

Outcomes according to fusion partner, induction regimen, and CR1 allogeneic transplantation in pediatric KMT2A-rearranged AML: the C-HUANAN-AML-15 multicenter cohort study

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Research Article

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Abstract

Background

KMT2A-rearranged (*KMT2A*-r) pediatric acute myeloid leukemia (AML) is clinically and prognostically heterogeneous, and optimal induction and post-remission strategies remain uncertain. We aimed to compare outcomes by fusion partner, by induction regimen (fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor, and idarubicin [FLAG-IDA] versus daunorubicin, cytarabine, and etoposide [DAE]), and by post-remission strategy (chemotherapy consolidation versus allogeneic hematopoietic stem cell transplantation in first complete remission [CR1 allo-HSCT]).

Methods

We retrospectively analyzed data from children with newly diagnosed AML (excluding acute promyelocytic leukemia) who were treated under C-HUANAN-AML-15 at 11 centers. Event-free survival (EFS) and overall survival (OS) were estimated using Kaplan–Meier analysis; cumulative incidence of relapse (CIR) was estimated in a competing-risk framework. Propensity-score matching was used to address measured baseline differences between induction groups. Post-remission comparisons were descriptive because groups reflected eventual treatment, although follow-up began at diagnosis.

Results

Among 875 children, 153 (17.5%) had *KMT2A*-r AML. Five-year EFS, OS, and CIR were 69.4%, 78.6%, and 18.2%, respectively, without significant differences compared with non-*KMT2A*-r AML. Outcomes varied by fusion partner (global $P < 0.001$ for each endpoint); corresponding estimates were 77.4%, 87.6%, and 12.2% for *KMT2A::MLLT3* and 63.7%, 71.5%, and 22.4% for non-*MLLT3* *KMT2A*-r AML. Five-year EFS was significantly higher with FLAG-IDA in unadjusted analysis (74.7% vs 46.3%; $P = 0.002$), but this difference was not significant after matching 42 FLAG-IDA-treated patients to 21 DAE-treated patients (73.9% vs 49.0%; $P = 0.054$); matched OS and CIR also did not differ. Among 69 FLAG-IDA-treated patients with non-*MLLT3* *KMT2A*-r AML, 5-year EFS was 72.6% after chemotherapy and 68.1% after CR1 allo-HSCT ($P = 0.865$); OS and CIR also did not differ.

Conclusions

Outcomes varied by fusion partner. FLAG-IDA was associated with higher unadjusted EFS, but its superiority over DAE was not established after matching. Descriptive analyses identified no advantage of CR1 allo-HSCT in FLAG-IDA-treated non-*MLLT3* disease; selection and immortal-time biases preclude causal conclusions. Prospective fusion- and response-adapted studies are warranted.

Trial registration:

Not applicable.

Background

KMT2A (histone-lysine N-methyltransferase 2A, formerly *MLL*) encodes a transcriptional coactivator with histone H3 lysine 4 methyltransferase activity that is essential for normal development and hematopoiesis [1]. *KMT2A* rearrangements define one of the most common genetically distinct subgroups of pediatric acute myeloid leukemia (AML), occurring in approximately 15–20% of cases overall and in approximately 40% of infant AML cases [2]. *KMT2A*-rearranged (*KMT2A*-r) AML is clinically and prognostically heterogeneous, with outcomes varying substantially according to fusion partner and additional cytogenetic abnormalities [3, 4]. In a recent international cohort of 1,256 children, 5-year event-free survival (EFS) ranged from 21.8% to 76.2% across recurrent *KMT2A*-r subgroups [5]. This marked heterogeneity raises two closely related therapeutic questions: whether intensified induction can improve disease control and whether allogeneic hematopoietic stem cell transplantation (allo-HSCT) in first complete remission (CR1) is necessary for all patients considered to have unfavorable-risk disease.

The FLAG-IDA regimen, comprising fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor, and idarubicin, has demonstrated activity in children with poor-prognosis or relapsed/refractory AML [6]. In the predominantly adult Medical Research Council AML15 trial, FLAG-IDA increased remission after the first induction course and reduced relapse but caused greater myelosuppression without improving overall survival (OS) [7]. Because frontline pediatric evidence is limited to small, noncomparative studies without *KMT2A*-r-specific estimates [8], whether FLAG-IDA offers an advantage over daunorubicin, cytarabine, and etoposide (DAE) in newly diagnosed pediatric *KMT2A*-r AML remains uncertain.

The optimal consolidation strategy is also unclear. In the C-HUANAN-AML-15 protocol, non-*KMT2A::MLLT3* status alone does not define high-risk disease. This distinction originates from the adult European LeukemiaNet (ELN) and National Comprehensive Cancer Network (NCCN) frameworks, which classify t(9;11)/*KMT2A::MLLT3* as intermediate risk and other *KMT2A* rearrangements as adverse risk [9, 10]. Pediatric evidence instead supports fusion-specific and response-informed risk stratification [2, 11]. Although a recent analysis found CR1 allo-HSCT to be associated with improved disease-free survival in children with contemporarily defined high-risk AML overall [12], its benefit may vary among *KMT2A*-r subgroups. In an international *KMT2A*-r cohort, HSCT was associated with reduced relapse in the fusion-defined high-risk group but not in the non-high-risk group, without a significant OS advantage [5]. HSCT also carries substantial financial and long-term health burdens, including adverse effects on quality of life and fertility. These concerns are especially relevant where fertility-preservation services remain incompletely integrated into pediatric oncology care [13–15].

Therefore, determining whether selected children can achieve durable disease control with intensive chemotherapy alone is essential. To address these questions, we retrospectively analyzed 875 children with newly diagnosed AML treated according to the C-HUANAN-AML-15 protocol at 11 centers in China, including 153 children with *KMT2A*-r AML. We aimed to characterize clinical features and outcomes; compare treatment response, relapse, and survival between FLAG-IDA and DAE induction; and explore the association of CR1 allo-HSCT with outcomes. We also examined the non-*KMT2A::MLLT3* subgroup separately because of its adverse-risk classification in adult ELN and NCCN frameworks. This analysis was exploratory because non-*KMT2A::MLLT3* status alone was not a high-risk criterion in the C-HUANAN-AML-15 protocol.

Methods

Study design and participants

This multicenter retrospective cohort study included patients aged < 14 years with newly diagnosed AML who were treated according to the C-HUANAN-AML-15 protocol at 11 tertiary centers in southern China between January 2015 and December 2023. AML was diagnosed by bone marrow morphology, immunophenotyping, cytogenetic analysis, and molecular testing in accordance with the World Health Organization criteria applicable at the time of diagnosis [16]. Patients with acute promyelocytic leukemia, Down syndrome, therapy-related AML, or myeloid neoplasms associated with germline predisposition were excluded. Analyses of *KMT2A*-r AML were restricted to patients meeting the molecular or cytogenetic criteria described below.

This study was approved by the Ethics Committee of Fujian Medical University Union Hospital (approval no. 2025KY266). Given that this was a retrospective study, the requirement for informed consent was waived. The study was conducted in accordance with the Declaration of Helsinki and applicable national regulations.

Treatment protocol

The C-HUANAN-AML-15 protocol [17], adapted from the United Kingdom Medical Research Council AML15 trial [7], comprised two induction courses (FLAG-IDA or DAE) followed by two consolidation courses. Consolidation comprised homoharringtonine, cytarabine, and etoposide, followed by mitoxantrone and cytarabine. A treatment schema is provided in Additional file 1 (Figure S1).

FLAG-IDA or DAE was selected according to the treating physician's judgment, institutional practice, and protocol implementation at the participating center. Allogeneic HSCT was performed according to protocol-defined indications, donor availability, and institutional practice.

Cytogenetic and molecular analyses

Diagnostic bone marrow aspirates were obtained prior to antileukemic therapy. Conventional chromosome analysis was performed in accredited cytogenetics laboratories at the participating centers. Bone marrow cells were cultured without mitogen stimulation for 24–48 h, harvested using standard procedures, and analyzed by G-banding. At least 20 metaphases were evaluated when sufficient metaphases were available. Karyotypes were reported according to the International System for Human Cytogenomic Nomenclature edition applicable at the time of testing and were harmonized for the present analysis.

