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RESEARCH ARTICLE

Hematopoietic stem cell transplantation for children with acute myeloid leukemia in second remission: A report from the Australasian Bone Marrow Transplant Recipient Registry and the Australian and New Zealand Children's Haematology Oncology Group

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Abstract

Background: Approximately one-third of children with acute myeloid leukemia (AML) relapse, requiring re-treatment and allogeneic hematopoietic stem cell transplantation (HSCT). Although achieving second complete remission (CR2) prior to HSCT is desirable, once CR2 is attained, it is unclear if there is any benefit from further chemotherapy prior to HSCT. Moreover, although pre-HSCT minimal residual disease (MRD) has prognostic value in acute lymphoblastic leukemia, the benefit of MRD reduction after achieving CR prior to HSCT is less clear for AML.

Procedure: To address these questions, we analyzed data from pediatric transplant centers in Australia and New Zealand concerning relapsed childhood AML cases occurring between 1998 and 2013. Given the retrospective nature of our analysis and assay data available, we analyzed patients on the basis of measurable residual disease (MeRD) by any methodology, rather than MRD in the conventional sense.

Results: We observed improved overall survival (OS) in children receiving two chemotherapy cycles, compared to one cycle or three or more cycles pre-HSCT. Improved OS with two cycles remained significant for patients without MeRD after cycle 1.

Abbreviations: ABMTRR, Australasian Bone Marrow Transplant Recipient Registry; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CBF, core binding factor; CR, complete remission; CR1, first complete remission; CR2, second complete remission; GVL, graft-versus-leukemia; HSCT, hematopoietic stem cell transplantation; MeRD, measurable residual disease; MRD, minimal residual disease; OS, overall survival.

Conclusions: These data suggest that a second chemotherapy cycle pre-HSCT may improve survival by lowering disease burden. Prospective trials assessing strategies to reduce pre-HSCT MRD in relapsed childhood AML are warranted.

KEYWORDS
AML, chemotherapy, MRD, pediatric, relapse, transplant

1 | INTRODUCTION

Optimization of therapy, including intensification, better risk stratification, and allocation to hematopoietic stem cell transplantation (HSCT), and improvements in supportive care have led to significant improvements in survival for children with acute myeloid leukemia (AML) in western countries including Australia in the last three decades.[1–3] Despite this, relapse occurs in one-third of patients and represents the most important contributor to mortality.[4] It is generally accepted that allogeneic HSCT affords patients with relapsed disease, the best chance of long-term cure.[4] Recently published analysis of relapsed childhood AML cases within the NOPHO-AML 93 and 2004 trials affirms that time from diagnosis to relapse is the strongest predictor of outcome for these patients, as well as confirming core binding factor (CBF) AML as an enduring favorable prognostic factor. They also demonstrated considerably worse prognosis for patients who relapsed following a HSCT performed in first complete remission (CR1), unsurprising as this is a subset enriched with high-risk patients who have already proven resistant to transplant conditioning and graft-versus-leukemia (GVL) effect.[5]

Data from predominantly adult AML cohorts indicate that the presence of minimal residual disease (MRD), as measured by flow cytometry or PCR, prior to allogeneic hematopoietic stem cell transplant (HSCT) is a robust prognostic marker, which independently predicts for increased risk of relapse posttransplant and shorter overall survival (OS) and disease-free survival.[6,7] However, in a pediatric setting, it has also been suggested that the dose effect of MRD pretransplant may not be as strong an influence on outcomes in AML as it is in acute lymphoblastic leukemia (ALL) and hence that attempts to reduce the level of MRD might be less beneficial in AML.[8] Furthermore, while outcomes for patients with ALL and morphological evidence of disease at the time of HSCT are dismal, a significant number of refractory AML patients can be salvaged by HSCT.[8,9] Moreover, once a patient has relapsed, the optimum number of cycles of chemotherapy prior to HSCT is unclear, particularly once second complete remission (CR2) has been achieved. In practice, the number of chemotherapy cycles is often influenced by the depth of response to the first re-induction cycle, patient performance status/co-morbidities, and logistical factors including donor and bed availability. With the available evidence for the prognostic significance of pretransplant MRD, it may appear desirable to aim for MRD negativity. However, ultimately the benefit of achieving this must be balanced with the potential toxicities of additional chemotherapy cycles. Furthermore, it has been demonstrated that in children with relapsed/refractory AML, there is reduced likelihood of achieving CR with each subsequent failed cycle,[10] and as this is a function of chemoresistance, one could hypothesize that this may also apply to achieving MRD negativity pre-HSCT.

