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Outstanding outcomes in infants with *KMT2A*-germline acute lymphoblastic leukemia treated with chemotherapy alone: results of the Children's Oncology Group AALL0631 trial

Among infants with acute lymphoblastic leukemia (ALL), approximately 70-75% have *KMT2A* rearrangement (*KMT2A-r*) and 25-30% have *KMT2A*-germline (*KMT2A-g*) leukemia. Event-free (EFS) and overall survival (OS) for *KMT2A*-g infant ALL are significantly better than those of *KMT2A*-r infant ALL, but inferior to outcomes in older children with ALL. Aside from the absence of *KMT2A*-r, the well-defined prognostic factors in older children with B-ALL (age, initial white blood cell [WBC] count, cytogenetics) are not clearly established, as *KMT2A*-g infant ALL accounts for only ~1% of childhood ALL. Pediatric cooperative group trials conducted between 1996 and 2016 shown that the 4-6-year EFS/OS for infants with *KMT2A*-g ALL have ranged from 60-74% and 75-87%, respectively.[1-4] Although the Japanese Infant Leukemia Study Group and the Japanese Pediatric Leukemia/Lymphoma Study Group reported remarkable 5-year EFS of 96% and 93% in *KMT2A*-g infant ALL in MLL96/98 and MLL-10, respectively, the cohort sizes were small, the sex ratios were skewed and the results have not been replicated in other cooperative groups.[5-7] Children's Oncology Group (COG) AALL0631 (clinicaltrials gov. Identifier: NCT00557193) was a phase III clinical trial for infants with newly diagnosed ALL with or without *KMT2A*-r.[8] The trial was approved by Institutional Review Boards at participating COG member institutions and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the parents or guardians according to federal and local regulations. The primary aim of AALL0631 was to test the safety and efficacy of the addition of the FLT3 inhibitor, lestaurtinib, to chemotherapy for infants with *KMT2A*-r.[8] Infants with *KMT2A*-g were treated on a chemotherapy only arm, with a modified Interfant-99 based induction[3,9] followed by modified COG P9407[9] therapy, with continuation therapy extending to 2 years from diagnosis (as compared to 46 weeks in the predecessor P9407 trial). The trial enrolled 64 infants with *KMT2A*-g and resulted in survival outcomes superior to those reported for infants with *KMT2A*-g in all prior COG and Interfant trials.

Infants less than 366 days of age with a new diagnosis of B- or T-cell lineage ALL, acute undifferentiated leukemia (AUL), or mixed phenotype acute leukemia (MPAL) with predominantly lymphoid morphology and immunophenotype were eligible to enroll. Neonates less than 4 weeks old and at least 36 weeks gestational age at the time of diagnosis were eligible. Patients with Down syndrome, mature B-cell leukemia, acute myeloid

Table 1. Patient characteristics.

	KMT2A-g <1 yr AALL0631	*KMT2A*-r <1 yr AALL0631	*P*	*KMT2A*-g <1 yr P9407	*P*	*KMT2A*-g 1-9 yr AALL03B1 + AALL08B1	*P*
Total	64	146		35		19,047	
Age at diagnosis							
Median age (range)	281 d (54 to 363 d)	169 d (0 to 360 d)	<.0001	291 d (17 to 365 d)	0.77	4.08 yr (1 to 9.98 yr)	
Sex							
Male:Female	1:1.1	1:1.4	0.45	1:0.4	0.03	1:0.8	0.31
Race							
White	53 (90%)	108 (83%)	0.45	25 (81%)	0.34	13,986 (85.6%)	0.58
Black or African American	5 (8%)	11 (8%)		4 (13%)		1,174 (7.2%)	
Asian	1 (2%)	8 (6%)		2 (6%)		908 (5.6%)	
American Indian	0	3 (2%)		0		167 (1.0%)	
Native Hawaiian	0	0		0		93 (0.6%)	
Unknown	5	16		4		2719	
Ethnicity							
Hispanic or Latino	15 (24%)	34 (24%)	1.00	6 (19%)	0.61	4,132 (22.8%)	0.76
Not Hispanic or Latino	47 (76%)	106 (76%)		26 (81%)		13,989 (77.2%)	
Unknown	2	6		3		926	
WBC count at diagnosis, $x10^9$/L							
Median (range)	38 (0.6 to 918.2)	160 (1.6 to 4,334.5)	<.0001	87.1 (2.5 to 540)	0.28	9.9 (0.1 to 5,784)	<.0001
Diagnosis							
B-lymphoblastic leukemia	58 (91%)	139 (96%)	0.0007	32 (91%)	1.0	15,424 (92.1%)	0.73
T-lymphoblastic leukemia	6 (9%)	0		3 (9%)		1,282 (7.7%)	
AUL or indeterminate	0	1 (1%)		0		15 (0.1%)	
MPAL	0	5 (3%)		0		32 (0.2%)	
Unknown	0	1		0		2,294	
CNS status							
CNS 1	41 (65%)	61 (42%)	0.01	20 (57%)	0.51	16,426 (88.3%)	<.0001
CNS 2	16 (25%)	58 (40%)		13 (37%)		1,895 (10.2%)	
CNS 3	6 (10%)	25 (17%)		2 (6%)		280 (1.5%)	
Unknown	1	2		0		446	