A *KMT2A* rearrangement was defined by at least one of the following: a clonal cytogenetic abnormality involving 11q23 with confirmed *KMT2A* involvement; a split or otherwise abnormal signal pattern detected using a *KMT2A* break-apart fluorescence in situ hybridization (FISH) probe; or an in-frame *KMT2A* fusion transcript identified by reverse-transcription polymerase chain reaction (RT-PCR) or RNA sequencing.

FISH was performed on interphase nuclei using a dual-color *KMT2A* break-apart probe targeting 11q23 (Wuhan HealthCare Biotechnology Co., Ltd., Wuhan, China), according to the manufacturer's instructions and locally validated procedures. The 5' *KMT2A* probe was labeled with a green fluorophore, and the 3' probe was labeled with a red fluorophore. A normal nucleus showed two fused red-green signals, whereas a typical rearranged pattern consisted of one fused signal, one separate red signal, and one separate green signal. Other abnormal

patterns consistent with deletion or an unbalanced rearrangement were interpreted together with the conventional cytogenetic and molecular findings. Four hundred interphase nuclei were evaluated per specimen. A result was considered positive when the proportion of nuclei with an abnormal signal pattern exceeded the laboratory-validated cutoff of 5.75%.

Fusion partners were assigned based on results from clinically validated diagnostic assays performed at the participating centers, including RT-PCR, RNA sequencing, or other definitive molecular assays. These results were abstracted from routine clinical diagnostic reports for the present analysis; raw sequencing data were not collected centrally or reanalyzed as part of this study. Cases with a positive *KMT2A* break-apart FISH result but without a molecularly identified fusion partner were categorized as *KMT2A*-rearranged, partner unknown. An isolated 11q23 abnormality without definitive evidence of *KMT2A* involvement was insufficient for classification as *KMT2A*-r.

Response and outcome definitions

Complete remission (CR) was defined according to the protocol as < 5% blasts in bone marrow, no circulating blasts or extramedullary leukemia, and evidence of recovery of normal hematopoiesis. CR with incomplete hematologic recovery (CRi) was recorded separately. Treatment response was assessed after each induction course at protocol-specified time points. Measurable residual disease (MRD) was assessed in bone marrow by multiparameter flow cytometry using leukemia-associated immunophenotype and different-from-normal approaches. For prognostic analyses, MRD positivity was defined as $\geq 1\%$ after the first induction course and $\geq 0.1\%$ after the second course.

OS was calculated from diagnosis to death from any cause; surviving patients were censored at the last follow-up. EFS was measured from diagnosis to the first occurrence of failure to achieve CR or CRi after two induction courses, relapse, a second malignant neoplasm, treatment abandonment, or death from any cause. Patients without an event were censored at the last follow-up. Relapse was defined as the reappearance of $\geq 5\%$ bone marrow blasts after CR, circulating leukemic blasts, or extramedullary leukemia.

The cumulative incidence of relapse (CIR) was evaluated from the date of CR1, with death without relapse treated as a competing event. Follow-up was administratively censored on April 1, 2024.

Statistical analysis

Continuous variables are summarized as medians with interquartile ranges (IQRs) or ranges and were compared using the Mann–Whitney U test. Categorical variables are reported as frequencies and percentages and were compared using the chi-square or Fisher’s exact test, as appropriate. Standardized mean differences (SMDs) are used to describe baseline differences between the induction groups.

OS and EFS were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). The proportional hazards assumption was assessed using Schoenfeld residuals. CIR was estimated in a competing-risk framework and compared using Gray’s test.

Because the induction regimen was not randomly assigned and substantially fewer patients received DAE than FLAG-IDA, propensity-score matching (PSM) was used for the primary adjusted comparison of the two regimens among eligible patients with *KMT2A*-r AML. The PSM included patients with an observed induction assignment and complete data for all prespecified pretreatment covariates, provided that adequate propensity-score overlap permitted matching. Outcome analyses were repeated in the matched cohort. Full details of propensity-score estimation, matching, balance assessment, and matched outcome analyses are provided in Additional file 2. Unadjusted analyses were also performed in the overall eligible cohort.

Post-remission treatment groups were classified according to the treatment eventually received, whereas follow-up began at diagnosis. Because complete transplantation dates were unavailable, time-dependent exposure modeling and a valid landmark analysis could not be performed; post-remission comparisons were therefore descriptive. Exploratory subgroup analyses were conducted by fusion partner, including *KMT2A::MLLT3* and non-*MLLT3* disease, and were interpreted cautiously because of limited sample sizes and event counts.

The PSM analysis used complete cases for all variables included in the propensity-score model. Endpoint-specific analyses included patients with available treatment assignment, follow-up time, and event status for the relevant outcome. Missing values were not imputed. Variables with a univariable Wald $P < 0.05$ were entered into selected multivariable Cox models. All tests were two-sided, and $P < 0.05$ was considered statistically significant. No adjustment for multiple comparisons was made for exploratory analyses. All statistical analyses were performed using R (version 4.5.3; R Foundation for Statistical Computing, Vienna, Austria) [18].

Results

Baseline characteristics and treatment response

Among 875 children with evaluable *KMT2A* status, 153 (17.5%) had *KMT2A*-r AML, and 722 (82.5%) had non-*KMT2A*-r AML. Compared with children who had non-*KMT2A*-r AML, children with *KMT2A*-r AML were younger (median age, 48.0 months [IQR 21.6–92.0] vs 78.5 months [IQR 37.0–123.9]; $P < 0.001$) and more frequently aged ≤ 24 months (32.0% vs 16.3%; $P < 0.001$). French–American–British M4/M5 morphology was also more frequent in the *KMT2A*-r AML group (77.1% vs 31.3%; $P < 0.001$). Conversely, extramedullary involvement (3.9% vs 11.2%; $P = 0.006$), FLT3 internal tandem duplication (6.5% vs 12.7%; $P = 0.030$), and biallelic *CEBPA* mutations (1.3% vs 6.5%; $P = 0.011$) were less frequent in the *KMT2A*-r group. Sex, presenting leukocyte count, *ASXL1* mutations, and *NPM1* mutations did not differ significantly between the groups (Table 1).

Table 1

Comparison of the characteristics of patients with KMT2A-rearranged AML and other AML subtypes

Characteristic	All patients (n = 875)	KMT2A-r AML (n = 153)	Other AML (n = 722)	Statistic	P value
Age, median (IQR), months	73.0 (33.0–120.0)	48.0 (21.6–92.0)	78.5 (37.0–123.9)	U = 42,100.5	< 0.001
≤ 24 months	167 (19.1%)	49 (32.0%)	118 (16.3%)	$\chi^2 = 20.106$	< 0.001
> 24 months	708 (80.9%)	104 (68.0%)	604 (83.7%)		
Male	504 (57.6%)	83 (54.2%)	421 (58.3%)	$\chi^2 = 0.853$	0.356
Female	371 (42.4%)	70 (45.8%)	301 (41.7%)		
WBC, median (IQR), $\times 10^9/L$	21.72 (8.28–57.38)	18.27 (5.70–55.80)	22.24 (8.90–57.40)	U = 50,297.5	0.082
WBC $\geq 50 \times 10^9/L$	242 (27.7%)	44 (28.8%)	198 (27.4%)	$\chi^2 = 0.112$	0.737
WBC $< 50 \times 10^9/L$	633 (72.3%)	109 (71.2%)	524 (72.6%)		
Extramedullary involvement: yes	87 (9.9%)	6 (3.9%)	81 (11.2%)	$\chi^2 = 7.508$	0.006
FAB M4/M5	344 (39.3%)	118 (77.1%)	226 (31.3%)	$\chi^2 = 111.106$	< 0.001
Other FAB subtypes	531 (60.7%)	35 (22.9%)	496 (68.7%)		
<i>FLT3-ITD</i> mutated	102 (11.7%)	10 (6.5%)	92 (12.7%)	$\chi^2 = 4.722$	0.030
<i>ASXL1</i> mutated	151 (17.3%)	26 (17.0%)	125 (17.3%)	$\chi^2 = 0.009$	0.924
<i>NPM1</i> mutated	16 (1.8%)	0 (0%)	16 (2.2%)	Fisher exact	0.090
Biallelic <i>CEBPA</i> mutated	49 (5.6%)	2 (1.3%)	47 (6.5%)	$\chi^2 = 6.464$	0.011
Continuous variables are presented as median (IQR) and were compared using the two-sided Mann–Whitney U test. Categorical variables are presented as n (%) and were compared using the Pearson chi-square test or two-sided Fisher exact test, as appropriate. P values are two-sided. FAB M4/M5 includes M4, M5, M4/M5, M5a, and M5b subtypes. Other FAB subtypes include all remaining FAB classifications.					