In order to address the question of optimal management of pediatric patients with relapsed AML prior to HSCT, we conducted a retrospective study utilizing data collected by the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). Given the retrospective nature of our analysis and assay data available, we analyzed patients on the basis of measurable residual disease (MeRD), rather than MRD, which requires uniform methodology and definition thresholds (e.g., <0.1%).

2 | SUBJECTS AND METHODS

2.1 | Patients and data collection

The ABMTRR has an ethical approval to operate as a registry and its database captures most HSCT activity in Australia and New Zealand. Each treating center obtains patient consent for their clinical data to be transferred to the ABMTRR database.[11] Additional data from six of seven pediatric transplant centers with eligible patients were available for this study. Patients were aged up to 15 years and received an HSCT for AML in CR2 in a pediatric transplant center in Australia or New Zealand between 1998 and 2013. This included patients who relapsed following a CR1 allogeneic or autologous transplant.

Data entry was enabled through a customized study module made available via ASTRO software, which is a database management program written exclusively for the ABMTRR. Records were completed for 83 patients from a total of 87. Existing data available from ABMTRR records included recipient sex, age at transplant, HSCT number and type of previous HSCT (autologous/allogeneic), cell source, HLA match, donor relation, and date of diagnosis of AML. Additional data collected from the customized study module included main cytogenetic feature(s) at diagnosis of AML and at relapse, molecular abnormalities at diagnosis, relapse and after each cycle of chemotherapy, details of chemotherapy protocols used, and disease status achieved after each chemotherapy cycle.

Data were collected only for patients who proceeded to transplant in CR2 so that strict entry criteria were met and the dataset was internally consistent. Data for children who had relapsed and then achieved CR2, but did not proceeded to transplant, were not included primarily because they were not the focus of the study, but also because identification and data retrieval for these patients were beyond the scope

and feasibility of the study. Patients with refractory disease states pre-HSCT were also omitted from the analysis.

2.2 | Remission and MeRD criteria

Complete remission (CR) was defined as <5% blasts by morphological assessment and was determined by the individual participating institution. As MRD monitoring in AML is not yet standardized in clinical practice, the term MeRD in this study denotes "measurable residual disease," defined as the presence of any detectable disease below the resolution of cytomorphology by any method available at the treating institution, which included FISH, flow cytometry, and PCR. If these ancillary tests were not performed, or data were not recorded, the presence of MeRD was defined in terms of morphological blast percentage ≥5%. Patients with detectable MeRD by morphology (i.e., ≥5%) after a cycle of chemotherapy were only included in the final analysis if they were subsequently in morphological CR (<5%) at the time of HSCT.

2.3 | Statistical analysis

All statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) software Version 23 (IBM, Armonk, NY, USA). Differences in OS were assessed with the log-rank test and illustrated using Kaplan-Meier product limit estimates. Kaplan-Meier survival curves were produced using Stata software Version IC 15 (Statacorp, College Station, TX).

Univariate and multivariate Cox regressions were carried out to determine the effect of factors on OS and disease-free survival. The following factors were assessed in both univariate and multivariate settings: number of cycles of chemotherapy post relapse (one vs two vs three or more); transplant number (first/second); stem cell source (cord blood/marrow); HLA match (6/6, 5/6); sex (male/female); age (0-5/6-15); donor (related/unrelated); length of time from diagnosis to transplant (up to 1 year/more than 1 year); length of time from diagnosis to CR1 (up to 40 days/more than 40 days); length of time from CR1 to first relapse (up to 365 days/more than 365 days); CBF AML (inv(16) and t(8;21)); and year of HCT (1998-2006 / 2007-2013). The close-out date for this study was August 1, 2016 and was chosen so as to provide up to 3 years follow-up for the most recent transplants included in the study (those transplanted in 2013).