KMT2A-g, *KMT2A*-germline; *KMT2A*-r: *KMT2A*-rearranged; yr: year; d: days; WBC: white blood cell; L: liter; AUL: acute undifferentiated leukemia; MPAL: mixed phenotype acute leukemia; CNS: central nervous system.

leukemia, or who had received prior anti-leukemic therapy (with the exception of limited corticosteroids or intrathecal chemotherapy) were ineligible. All patients had karyotypes and fluorescence *in situ* hybridization (FISH) to determine *KMT2A* status performed in COG-approved laboratories, with central review of results (AJC and NAH). Informative *KMT2A* FISH data were required to continue on AALL0631 post-induction therapy.

AALL0631 opened to accrual in January 2008 and the original COG P9407-based induction regimen (cohort 1) resulted in excessive toxic mortality due to infections (4 of 26 patients, 15.4%).[9] The study was temporarily closed to accrual in November 2008 and amended to substitute an Interfant-99 based induction[3] with additional supportive care guidelines (cohort 2). This led to significantly less induction mortality and maintained complete remission rates.[9] Post-induction, infants with *KMT2A*-g were non-randomly assigned to the Standard Risk (SR) arm (*Online Supplementary Table S1*). The study met accrual goals and closed to enrollment in June 2014.

Data as of March 31, 2019, are included in this report. Median follow-up was 6.3 years. EFS was defined as the time from study entry to first event (treatment failure, relapse, second malignant neoplasm [SMN], or death) or censored at date of last contact. OS was defined as the time from study entry to death or censored at last contact. Estimates of EFS and OS were calculated using the Kaplan-Meier method with standard errors (SE) using Peto's formula.[10,11] Two-sided log-rank tests were used to compare survival between curves. Fisher's exact tests were used to compare proportions and Wilcoxon rank-sum tests were used to compare distributions of continuous measures. Statistical significance was defined as *P*-value less than 0.05.

AALL0631 enrolled 210 eligible patients, including 64 (30.5%) with *KMT2A*-g (4 in cohort 1 and 60 in cohort 2). Patient characteristics were compared to infants with *KMT2A*-r in AALL0631, infants with *KMT2A*-g in P9407, and children age 1-9 years with *KMT2A*-g ALL and without Down Syndrome or Philadelphia chromosome-positive ALL, enrolled on the COG ALL classification studies AALL03B1 and AALL08B1 from March 1, 2004 to July 20, 2018, using frozen data from December 31, 2020 (Table 1). Notable differences in comparison to infants with *KMT2A*-r include older age and lower WBC count at diagnosis. Among infants with *KMT2A*-g, the proportion of females was higher in AALL0631 than in P9407. Central nervous system (CNS) leukemia was more common in infants than in children age 1-9 years with *KMT2A*-g, but less frequent than in infants with *KMT2A*-r (Table 2). The cytogenetic findings for infants with *KMT2A*-g are listed in the *Online Supplementary Table S2*.

Among 64 infants with *KMT2A*-g, 62 were evaluable for morphologic remission at the end of induction (week 6). One patient was removed from protocol prior to post-induction evaluation of remission due to withdrawal of consent and one did not have bone marrow morphology evaluated due to an administrative error. Of the 62 patients with marrow assessed, 55 (89%) achieved remission and seven (11%) did not achieve remission (all had ≥5% marrow blasts). Four patients went off protocol prior to post-induction therapy, one each for: withdrawal of consent, physician preference, family preference, and severe adverse event (cerebral edema). All remaining 60 patients (100%) achieved remission by the end of induction intensification (week 10). There were no treatment failure events.