[insert Table 1 here]

A flowchart of patient inclusion is shown in Fig. 1. FLAG-IDA and DAE were used as the first induction regimen in 124 (81.0%) and 29 (19.0%) patients, respectively. Morphologic CR was achieved after the first induction course in 129 of 150 (86.0%) evaluable patients and by the end of the second course in 133 of 140 (95.0%). MRD $\geq 0.1\%$ after the second course was detected in 20 of 140 (14.3%) evaluable patients. The first-course CR rate did not differ significantly between patients who received FLAG-IDA and those who received DAE (106/122 [86.9%] vs 23/28 [82.1%]; $P = 0.548$). The second-course MRD-positive rates were 14 of 116 (12.1%) with FLAG-IDA and 6 of 24 (25.0%) with DAE ($P = 0.113$).

Outcomes according to KMT2A status and fusion partner

The median follow-up for the *KMT2A*-r cohort was 47.1 months using the reverse Kaplan–Meier method. EFS data were available for all 875 patients, OS data for 872, and CIR data for 800 patients with evaluable relapse and competing-event information. Among the 153 children with *KMT2A*-r AML, 42 experienced an EFS event, and 27 died. The 5-year EFS, OS, and CIR were 69.4% (95% CI 61.8–77.8%), 78.6% (95% CI 71.7–86.2%), and 18.2% (95% CI 11.0–25.3%), respectively. In the non-*KMT2A*-r group, the corresponding estimates were 65.7% (95% CI 62.2–69.4%), 77.0% (95% CI 73.7–80.4%), and 19.3% (95% CI 16.1–22.5%). No significant between-group differences were observed in EFS ($P = 0.212$), OS ($P = 0.509$), or CIR (Gray’s test, $P = 0.588$) (Additional file 3, Figure S2).

The most frequent fusion partner was *MLLT3* ($n = 64$, 41.8%), followed by *MLLT10* ($n = 23$, 15.0%), *AFDN* (formerly *MLLT4*; $n = 14$, 9.2%), *ELL* ($n = 10$, 6.5%), *MLLT1* ($n = 8$, 5.2%), *MLLT11* ($n = 4$, 2.6%), and *AFF1* ($n = 2$, 1.3%). The remaining 28 (18.3%) patients had another fusion partner or a molecularly unclassified partner. Outcomes differed significantly across fusion-partner groups (global $P < 0.001$ for EFS, OS, and CIR) (Additional file 4, Figure S3). For *KMT2A::MLLT3*, the 5-year EFS, OS, and CIR were 77.4% (95% CI 67.0–89.4%), 87.6% (95% CI 79.3–96.7%), and 12.2% (95% CI 2.6–21.8%), respectively. The corresponding estimates for *KMT2A::MLLT10* were 81.3% (95% CI 66.4–99.7%), 78.9% (95% CI 62.4–99.9%), and 14.2% (95% CI 0–29.4%). Patients with *KMT2A::AFDN* had a 5-year EFS of 48.0% (95% CI 25.5–90.5%), OS of 49.5% (95% CI 27.3–89.4%), and CIR of 30.0% (95% CI 0–60.2%). Estimates for the small *MLLT11*, *MLLT1*, and *AFF1* subgroups were imprecise and were therefore not interpreted individually.

In the five-group analysis, the 5-year EFS, OS, and CIR estimates were 77.4%, 87.6%, and 12.2% for *KMT2A::MLLT3*; 63.7%, 71.5%, and 22.4% for non-*MLLT3* *KMT2A*-r AML; 83.4%, 89.1%, and 9.0% for non-*KMT2A*-r low-risk AML; 62.1%, 72.4%, and 27.3% for non-*KMT2A*-r intermediate-risk AML; and 44.5%, 64.2%, and 26.2% for non-*KMT2A*-r high-risk AML, respectively (Fig. 2). Global differences were significant for all three outcomes (all $P < 0.001$). Numerically, the estimates for *KMT2A::MLLT3* approached those of non-*KMT2A*-r low-risk AML, whereas those for non-*MLLT3* *KMT2A*-r AML approached those of the intermediate-risk group. However, only global tests were performed; these findings should not be interpreted as evidence of pairwise equivalence.

FLAG-IDA versus DAE induction

In the unadjusted cohort, FLAG-IDA was associated with higher 5-year EFS than DAE (74.7% [95% CI 67.1–83.2%] vs 46.3% [95% CI 28.8–74.4%]; $P = 0.002$). Five-year OS was 81.2% (95% CI 74.0–89.0%) with FLAG-IDA and 65.3% (95% CI 46.8–91.1%) with DAE ($P = 0.081$). The corresponding 5-year CIR estimates were 15.9% (95% CI 8.9–22.9%) and 29.7% (95% CI 4.4–54.9%), respectively (Gray’s test, $P = 0.224$) (Fig. 3).

PSM paired 21 DAE-treated patients with 42 FLAG-IDA-treated patients. The mean absolute SMD decreased from 0.222 before matching to 0.066 after matching, although the maximum residual SMD was 0.309 (Additional file 5, Figure S4). In the matched cohort, the 5-year EFS was 73.9% (95% CI 61.2–89.4%) with FLAG-IDA and 49.0% (95% CI 29.6–81.1%) with DAE ($P = 0.054$). The corresponding 5-year OS estimates were 80.4% (95% CI 68.4–94.7%) and 70.5% (95% CI 51.7–96.2%), respectively ($P = 0.308$), while the 5-year CIR estimates were 18.1% (95% CI 5.8–30.5%) and 28.0% (95% CI 2.0–54.1%), respectively (Gray’s test, $P = 0.603$) (Fig. 4).

Exploratory post-remission treatment-stratified analyses

Post-remission treatment could be classified for 141 children with *KMT2A*-r AML, with 72 receiving chemotherapy consolidation and 69 undergoing CR1 allo-HSCT. In this exploratory treatment-stratified analysis, the 5-year EFS

was 78.8% (95% CI 68.8–90.2%) after chemotherapy and 71.3% (95% CI 60.5–84.1%) after CR1 allo-HSCT ($P = 0.294$). The corresponding 5-year OS was 87.3% (95% CI 79.4–96.0%) and 73.7% (95% CI 62.9–86.3%), respectively ($P = 0.070$), whereas the corresponding 5-year CIR was 19.7% (95% CI 9.2–30.2%) and 16.8% (95% CI 7.1–26.5%), respectively (Gray's test, $P = 0.788$) (Additional file 6, Figure S5).

Fusion partner–stratified analyses yielded similar findings. Among patients with *KMT2A::MLLT3*, 38 received chemotherapy consolidation, and 22 underwent CR1 allo-HSCT. No significant differences were observed in EFS ($P = 0.214$), OS ($P = 0.127$), or CIR (Gray's test, $P = 0.811$) (Additional file 7, Figure S6). Similarly, among patients with non-*MLLT3 KMT2A-r* AML, 34 received chemotherapy consolidation, and 47 underwent CR1 allo-HSCT, with no significant differences in EFS ($P = 0.994$), OS ($P = 0.402$), or CIR (Gray's test, $P = 0.559$) (Additional file 8, Figure S7).

