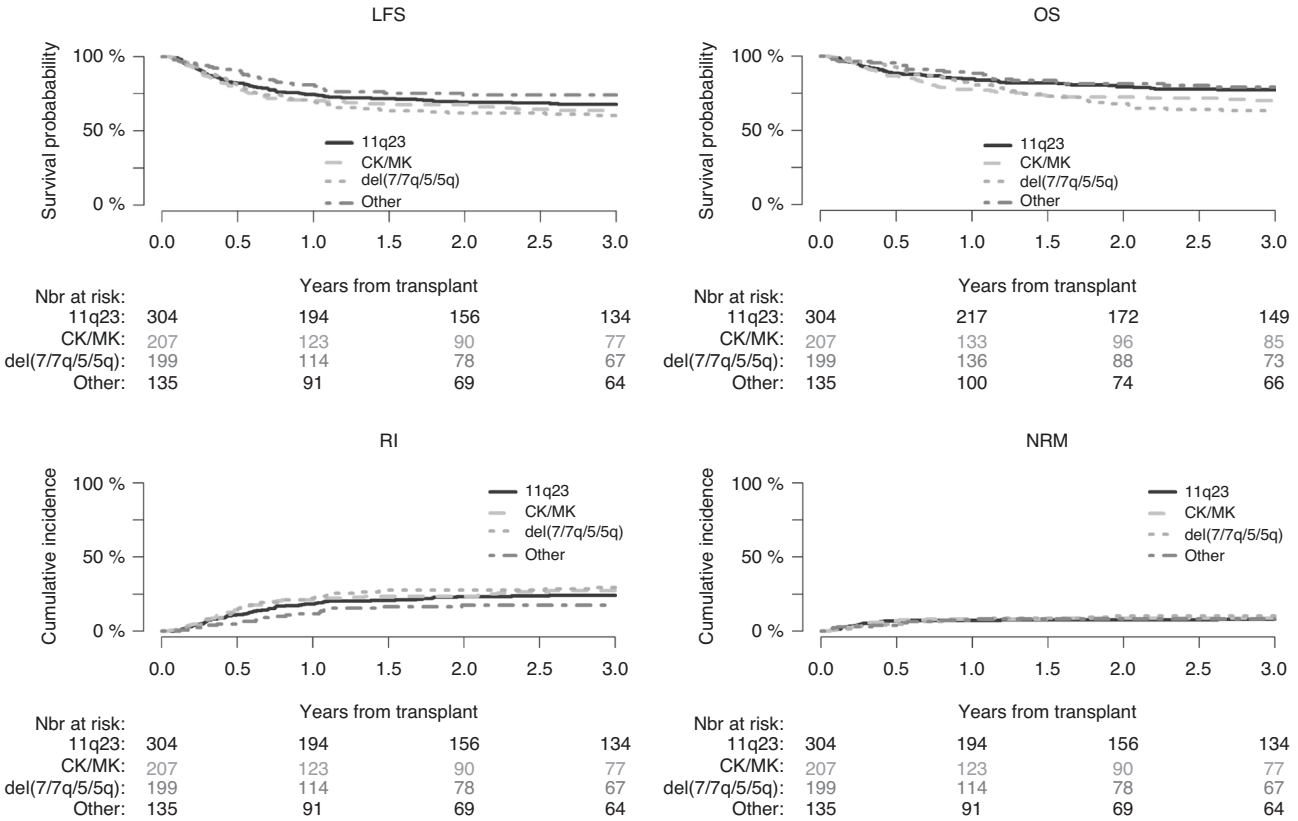

Fig. 1 Survival curves. Kaplan–Meier curves showing leukemia-free survival (LFS, top left) and overall survival (OS, top right), and cumulative incidence curves showing relapse incidence (RI, bottom left) and non-relapse mortality (NRM, bottom right), with stratification by cytogenetic subgroup. CK/MK: complex or monosomal karyotype.

effects, the role of HSCT in CR1 for some children with HR-AML requires further investigation [5–8].