The principal focus of our analysis was to determine whether the number of cycles of chemotherapy administered prior to CR2 HSCT affected OS, and the extent to which this was dependent on MeRD status.

3 | RESULTS

3.1 | Patient characteristics

Complete survey module data were available for 83 children with AML transplanted in CR2 in Australia and New Zealand between 1998 and 2013. Selected characteristics at baseline and relapse are shown in

TABLE 1 Characteristics at baseline and relapse for patients undergoing HSCT in CR2

Characteristic	Category	*n*
N		83
Sex	Male	42 (51%)
	Female	41 (49%)
Age at transplant	0-4	28 (34%)
	5-9	23 (28%)
	10-15	32 (39%)
	Median age (range)	7 (0-15)
Transplant number	First	63 (76%)
	Second[a]	20 (24%)
Previous CR1 transplant type	Autologous	16 (19%)
	Allogeneic—sibling donor	4 (5%)
Cell source	Bone marrow	37 (45%)
	Cord blood including double	40 (48%)
	Peripheral blood	5 (6%)
	Marrow and cord blood	1 (1%)
HLA match (A, B, DR)	6/6 HLA match	50 (60%)
	5/6 HLA match	20 (24%)
	<5/6 HLA match	13 (16%)
Donor relation	Sibling	21 (25%)
	Other related	1 (1%)
	Unrelated	61 (73%)
Days from diagnosis to first relapse	Median (range)	341 (58-3408)
	≤365 days	46 (55%)
	>365 days	33 (40%)
	Not recorded	4 (5%)
Type of first relapse	Isolated bone marrow	68 (82%)
	Isolated extramedullary relapse	4 (5%)
	Combined marrow and extramedullary sites	6 (7%)
	Not specified/unknown	5 (6%)
Main cytogenetic feature(s) at diagnosis of AML (multiple responses allowed)		
	inv16 or t(16;16)	8 (10%)
	MLL (11q23) rearrangement	9 (11%)
	Any abnormality involving 12p	2 (2%)
	+8	5 (6%)
	−5	1 (1%)
	5q−	0 (0%)
	−7	1 (1%)
	Normal karyotype	18 (22%)
	Other abnormality	29 (35%)
Molecular abnormalities detected at diagnosis of AML	PML-RARA	3 (4%)

(Continues)

TABLE 1 (Continued)

Characteristic	Category	*n*
	RUNX1/RUNX1T1 (AML1/ETO) [t(8;21)]	2 (2%)
	CBFB/MYH11 [inv16 (p13q22)]	2 (2%)
	FLT3-ITD	0 (0%)
	FLT3-D835	2 (2%)
	CEBPA mutation	0 (0%)
	NPM1 mutation	0 (0%)
	Other	4 (5%)
Number of chemotherapy cycles administered prior to HSCT	One	25 (30%)
	Two	43 (52%)
	Three	9 (11%)
	Four	6 (7%)
Chemotherapy protocol used to induce first remission	North American protocols	
	COG CCG 2961	3 (4%)
	COG AALL03P1	1 (1%)
	COG AAML0531	19 (23%)
	COG AAML1031	4 (5%)
	European protocols	
	MRC UK AML12	11 (13%)
	MRC UK AML15	3 (4%)
	Australian-NZ protocols	
	ANZCCSG Study 1	11 (13%)
	ANZCCSG Study 2	13 (16%)
	Not specified	11 (13%)
	Other	7 (8%)

[a]First HSCT performed in CR1.

Table 1, whereas the MeRD status and path of each patient toward CR2 HSCT are shown in Figure 1.

3.2 | Re-induction chemotherapy

The majority of patients received high-dose cytarabine for their first and second cycles of chemotherapy at relapse (81% and 85%, respectively). High-dose cytarabine was most commonly used as part of FLAG-Ida (41% cycle 1, 10% cycle 2) or FLAG (16% cycle 1, 40% cycle 2) regimens. While 51% of patients received an anthracycline or anthracenedione (liposomal daunorubicin, idarubicin, or mitoxantrone) in cycle 1, only 9% received such agents during their second cycle, presumably due to cumulative anthracycline doses and the subsequent risk of cardiotoxicity. Patients received myeloablative conditioning regimens for transplant, except for a single patient (1%) who received reduced-intensity conditioning with fludarabine and melphalan (Table S2).