The 5-year EFS (±SE) was 87.3 ± 4.7% and 5-year OS (±SE) was 93.6 ± 3.5% for infants with *KMT2A*-g. There were no deaths as first events. Eight infants relapsed (5 bone marrow and 3 isolated CNS). All relapses occurred within the first 3 years after diagnosis; five during continuation chemotherapy and three within 12 months after completion of continuation therapy. One infant developed a SMN (mucoepidermoid carcinoma) during the 5-year follow-up period after the completion of chemotherapy. The relapse pattern was similar to that of P9407, which recorded five relapses, two marrow and three isolated extramedullary (1 subcutaneous, 1 CNS, 1 testicular), in 35 infants with *KMT2A*-g.

Table 2. Univariate analysis of prognostic factors in infants with *KMT2A*-g leukemia.

	N	5-year EFS (SE)	Estimated hazard ratio	*P*
Sex				
Female	33	96.9% (3.3%)	ref	0.045
Male	31	77.4% (8.9%)	4.39	
Age at diagnosis				
<6 months	12	81.8% (13.2%)	ref	0.68
≥6 months	52	88.5% (4.9%)	0.72	
WBC count (cells per L)				
$<50x10^9$	37	91.7% (5.1%)	ref	0.32
$≥50x10^9$	27	81.5% (8.5%)	1.95	
WBC count (cells per L)				
$<300x10^9$	57	85.7% (5.3%)		0.29
$≥300x10^9$	7	100%		
Diagnosis				
B-lymphoblastic leukemia	58	86.0% (5.2%)		0.31
T-lymphoblastic leukemia	6	100%		
Cytogenetics				
Normal diploid	17	87.5% (9.8%)	ref	0.36
Abnormal	36	91.7% (5.1%)	0.48	
Unknown	11			
CNS status				
CNS 1	41	92.5% (4.6%)	ref	0.10
CNS 2	16	75.0% (11.3%)	4.23	
CNS 3	6	83.3% (19.6%)	2.13	
Unknown	1			

KMT2A-g: *KMT2A*-germline; EFS: event-free survival; SE: standard error; WBC: white blood cell; L: liter; CNS: central nervous system; MRD: minimal residual disease.

The Kaplan-Meier survival curves for OS and EFS for the overall cohort and EFS curves for subgroups by sex, age < or ≥6 months at diagnosis, and WBC count < or ≥50,000 cells/μL at diagnosis are shown in Figure 1. The 5-year EFS among girls was superior to that of boys (96.9 ± 3.3% *vs*. 77.4 ± 8.9%, *P*=0.045; estimated hazard ratio: 4.4). In univariate analyses, age <6 months, WBC count ≥50,000 cells/μL, WBC count ≥300,000 cells/μL, B-cell *vs*. T-cell phenotype, normal diploid *vs.* abnormal cytogenetics, and CNS classification were not prognostic of 5-year EFS (Table 2).

In cases with karyotypic data (n=53), the most frequent recurrent cytogenetic abnormalities involved chromosome 9p (10 patients, 19%) and t(1;19)(q23;p13.3) or 19p13.3 variant (5 patients, 9%). The recurrent chromosome abnormality dic(9;20)(p13.2;q11) was identified in five of 53 cases (9%). Translocation of chromosome 5p15 with chromosome 15 was observed in two cases. Abnormalities of chromosome bands 15q11-15 have previously been identified in cases of infant ALL, occur in 1% of pediatric ALL overall, and may indicate a favorable prognosis, if *NUTM1* fusion is involved.[12-14] Molecular studies for *PAX5* and *NUTM1* rearrangements were not performed in AALL0631, and the prognostic significance