We noted a statistically significant protective effect of transplants from unrelated donors, as compared with those from matched related donors, with respect to reducing the relapse incidence. The hazard ratio for the relapse incidence for recipients of transplants from mismatched related donors was favorable, but did not meet statistical significance. Advances in high-resolution human leukocyte antigen (HLA) typing, GVHD prophylaxis, and improved supportive care have expanded the use of alternative donors. Recent studies have shown comparable outcomes after allogeneic HSCT from matched unrelated and HLA-identical sibling donors [21–24]. Haploidentical-donor HSCT approaches using post-transplant cyclophosphamide and selective alpha/beta T-cell depletion of the graft have reportedly resulted in OS and LFS on par with those after HLA-matched transplants in retrospective studies, with haploidentical approaches being associated with lower rates of severe acute and chronic GVHD [25–29]. Prospective randomized evaluation of haploidentical donor HSCT to MUD HSCT is ongoing in a Children's Oncology Group clinical trial (ASCT2031, NCT05457556). Our data suggest that grafts from alternative donors exert a greater immunotherapeutic effect than those from matched related donors as they provide an opportunity to leverage the alloreactivity after HSCT to target refractory leukemias. This observation should however be confirmed in larger prospective studies. Relapse remains the most common cause of treatment failure in this population, and the benefit of the GVL effect must be optimized to improve outcomes.

Limitations

This study had several limitations. First, it was a retrospective analysis and some data were missing, with information on pre- and post-HSCT chemotherapy being unavailable. Also missing was information on specific gene aberrations, such as those in *FLT3*, *NPM1*, *CEBPA*, and *TP53*, which are clearly prognostically heterogeneous [30–32]. By adjusting for the time from diagnosis to HSCT, we tried to avoid the potential bias of selecting patients who had undergone fewer induction cycles than others. We further included patients based on their cytogenetic abnormalities, irrespective of whether they had de novo, therapy-related, or secondary AML. Given that they historically have had a poor prognosis [33], patients with therapy-related, or secondary AML are often excluded from studies of this type. Monosomy 7/del7q or monosomy 5/del5q subgroup was relatively enriched for these patients with secondary AML and might have driven the poor outcomes in this subgroup. Third, we focused exclusively on patients in CR1 who proceeded to consolidative HSCT. Patients with PR cytogenetics with an early relapse or toxicity that precluded HSCT were excluded. Fourth, pre-HSCT MRD data were available for only half of the patients since this data is not collected mandatorily in the registry. Poor response to induction chemotherapy could have skewed the results of this study in a way unrelated to the cytogenetic risk category. Interestingly, however, despite the fact that many more patients in the other PR cytogenetic abnormality subgroup (almost 24%, as compared with just 11%–17% in the 11q23 abnormality, monosomy 7/del7q or monosomy 5/del5q, and complex or monosomal karyotype risk groups) were not in molecular remission at the time of HSCT, patients with other PR cytogenetic abnormalities had the best outcomes. Lastly, as most patients had received a myeloablative conditioning regimen, we could not explore the effect of different conditioning intensities on outcomes. However, a retrospective study has shown that relapse rates are not higher after reduced-intensity regimens, as compared with myeloablative regimens, and that myeloablative regimens are not associated with

Table 3. Multivariable analysis showing hazard ratios of various variables included in the model for post-allogeneic HSCT outcomes.