3.3 | Pre-HSCT chemotherapy, MeRD, and outcome

OS was first assessed after patients were stratified according to the number of cycles of chemotherapy received prior to HSCT. The 5-year OS probability of patients who had undergone two cycles of chemotherapy post relapse (73.3%) was significantly superior to that of patients who had one (46.5%) or three or more (40.0%), $P = .04$ (Figure 2). Just over half of the deaths in our cohort were due to relapse or progression of the disease. Other deaths were due to graft-versus-host disease, organ toxicity, infection, and other transplant-related causes (Table 2).

Next, we incorporated MeRD status to assess the impact it may have on these outcomes. In our cohort, 77% (64/83) of children became MeRD negative after cycle 1, 65% (11/17) of those MeRD positive after cycle 1 were rendered MeRD negative after receiving cycle 2, and 50% (2/4) of patients converted from MeRD positive to negative after cycle 3 (Figure 1). The percentage of blasts, assessed by morphology at each time point, is summarized in Table S1. We first assessed those patients with no detectable disease following cycle 1 ($n = 64$). This analysis aimed to assess whether additional chemotherapy cycles, after achievement of MeRD negativity, would lead to benefit due to improved depth of response, or potentially to worse outcomes due to treatment-related morbidity or mortality. Similar to the overall patient group, a statistically significant survival benefit was seen in the group receiving two cycles of chemotherapy, having a 5-year OS of 79.4%, compared to 46.4% for those who proceeded to transplant after cycle 1, and 37.5% for those who had three or more cycles (Figure 3). A similar analysis of the subset who were MRD positive after cycle 1 ($n = 17$) would have been desirable, however only two patients proceeded to transplant with positive MeRD after cycle 1, which precluded this analysis.

The impact of pre-HSCT MeRD status alone was then assessed. No significant difference in OS was observed between those MeRD negative or positive at the time of HSCT; however, as detailed in Figure 1, only nine patients underwent HSCT with positive MeRD, thereby limiting the power of this analysis.

3.4 | Impact of other covariates on outcome

By univariate modeling, CBF AML conferred a statistically significant survival advantage compared to other AML types ($P = .03$). Of the 18 cases where CBF was detected at diagnosis, 16 had two cycles of chemotherapy prior to HSCT, thereby accounting for the loss of its significance in multivariate analysis. There was also a weak trend toward improved survival for those relapsing greater than 365 days after initial diagnosis ($P = .3$). As detailed in Table 1, 24% of patients had undergone an autologous or allogeneic HSCT in CR1. Having a prior CR1 HSCT was not associated with poor risk in our study ($P = .7$) by univariate analysis, although only 5% of patients had undergone an allogeneic procedure, all with matched sibling donors. With respect to autologous transplants for pediatric AML in CR1, the pattern has been one of gradual decline over the years: 64 in 1998-2006 and 12 in 2007-2013. For all other covariates tested in univariate and