Among 117 FLAG-IDA-treated patients, EFS and CIR did not differ significantly between the two post-remission strategies ($P = 0.186$ and $P = 0.458$, respectively). Meanwhile, 5-year OS was higher in the chemotherapy group than in the CR1 allo-HSCT group (90.3% [95% CI 82.6–98.8%] vs 74.5% [95% CI 63.3–87.7%]; $P = 0.046$) (Fig. 5). In the clinically relevant subgroup of 69 FLAG-IDA-treated patients with non-*MLLT3 KMT2A-r* AML, 26 received chemotherapy consolidation, and 43 underwent CR1 allo-HSCT. The 5-year EFS was 72.6% (95% CI 57.2–92.2%) after chemotherapy and 68.1% (95% CI 54.0–85.9%) after CR1 allo-HSCT ($P = 0.865$). The 5-year OS after chemotherapy and CR1 allo-HSCT was 84.4% (95% CI 71.5–99.7%) and 69.3% (95% CI 54.9–87.5%), respectively ($P = 0.307$); the corresponding 5-year CIR was 23.5% (95% CI 6.6–40.4%) and 22.6% (95% CI 8.3–36.8%), respectively (Gray's test, $P = 0.898$) (Fig. 6). Among FLAG-IDA-treated patients with *KMT2A::MLLT3*, no significant differences in EFS ($P = 0.127$), OS ($P = 0.125$), or CIR ($P = 0.324$) were observed between those receiving chemotherapy ($n = 29$) and those undergoing CR1 allo-HSCT ($n = 19$) (Additional file 9, Figure S8). As patients were classified according to their eventual post-remission treatment while survival was measured from diagnosis, these comparisons were descriptive and subject to treatment-selection and immortal-time bias. Thus, these findings should not be interpreted as causal estimates of transplantation efficacy.

Prognostic factor analyses

Among the 144 patients included in the Cox analyses, 34 EFS events and 26 deaths occurred. In the univariable analyses, DAE induction was associated with inferior EFS relative to FLAG-IDA (HR 2.33, 95% CI 1.08–5.00; $P = 0.030$). Failure to achieve morphologic CR after the first induction course was associated with inferior EFS (HR 3.28, 95% CI 1.57–6.86; $P = 0.002$) and OS (HR 2.92, 95% CI 1.27–6.72; $P = 0.012$). MRD $\geq 0.1\%$ after the second course was also associated with inferior EFS (HR 3.19, 95% CI 1.47–6.91; $P = 0.003$) and OS (HR 2.68, 95% CI 1.06–6.77; $P = 0.037$). Non-*MLLT3* status showed non-significant adverse trends for EFS (HR 2.00, 95% CI 0.95–4.19; $P = 0.066$) and OS (HR 2.15, 95% CI 0.90–5.13; $P = 0.083$). Age, sex, presenting leukocyte count, extramedullary involvement, and first-course MRD were not associated with EFS or OS (Table 2). The selected multivariable EFS model included 140 patients and 32 events. No variable retained statistical significance: the adjusted HRs were 1.96 for DAE induction (95% CI 0.86–4.44; $P = 0.107$), 2.32 for failure to achieve first-course CR (95% CI 0.98–5.50; $P = 0.056$), and 2.14 for second-course MRD positivity (95% CI 0.89–5.14; $P = 0.089$). Similarly, neither failure to achieve first-course CR nor second-course MRD positivity remained significant in the selected OS model (Table 2).

Table 2

Univariable and selected multivariable Cox regression of EFS and OS in overall *KMT2A*-rearranged AML cohort

EFS (n = 144; events = 34; selected model n = 140, events = 32, variables = 3)							
Variable	Comparison	Reference n/events	Comparison n/events	Univariable HR (95% CI)	P value	Selected multivariable HR (95% CI)	P value
Age at diagnosis	≥ 1 year vs < 1 year	14/6	130/28	0.48 (0.20– 1.17)	0.106	—	—
Sex	Male vs female	66/17	78/17	0.82 (0.42– 1.60)	0.552	—	—
Presenting WBC count	≥ 50 vs < 50 ×10 ⁹ /L	106/23	38/11	1.31 (0.64– 2.68)	0.467	—	—
Extramedullary involvement	Yes vs no	139/33	5/1	0.72 (0.10– 5.29)	0.750	—	—
<i>KMT2A</i> fusion partner	Non- <i>MLLT3</i> vs <i>MLLT3</i>	61/10	83/24	2.00 (0.95– 4.19)	0.066	—	—
Induction regimen	DAE vs FLAG-IDA	119/25	25/9	2.33 (1.08– 5.00)	0.030	1.96 (0.86– 4.44)	0.107
Morphologic CR after course 1	No vs yes	124/24	20/10	3.28 (1.57– 6.86)	0.002	2.32 (0.98– 5.50)	0.056
MRD after course 1	≥ 1% vs < 1%	87/21	50/12	1.12 (0.55– 2.27)	0.763	—	—
MRD after course 2	≥ 0.1% vs < 0.1%	120/23	20/9	3.19 (1.47– 6.91)	0.003	2.14 (0.89– 5.14)	0.089
OS (n = 144; events = 26; selected model n = 140, events = 24, variables = 2)							
Variable	Comparison	Reference n/events	Comparison n/events	Univariable HR (95% CI)	P value	Selected multivariable HR (95% CI)	P value
Age at diagnosis	≥ 1 year vs < 1 year	14/4	130/22	0.61 (0.21– 1.77)	0.361	—	—
Sex	Male vs female	66/15	78/11	0.61 (0.28– 1.33)	0.215	—	—
Data are HRs (95% CIs). Variables with univariable Wald $P < 0.05$ entered the selected model. NE, not reliably estimable because of zero events in one category or model singularity; —, not entered or no selected model. <i>MLLT3</i> denotes <i>KMT2A::MLLT3</i> ; <i>KMT2A::MLLT11</i> was grouped as non- <i>MLLT3</i> .							

EFS (n = 144; events = 34; selected model n = 140, events = 32, variables = 3)							
Presenting WBC count	≥ 50 vs < 50 ×10 ⁹ /L	106/17	38/9	1.40 (0.62–3.13)	0.418	—	—
Extramedullary involvement	Yes vs no	139/26	5/0	NE	—	—	—
<i>KMT2A</i> fusion partner	Non- <i>MLLT3</i> vs <i>MLLT3</i>	61/7	83/19	2.15 (0.90–5.13)	0.083	—	—
Induction regimen	DAE vs FLAG-IDA	119/19	25/7	2.32 (0.97–5.53)	0.057	—	—
Morphologic CR after course 1	No vs yes	124/18	20/8	2.92 (1.27–6.72)	0.012	2.18 (0.83–5.75)	0.115
MRD after course 1	≥ 1% vs < 1%	87/16	50/9	1.04 (0.46–2.37)	0.916	—	—
MRD after course 2	≥ 0.1% vs < 0.1%	120/18	20/6	2.68 (1.06–6.77)	0.037	1.97 (0.71–5.47)	0.191
Data are HRs (95% CIs). Variables with univariable Wald $P < 0.05$ entered the selected model. NE, not reliably estimable because of zero events in one category or model singularity; —, not entered or no selected model. <i>MLLT3</i> denotes <i>KMT2A::MLLT3</i> ; <i>KMT2A::MLLT11</i> was grouped as non- <i>MLLT3</i> .							

[insert Table 2 here]

Fusion-partner-stratified analyses were limited by small event numbers. Among 61 patients with *KMT2A::MLLT3*, DAE induction was associated with inferior EFS (HR 5.72, 95% CI 1.64–19.93; $P = 0.006$), whereas failure to achieve first-course CR was associated with inferior OS (HR 5.37, 95% CI 1.04–27.83; $P = 0.045$). Among 83 patients with non-*MLLT3* *KMT2A*-r AML, failure to achieve first-course CR was associated with inferior EFS (HR 2.88, 95% CI 1.23–6.74; $P = 0.015$); no evaluated factor was significantly associated with OS. Because only one variable met the entry criterion in each of these models, the estimates do not represent genuinely adjusted multivariable comparisons (Additional file 10, Table S1).

Among 119 FLAG-IDA-treated patients, non-*MLLT3* status remained associated with inferior EFS in the selected multivariable model (adjusted HR 3.35, 95% CI 1.13–9.96; $P = 0.029$). Failure to achieve first-course CR and second-course MRD positivity were associated with inferior EFS in univariable analyses but did not remain significant after adjustment. No evaluated factor was significantly associated with OS in the overall FLAG-IDA subgroup (Table 3).