Variable	Modality	Overall survival		Non-relapse mortality		Relapse incidence		Leukemia-free survival	
		HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Poor-risk abnormality group	Monosomy 7/del7q or monosomy 5/del5q	1		1		1		1	
	11q23 abnormalities	0.66 (0.44–0.97)	**0.03**	0.86 (0.45–1.66)	0.66	0.78 (0.52–1.16)	0.22	0.79 (0.56–1.12)	0.19
	Complex/monosomal karyotype	0.98 (0.66–1.46)	0.94	0.96 (0.48–1.94)	0.92	1.00 (0.65–1.53)	1	0.97 (0.67–1.39)	0.86
	Other poor-risk abnormalities	0.55 (0.33–0.91)	**0.02**	0.73 (0.33–1.65)	0.46	0.49 (0.28–0.86)	**0.01**	0.55 (0.35–0.87)	**0.01**
Age at HSCT	4–12 years	1		1		1		1	
	0–4 years	1.10 (0.73–1.65)	0.66	1.46 (0.71–3.00)	0.3	0.86 (0.58–1.28)	0.45	0.96 (0.68–1.36)	0.83
	12–18 years	1.63 (1.14–2.35)	**0.008**	2.23 (1.16–4.30)	**0.02**	1.00 (0.69–1.44)	0.99	1.23 (0.90–1.69)	0.19
Donor type	Matched related	1		1		1		1	
	Unrelated donor	0.84 (0.58–1.22)	0.36	1.20 (0.62–2.31)	0.59	0.66 (0.45–0.98)	**0.04**	0.78 (0.56–1.10)	0.15
	Mismatched related	0.82 (0.49–1.39)	0.46	0.97 (0.38–2.45)	0.95	0.86 (0.51–1.46)	0.58	0.89 (0.56–1.39)	0.6
	Umbilical cord blood	1.13 (0.69–1.83)	0.63	1.29 (0.56–2.97)	0.55	1.10 (0.68–1.79)	0.7	1.14 (0.75–1.73)	0.54
CMV serostatus	Negative donor to negative recipient	1		1		1		1	
	Negative donor to positive recipient	0.91 (0.60–1.38)	0.66	1.41 (0.73–2.73)	0.31	0.79 (0.50–1.24)	0.31	0.93 (0.64–1.35)	0.71
	Positive donor to negative recipient	0.98 (0.59–1.62)	0.94	1.40 (0.64–3.09)	0.4	0.88 (0.50–1.53)	0.64	1.01 (0.64–1.59)	0.96
	Positive donor to positive recipient	0.90 (0.62–1.31)	0.57	0.86 (0.44–1.7)	0.67	1.07 (0.73–1.57)	0.73	0.99 (0.71–1.39)	0.97
Female donor to male recipient	No	1		1		1		1	
	Yes	0.95 (0.67–1.35)	0.77	1.11 (0.63–1.97)	0.72	1.00 (0.70–1.43)	1	1.04 (0.77–1.41)	0.8
Diagnosis to HSCT (effect for 3-month increment)		0.95 (0.77–1.17)	0.62	1.00 (0.70–1.41)	0.98	0.87 (0.69–1.09)	0.22	0.89 (0.74–1.08)	0.25
Year of HSCT (effect for 5-year increment)		1.00 (0.83–1.20)	0.96	0.92 (0.69–1.24)	0.58	1.04 (0.86–1.26)	0.69	1.01 (0.86–1.18)	0.94

Statistically significant *P* values are in bold.

higher transplant-related mortality when compared with reduced-intensity regimens in children with AML [34].

CONCLUSIONS

PR cytogenetic abnormalities at diagnosis remain predictive of OS after HSCT for AML in pediatric patients. Monosomy 7/del7q or monosomy 5/del5q, which overlapped with the therapy-related or secondary AML cohort, confer a poor prognosis even after HSCT, whereas 11q23 abnormalities and other PR cytogenetic abnormalities predict a more favorable outcome after HSCT. Our data also suggest that an HSCT from an unrelated donor offers greater protection against relapse than an HSCT from a matched related donor, but this observation requires further validation.

DATA AVAILABILITY

Deidentified dataset maybe shared upon request to the corresponding author.

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ACKNOWLEDGEMENTS

We would like to thank Keith A. Laycock, PhD, ELS for scientific editing of the manuscript. We would like to thank our colleagues, advanced practice providers, nurses, data managers and other healthcare professional who participated in patient care. We would also like to thank the parents who entrusted the care of our children to us. This work was supported by funds from the American Lebanese Syrian Associated Charities (ALSAC) (to Akshay Sharma).

AUTHOR CONTRIBUTIONS

AS, NSB and SVB conceptualized and designed the study, interpreted the results, wrote the first draft of the manuscript, and made revisions. J-EG and AD provided data management and performed statistical analysis. KK and SC oversaw the study and provided supervision. Several authors were involved in caring for the patients included in this study at their respective centers. All authors critically reviewed the manuscript, provided comments, and approved the final version.

COMPETING INTERESTS

AS has received consultant fees from Spotlight Therapeutics, Medexus Inc., Vertex Pharmaceuticals, Sangamo Therapeutics, and Editas Medicine. He is a medical monitor for an RCI BMT CSIDE clinical trial for which he receives financial compensation. He has also received research funding from CRISPR Therapeutics and honoraria from Vindico Medical Education. AS is the St. Jude Children's Research Hospital site principal investigator of clinical trials for genome editing of sickle cell disease sponsored by Vertex Pharmaceuticals/CRISPR Therapeutics (NCT03745287), Novartis Pharmaceuticals (NCT04443907), and Beam Therapeutics (NCT05456880). The industry sponsors provide funding for the clinical trial, which includes salary support paid to AS's institution. AS has no direct financial interest in these therapies.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41409-024-02197-3.

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