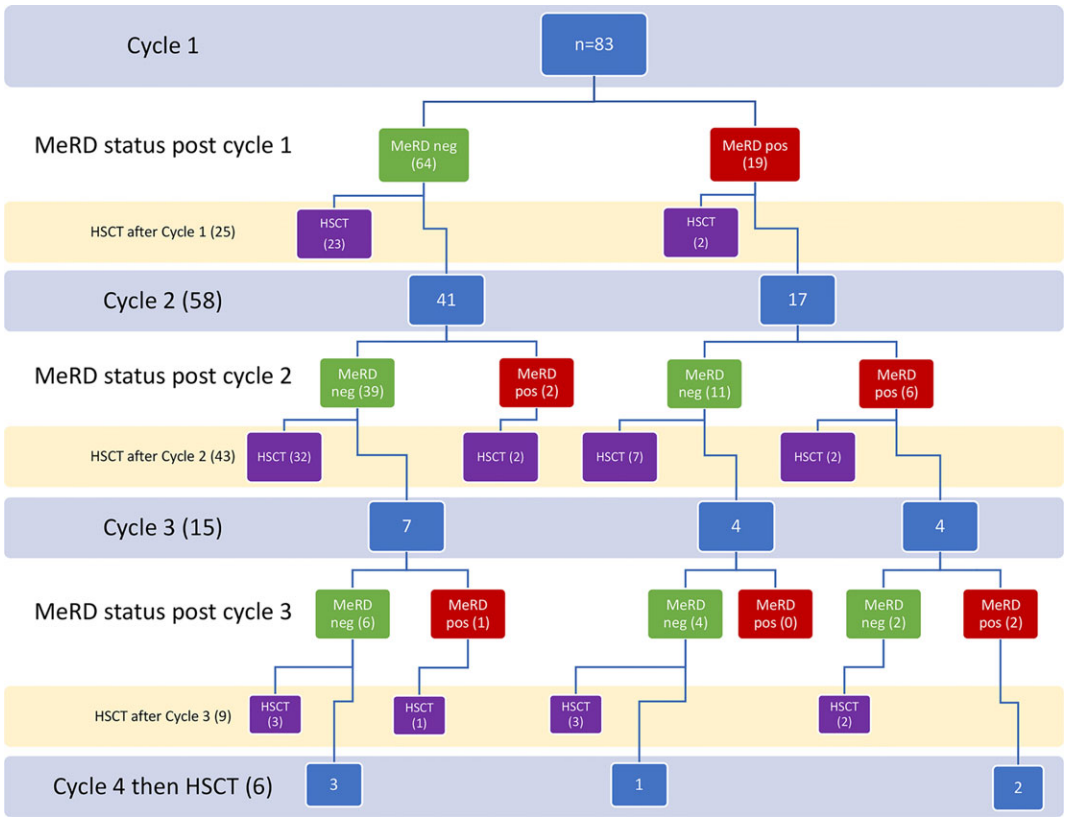

FIGURE 1 Flow diagram depicting number of cycles received, MeRD status after each cycle, and timing of HSCT for all patients

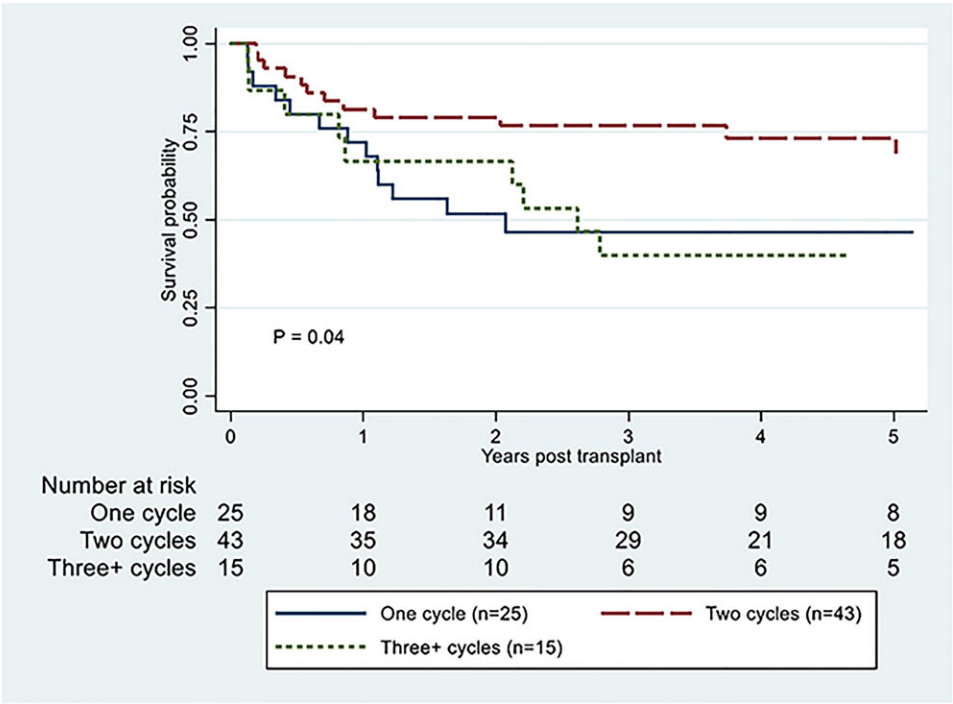

FIGURE 2 Kaplan-Meier plot of 5-year overall survival according to the number of chemotherapy cycles received pre-HSCT (all patients, $n = 83$). 5-year OS— one cycle ($n = 25$) 46.5%; two cycles ($n = 43$) 73.3%; three or more cycles ($n = 25$) 40.0% ($P = .04$)