Table 3

Univariable and selected multivariable Cox regression of EFS and OS in patients receiving FLAG-IDA induction

EFS (n = 119; events = 25; selected model n = 116, events = 24, variables = 3; EPV = 8.0, exploratory)							
Variable	Comparison	Reference n/events	Comparison n/events	Univariable HR (95% CI)	P value	Selected multivariable HR (95% CI)	P value
Age at diagnosis	≥ 1 year vs < 1 year	10/3	109/22	0.68 (0.20– 2.28)	0.533	—	—
Sex	Male vs female	56/14	63/11	0.65 (0.30– 1.44)	0.291	—	—
Presenting WBC count	≥ 50 vs < 50 ×10 ⁹ /L	88/17	31/8	1.35 (0.58– 3.12)	0.487	—	—
Extramedullary involvement	Yes vs no	115/25	4/0	NE	—	—	—
<i>KMT2A</i> fusion partner	Non- <i>MLLT3</i> vs <i>MLLT3</i>	49/5	70/20	3.28 (1.23– 8.76)	0.018	3.35 (1.13– 9.96)	0.029
Morphologic CR after course 1	No vs yes	103/18	16/7	3.03 (1.27– 7.27)	0.013	2.09 (0.83– 5.27)	0.119
MRD after course 1	≥ 1% vs < 1%	77/17	39/8	0.99 (0.43– 2.29)	0.977	—	—
MRD after course 2	≥ 0.1% vs < 0.1%	102/17	14/7	3.68 (1.52– 8.88)	0.004	2.37 (0.94– 6.01)	0.069
OS (n = 119; events = 19; no selected multivariable model)							
Variable	Comparison	Reference n/events	Comparison n/events	Univariable HR (95% CI)	P value	Selected multivariable HR (95% CI)	P value
Age at diagnosis	≥ 1 year vs < 1 year	10/2	109/17	0.78 (0.18– 3.39)	0.743	—	—
Sex	Male vs female	56/12	63/7	0.50 (0.19– 1.26)	0.140	—	—
Presenting WBC count	≥ 50 vs < 50 ×10 ⁹ /L	88/12	31/7	1.56 (0.61– 3.96)	0.350	—	—
Data are HRs (95% CIs).							
Variables with univariable Wald $P < 0.05$ entered the selected model. NE, not reliably estimable because of zero events in one category or model singularity; —, not entered or no selected model. <i>MLLT3</i> denotes <i>KMT2A::MLLT3</i> ; <i>KMT2A::MLLT11</i> was grouped as non- <i>MLLT3</i> .							

EFS (n = 119; events = 25; selected model n = 116, events = 24, variables = 3; EPV = 8.0, exploratory)							
Extramedullary involvement	Yes vs no	115/19	4/0	NE	—	—	—
<i>KMT2A</i> fusion partner	Non- <i>MLLT3</i> vs <i>MLLT3</i>	49/4	70/15	2.98 (0.99–8.99)	0.052	—	—
Morphologic CR after course 1	No vs yes	103/14	16/5	2.31 (0.83–6.42)	0.108	—	—
MRD after course 1	≥ 1% vs < 1%	77/14	39/5	0.72 (0.26–2.01)	0.534	—	—
MRD after course 2	≥ 0.1% vs < 0.1%	102/14	14/4	2.46 (0.81–7.48)	0.113	—	—
Data are HRs (95% CIs).							
Variables with univariable Wald $P < 0.05$ entered the selected model. NE, not reliably estimable because of zero events in one category or model singularity; —, not entered or no selected model. <i>MLLT3</i> denotes <i>KMT2A::MLLT3</i> ; <i>KMT2A::MLLT11</i> was grouped as non- <i>MLLT3</i> .							

[insert Table 3 here]

No significant prognostic factor was identified among the 49 FLAG-IDA-treated patients with *KMT2A::MLLT3*, who experienced only five EFS events and four deaths. Among 70 FLAG-IDA-treated patients with non-*MLLT3* *KMT2A*-r AML, failure to achieve first-course CR was associated with inferior EFS (adjusted HR 3.87, 95% CI 1.51–9.91; $P = 0.005$). Male sex was associated with lower hazards of EFS (adjusted HR 0.33, 95% CI 0.13–0.82; $P = 0.017$) and OS (HR 0.31, 95% CI 0.11–0.92; $P = 0.034$). The OS estimate arose from a one-covariate selected model and should not be interpreted as an adjusted association (Additional file 11, Table S2). All selected models and subgroup analyses were exploratory because of data-driven variable selection, limited event numbers, and the absence of multiplicity adjustment. No material violation of the proportional hazards assumption was detected.

Discussion

The findings of this multicenter study suggest that *KMT2A* rearrangement alone does not define a uniformly adverse form of pediatric AML. Outcomes for *KMT2A*-r and non-*KMT2A*-r AML did not differ significantly, but important variation by fusion partner was observed. Treatment response also appeared to provide prognostic information beyond genotype. FLAG-IDA was associated with higher EFS in the unadjusted comparison, although this association was weaker after PSM, and the post-remission analyses did not identify a consistent benefit of CR1 allo-HSCT. These treatment comparisons are hypothesis-generating rather than causal.

The fusion-partner findings support the biological and clinical heterogeneity of *KMT2A*-r AML. *KMT2A::MLLT3* was associated with relatively favorable outcomes, whereas *KMT2A::AFDN* showed an adverse pattern, consistent with previous pediatric reports [5, 19, 20]. The broader non-*MLLT3* category is clinically convenient but biologically imprecise and should not be regarded as a uniform high-risk group. Although adult ELN and NCCN frameworks distinguish *KMT2A::MLLT3* from other *KMT2A* rearrangements [9, 10], pediatric risk assignment is better informed

by the specific fusion and response to treatment [2, 5, 11]. Given the small subgroup and wide CIs, the favorable outcome observed for *KMT2A::MLLT10* warrants particular caution. This finding contrasts with Children's Oncology Group data linking *MLLT10* structural variants to adverse outcomes [21] and does not justify reclassification of this fusion.

Treatment sensitivity further refined prognosis. Failure to achieve morphologic remission after the first induction course and persistent MRD after the second course were associated with adverse outcomes in univariable analyses, consistent with previous pediatric AML and *KMT2A-r* studies [11, 17, 22–24]. Their attenuation in the overall multivariable models likely reflects limited event numbers, missing response data, and correlation between sequential response measures rather than an absence of prognostic relevance. Notably, first-course resistance remained informative among FLAG-IDA-treated patients with non-*MLLT3* disease. These findings favor combining fusion partner with serial response assessment rather than relying on either feature alone. By contrast, the apparent protective association of male sex in one small subgroup was not prespecified and should be regarded as a chance finding unless independently reproduced.

The comparison of induction regimens provides a clinically relevant but inconclusive signal in favor of FLAG-IDA. Its association with higher EFS in the unadjusted cohort was attenuated after matching, with no statistically significant difference in OS or CIR. This pattern is broadly consistent with the predominantly adult AML15 trial, in which FLAG-IDA improved early disease control but not OS and caused greater myelosuppression [7]. Frontline pediatric evidence remains limited, particularly for *KMT2A-r* AML [8, 25–28]. Moreover, the matched cohort was small and retained residual imbalance, while unmeasured factors such as treatment period, center practice, organ function, and infection risk may have influenced regimen selection. Because toxicity was not comprehensively captured, these data cannot establish the net clinical benefit or superiority of FLAG-IDA over DAE.

Likewise, the absence of a detectable advantage of CR1 allo-HSCT requires careful interpretation. Previous studies have suggested that transplantation benefits are concentrated among children with sufficiently high baseline or response-defined risk. A recent Children's Oncology Group analysis reported improved disease-free survival with CR1 HSCT in contemporary high-risk pediatric AML [12], whereas the international *KMT2A-r* study found a reduction in relapse only in its fusion-defined high-risk group and no significant OS benefit [11]. These observations argue against applying a single transplantation strategy to all *KMT2A-r* cases. They also underscore the need to balance relapse reduction against transplant-related mortality, chronic graft-versus-host disease, impaired fertility, financial burden, and long-term morbidity [13–15, 29–32].