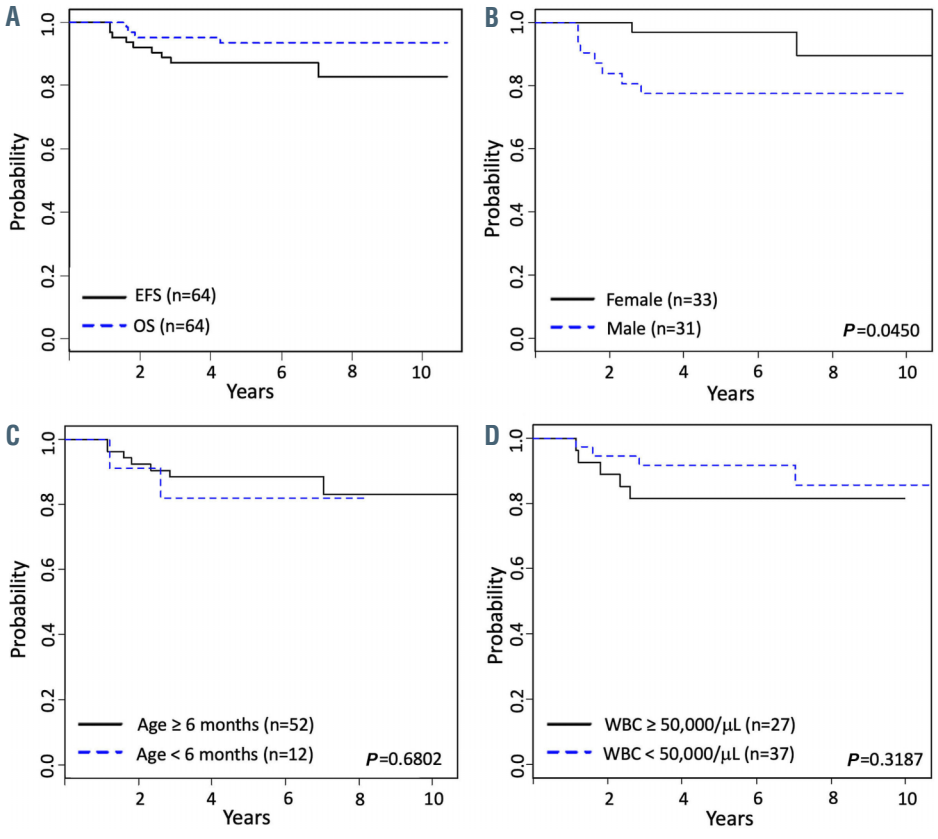

Figure 1. Kaplan-Meier survival curves for infants with *KMT2A-germline* leukemia. (A) Event-free survival (EFS) and overall survival (OS) for the standard risk group, *KMT2A*-germline. (B) EFS was lower for males *vs.* females. (C) There were no differences in EFS for infants < *vs.* ≥6 months at diagnosis or (D) with white blood cell (WBC) count < *vs.* ≥50,000/µL at diagnosis.

of the cytogenetic findings in *KMT2A*-g cases could not be determined, given the sample size and rarity of events.

The most common reported toxicities were infectious, gastrointestinal, metabolism/nutrition disorders and neutropenia. Grade 3 or 4 infections were reported for 20% or greater of infants during each chemotherapy course and were observed in approximately 40% of infants during each of the continuation phases (*Online Supplementary Table S3*). Gastrointestinal toxicities were reported most often in the induction intensification and consolidation phases, the two phases containing high-dose methotrexate. Neurologic, respiratory, skin, cardiac, and vascular toxicities were less commonly reported. The toxicities were comparable to those observed in prior infant ALL trials, with notably fewer toxic deaths than P9407, which resulted in five deaths as first events.[1,3,5]

The high dose intensity of AALL0631, similar to that of P9407, and the extended duration of AALL0631 therapy may both have contributed to the observed excellent outcomes for infants with *KMT2A*-g. AALL0631, in comparison to the standard arm of the contemporary Interfant-06 trial, gave considerably higher doses of chemotherapy. Considering age-based dose reductions in Interfant-06, the differences in cumulative chemotherapy doses were greatest in the youngest infants. Though well tolerated, the chemotherapy intensity of AALL0631 is also higher than that given to older children with *KMT2A*-g ALL on COG trials. The optimal therapy that will minimize toxicity risks and achieve superior survival for this very rare subset of pediatric ALL patients has yet to be defined. Future trials could consider the incorporation of targeted immunotherapy agents and prioritize the identification of prognostic factors that will enable some infants with *KMT2A*-g ALL to be treated less intensively.

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