TABLE 2 Cause of death up to 5 years post-transplant

Cause of death	Cycles of chemotherapy			Total number	Percentage
	1	2	≥3		
Relapse/progression	8	3	7	18	55
Graft-versus-host disease	1	2	2	5	15
Organ toxicity	2	2	0	4	12
Infection	0	1	1	2	6
Other transplant related	2	1	1	4	12
Total deaths within 5 years	**13**	**9**	**11**	33	100

multivariate analyses, except year of transplant (see below), there was no significant effect on survival.

The five-year survival probability of HSCT recipients in this study transplanted between 1998 and 2004 inclusive ($n = 36$) was 43.9%, while the 5-year survival probability of HSCT recipients transplanted between 2005 and 2013 inclusive ($n = 47$) was 70.9%. The difference was tested by Kaplan-Meier curves and univariate Cox regression and was statistically significant ($P = .01$). When the variables "Transplanted 1998–2004″ and "2 cycles of chemotherapy" were entered together in a multivariate Cox regression, neither attained statistical significance ($P = .08$ and .1, respectively), indicating some correlation between the two variables.

4 | DISCUSSION

Despite the poorer outcomes for many children with relapsed AML, in the absence of novel therapies, HSCT remains the only treatment modality that is capable of curing a substantial proportion of these high-risk patients.[8] Recently published data from the United Kingdom showed that children with primary refractory or relapsed/refractory AML undergoing HSCT with overt disease had a 5-year leukemia-free survival of 43%.[9] Similarly, AML patients not in remission (≥5% blasts) in the cohort reported by Leung et al. had a 5-year estimated survival of 58%.[8] These figures highlight that myeloablative conditioning and the GVL effect are able to salvage some of the highest risk patients, as well as reflecting the improvements that have been made to HSCT procedures.

However, the question of how many cycles of chemotherapy are optimal for relapsed patients prior to HSCT has remained unanswered and this retrospective study sheds some light on this important clinical question. The initial priority remains to achieve disease response, ideally CR, due to the negative impact of morphologic leukemia burden at the time of HSCT.[8,9,12,13] Reinduction chemotherapy in relapsed childhood AML leaves little room for treatment intensification, and so, in the absence of novel therapies, there are limited options for pretransplant disease reduction besides additional chemotherapy cycles, which also risks increased treatment-related morbidity and mortality.

Our retrospective analysis demonstrates a statistically significant survival advantage for those patients transplanted in CR2 who received two cycles of chemotherapy pre-HSCT, compared to those