The present transplantation analyses could not determine whether chemotherapy and HSCT are equivalent. Post-remission groups were defined by the treatment eventually received, whereas follow-up began at diagnosis, creating immortal-time bias. Confounding by indication also could not be excluded because patients with adverse genetics, persistent disease, or induction complications may have been preferentially selected for transplantation. The isolated OS advantage observed with chemotherapy after FLAG-IDA, without corresponding EFS or CIR improvement and without replication in fusion-defined subgroups, should therefore not be interpreted as evidence that HSCT is harmful. Propensity-score methods address only measured baseline differences [33], whereas reliable estimation of transplantation effects requires complete treatment dates and either time-dependent exposure modeling or a prespecified landmark design [34].

The therapeutic relevance of these findings will likely evolve as targeted agents enter frontline care. Gemtuzumab ozogamicin has reduced relapse in pediatric *KMT2A*-r AML [35], and menin inhibition has produced meaningful responses in relapsed or refractory *KMT2A*-rearranged leukemia [36, 37]. Future studies should determine whether these agents can deepen remission, modify the prognostic effect of individual fusions, or reduce reliance on transplantation. Such studies should incorporate comprehensive fusion and co-mutation profiling, standardized serial MRD assessment, toxicity reporting, and prospectively defined transplantation analyses.

The strengths of this study include its multicenter setting, treatment under a common protocol, and integrated evaluation of fusion partner, induction response, MRD, relapse, survival, and post-remission therapy. This study also has some limitations. The retrospective design and residual confounding limit causal interpretation of treatment comparisons. The marked imbalance between induction groups and small fusion-defined subgroups reduced precision and robustness, while non-uniform molecular and MRD assessment may have introduced misclassification across centers. Limited event numbers made the prognostic models unstable and particularly vulnerable to data-driven selection. Incomplete transplantation dates precluded time-appropriate analyses, incomplete toxicity data prevented assessment of net clinical benefit, and the follow-up duration may not capture all late events. Accordingly, non-significant comparisons should not be interpreted as evidence of equivalence.

Conclusions

FLAG-IDA was associated with higher unadjusted EFS, but superiority over DAE was not established after PSM. The descriptive post-remission analyses likewise did not establish a benefit of CR1 allo-HSCT. Pediatric *KMT2A*-r AML is best viewed as a collection of fusion-defined diseases whose prognosis is further shaped by treatment response. Clinically, these findings support incorporating fusion partner and serial response measures into risk assessment, but they do not justify changing induction or transplantation practice on their own. Prospective, response-adapted studies are needed to identify which children require intensified induction or transplantation and which may be treated effectively with chemotherapy-based consolidation.

Abbreviations

AML
acute myeloid leukemia
allo-HSCT
allogeneic hematopoietic stem cell transplantation
CI
confidence interval
CIR
cumulative incidence of relapse
CR
complete remission
CR1
first complete remission
CRi
complete remission with incomplete hematologic recovery
DAE

daunorubicin,cytarabine,and etoposide
EFS
event-free survival
ELN
European LeukemiaNet
FISH
fluorescence in situ hybridization
FLAG-IDA
fludarabine,high-dose cytarabine,granulocyte colony-stimulating factor,and idarubicin
HR
hazard ratio
IQR
interquartile range
KMT2A-r
KMT2A-rearranged
MRD
measurable residual disease
NCCN
National Comprehensive Cancer Network
OS
overall survival
PSM
propensity-score matching
RT-PCR
reverse-transcription polymerase chain reaction
SMD
standardized mean difference

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Ethics Committee of Fujian Medical University Union Hospital (approval No. 2025KY266). The requirement for informed consent was waived by the Ethics Committee of Fujian Medical University Union Hospital because of the retrospective nature of the study. The study was conducted in accordance with the Declaration of Helsinki and applicable national regulations.

Consent for publication

Not applicable.

Availability of data and materials

No new DNA or RNA sequencing datasets were generated or analyzed specifically for this study. *KMT2A* rearrangement and fusion-partner information analyzed in this study was derived from routine clinical diagnostic

reports at the participating centers. The de-identified clinical data that support the findings of this study are available from the corresponding author upon reasonable request, subject to institutional and ethical requirements for the protection of patient confidentiality.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ML, CXC, CPW, and YZZ conceptualized the study, performed the formal analysis, developed the methodology, and conducted the investigation. ML, CXC, CPW, and YZZ contributed to software development and project administration. XQF, CFL, MCZ, HRM, LHY, HJ, XLH, HW, HGX, CC, SHL, and NNL curated the data and provided resources. SHL, NNL, and YZZ supervised the study. ML, CXC, and CPW contributed to visualization. ML, CPW, and CXC wrote the original draft, and YZZ contributed to reviewing and editing the manuscript. All authors contributed to validation, read, and approved the final manuscript.

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Authors' information

CFL is the principal investigator of the C-HUANAN-AML-15 protocol, and XQF chairs the C-HUANAN-AML working group.

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Figures

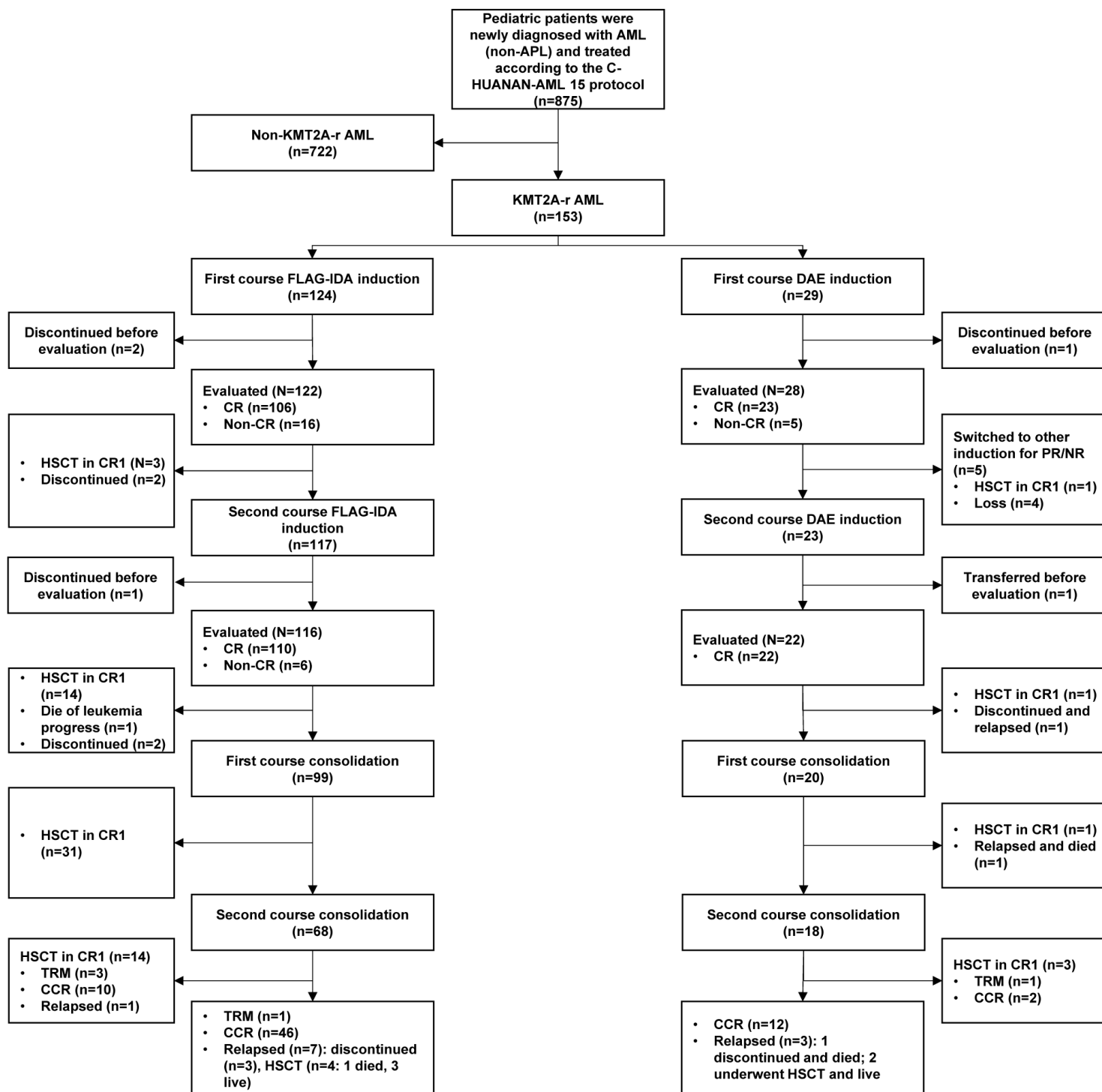


Figure 1

Study flow diagram and analysis population definitions.

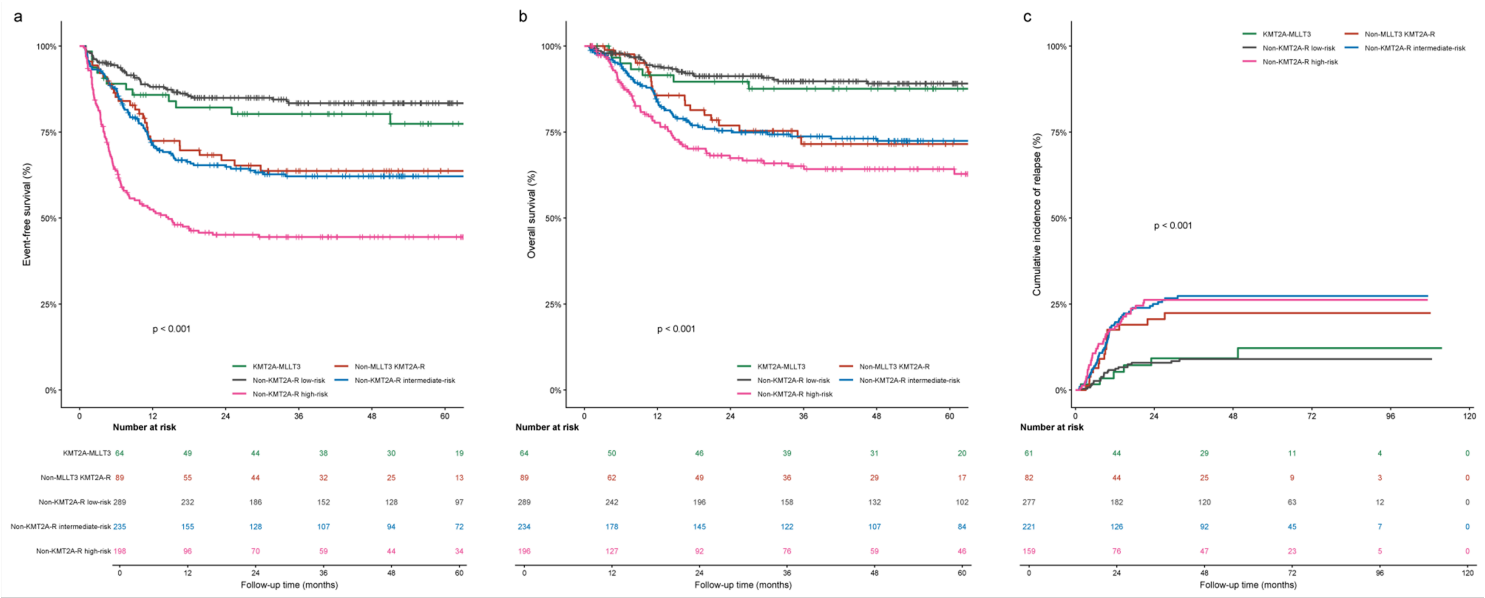


Figure 2

Outcomes according to *KMT2A* fusion status and risk group. (a) Event-free survival (EFS), (b) overall survival (OS), and (c) cumulative incidence of relapse (CIR) were compared among patients with *KMT2A::MLLT3*, non-*MLLT3 KMT2A*-rearranged acute myeloid leukemia, and non-*KMT2A*-rearranged acute myeloid leukemia, classified as low, intermediate, or high risk.

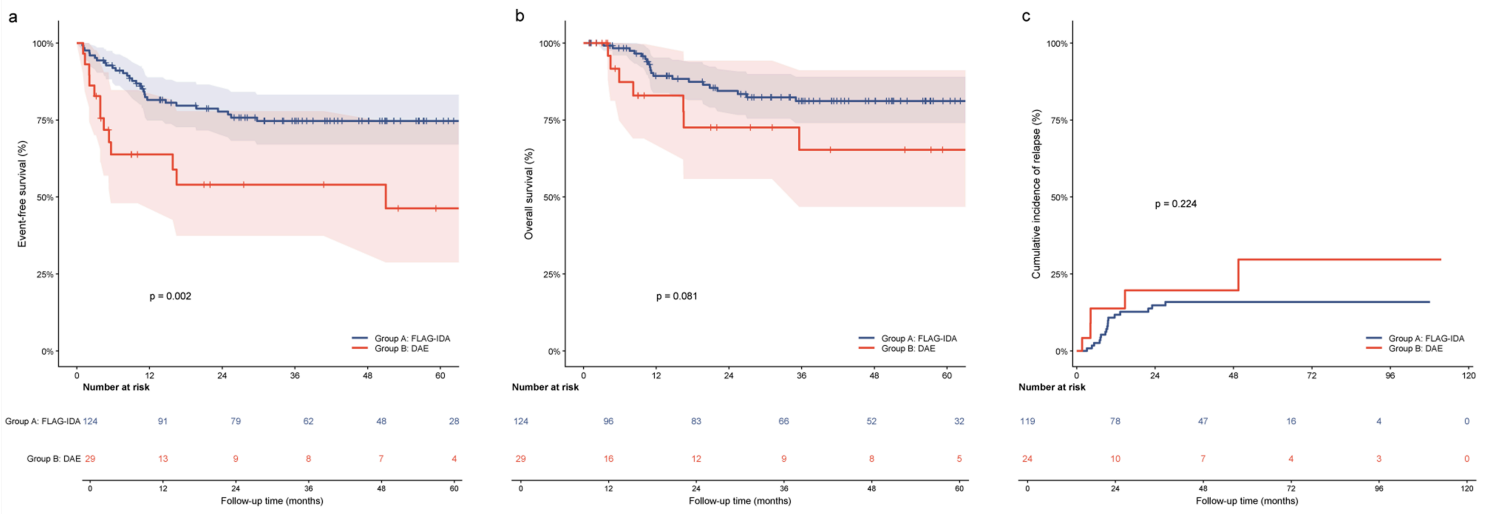


Figure 3

Outcomes according to first induction regimen in children with *KMT2A*-rearranged acute myeloid leukemia. (a) Event-free survival (EFS), (b) overall survival (OS), and (c) cumulative incidence of relapse (CIR) were compared between patients receiving FLAG-IDA and DAE as the first induction regimen. FLAG-IDA, fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor, and idarubicin; DAE, daunorubicin, cytarabine, and etoposide.