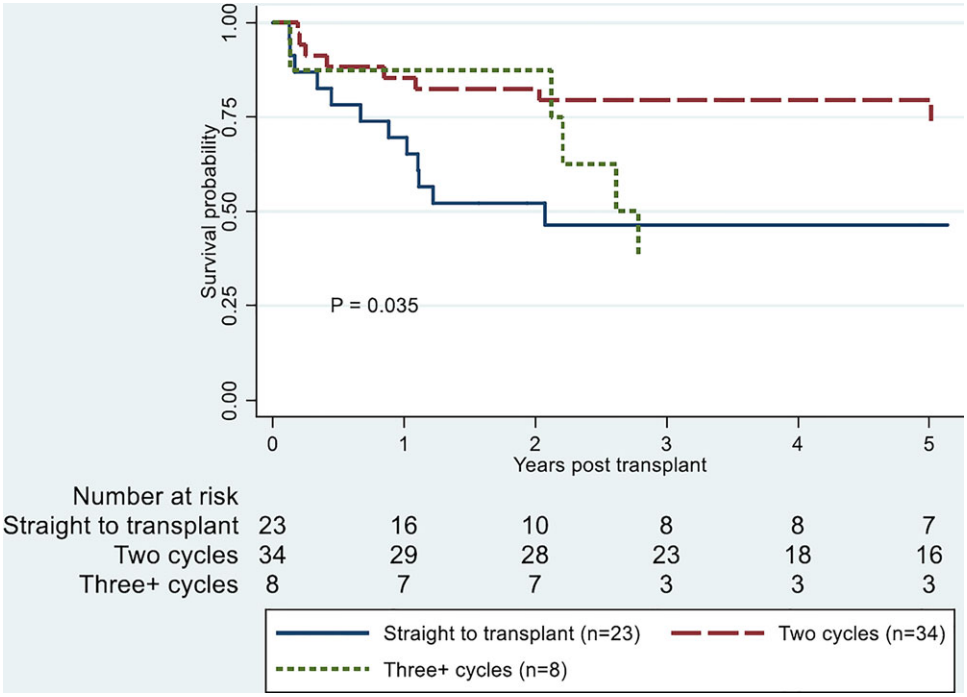

FIGURE 3 Kaplan-Meier plot of 5-year overall survival for patients who achieved MeRD-negativity after reinduction cycle 1, stratified according to the total number of cycles received pre-HSCT ($n = 65$). 5-year OS— one cycle ($n = 23$) 46.4%; two cycles ($n = 34$) 79.4%; three or more cycles ($n = 8$) 37.5% ($P = .035$)

who received one or at least three cycles, both in the whole cohort as well as in those patients with no detectable disease after the first cycle. It was also evident that relatively fewer patients became MeRD negative with each course of chemotherapy. Within the constraints of small numbers, this supports the notion that clearance of MeRD in relapsed AML, like achievement of CR status,[10] becomes more difficult with each subsequent cycle. Despite this, results suggest that two cycles of chemotherapy may strike a balance between disease control and the potential for increased toxicity and chemoresistance in relapsed childhood AML. It should also be noted that the inferior outcomes for those receiving three or more cycles of chemotherapy may have also been influenced by difficulty and/or delay in finding an optimal donor.

Although we did not have access to detailed toxicity data such as invasive infection rates after each cycle of reinduction chemotherapy, the improved outcome for patients receiving two cycles of chemotherapy compared to one cycle suggests that any possible increase in toxicity may have been offset by improved control of leukemia.

Our findings of CBF AML as a good prognostic factor at relapse and a trend toward improved prognosis for those relapsing after 365 days are in line with those recently reported by Karlsson et al.[5]

In addition to limitations of a retrospective analysis and small numbers, incomplete data also may have led to underrepresentation of MeRD. The reason for this is that the ancillary test data used to define MeRD status were not recorded in approximately one-third of cases, which means that MeRD negativity defaulted to a definition according to bone marrow blast count <5% by morphology. Many studies have shown poor correlation between posttreatment blast counts and residual disease assessed by multicolor flow cytometry, both in terms of false negatives and false positives.[14,15] The underrepresentation likely contributed to relatively low numbers of patients who entered HSCT with positive MeRD ($n = 7$) and in turn to a lack of significant difference in survival between MeRD positive and negative groups pre-HSCT. A second contributor to this lack of difference may also be the analytical sensitivity of the assays used. FISH cannot attain the now commonly accepted benchmark of 0.1% (10^{-3}) for MRD detection and there were no uniform approaches to measuring MRD by multiparameter flow cytometry. The combination of incomplete data and assay insensitivity is also likely the explanation for why the benefit of two cycles of chemotherapy extended to those already MeRD negative after cycle 1, as it can be hypothesized that these patients benefitted from a greater depth of response provided by this second cycle.

It is acknowledged that outcomes of pediatric patients who achieve CR2 but do not proceed to transplant may be different to the group of children represented in this study, but as explained in Section 2, it was not practical to include these children in this study. Subsequent retrospective or prospective studies should be considered to examine outcomes for this group of patients. Despite these limitations, our data support the hypothesis that two cycles of chemotherapy pretransplant lead to improved outcomes in relapsed childhood AML and warrant further investigation in prospective studies of MRD-directed therapy incorporating sensitive and standardized assays.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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