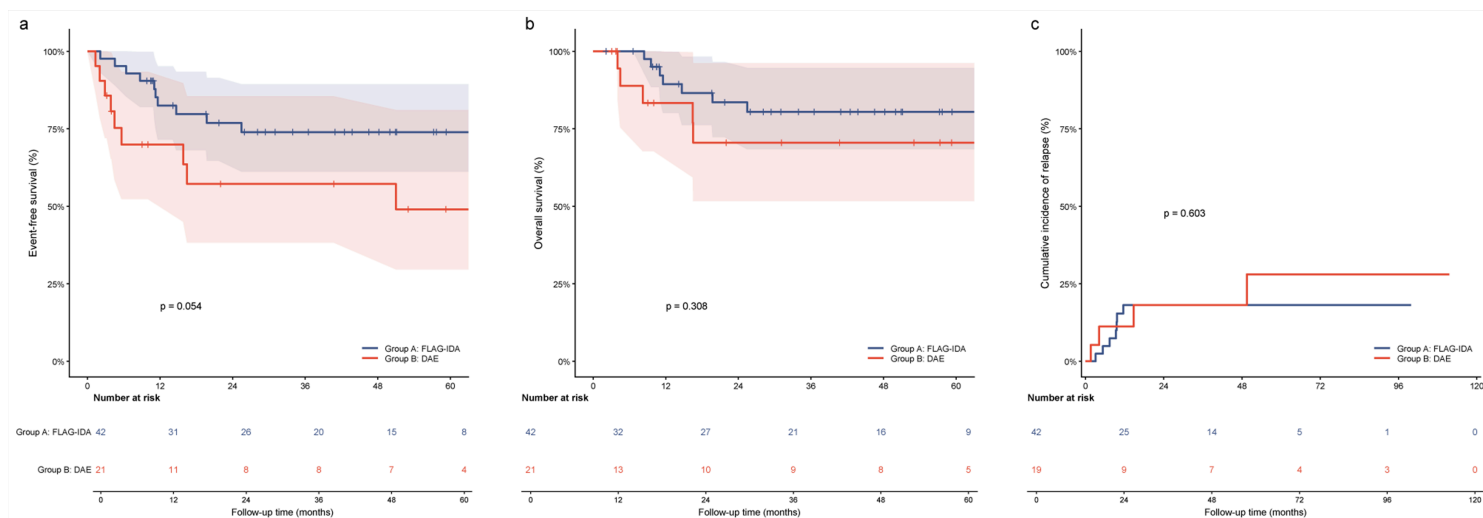


Figure 4

Outcomes according to induction regimen after propensity-score matching. (a) Event-free survival (EFS), (b) overall survival (OS), and (c) cumulative incidence of relapse (CIR) were compared between 42 FLAG-IDA-treated patients and 21 DAE-treated patients selected by 1:2 propensity-score matching. FLAG-IDA, fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor, and idarubicin; DAE, daunorubicin, cytarabine, and etoposide.

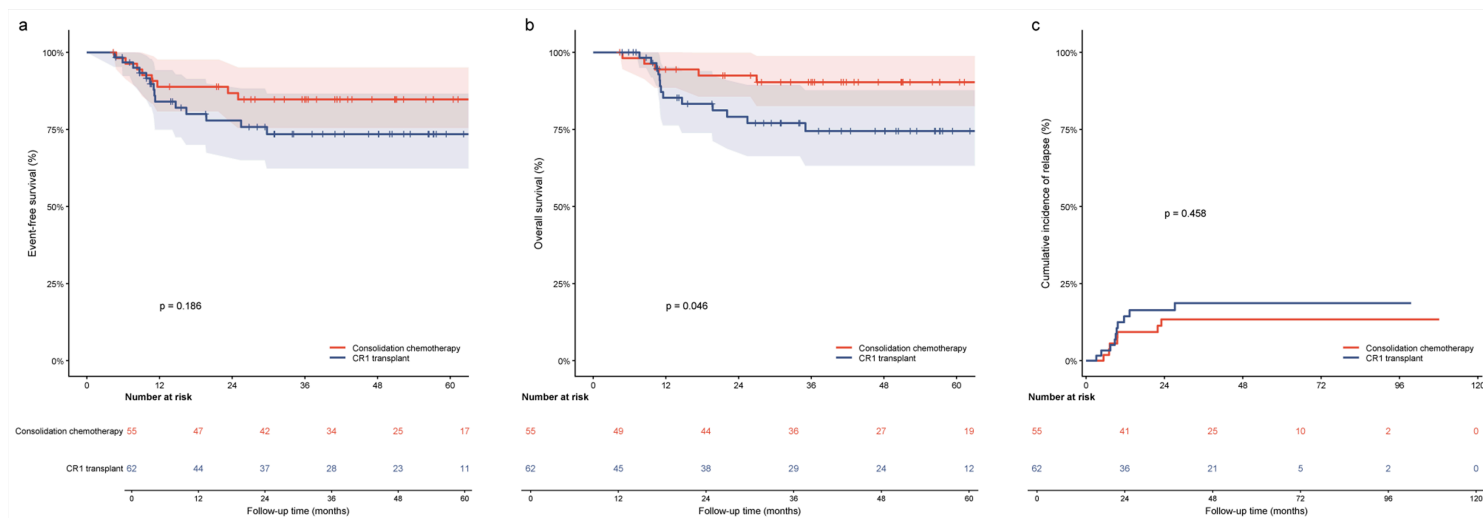


Figure 5

Outcomes according to post-remission treatment among FLAG-IDA-treated patients with *KMT2A*-rearranged acute myeloid leukemia. (a) Event-free survival (EFS), (b) overall survival (OS), and (c) cumulative incidence of relapse (CIR) were compared between patients receiving chemotherapy consolidation (n = 55) and those undergoing allogeneic hematopoietic stem cell transplantation in first complete remission (CR1 allo-HSCT; n = 62). FLAG-IDA, fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor, and idarubicin.

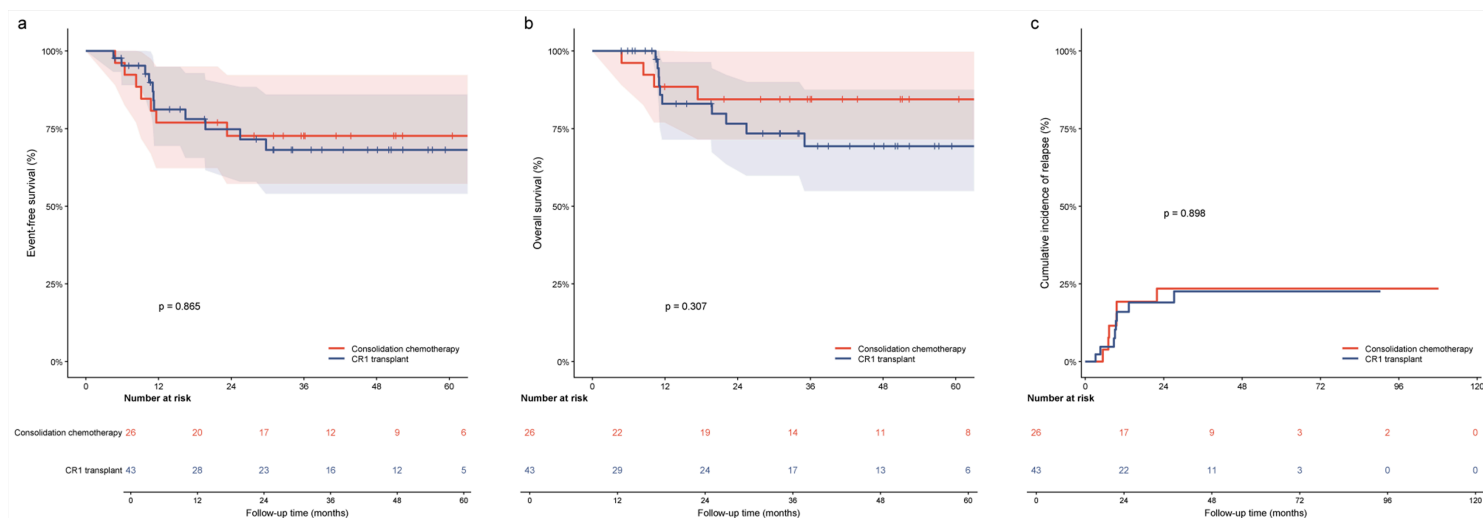


Figure 6

Outcomes according to post-remission treatment among FLAG-IDA-treated patients with non-*MLLT3 KMT2A*-rearranged acute myeloid leukemia. (a) Event-free survival (EFS), (b) overall survival (OS), and (c) cumulative incidence of relapse (CIR) were compared between chemotherapy consolidation (n = 26) and allogeneic hematopoietic stem cell transplantation in first complete remission (CR1 allo-HSCT; n = 43). FLAG-IDA, fludarabine, high-dose cytarabine, granulocyte colony-stimulating factor, and idarubicin.

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