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A Pilot Study of Azacitidine as Epigenetic Priming for Chemotherapy in Infants Less Than 1 Year of Age with KMT2A-Rearranged Acute Lymphoblastic Leukemia (ALL); Results from the Children's Oncology Group (COG) Trial AALL15P1

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Introduction

Acute lymphoblastic leukemia (ALL) with *KMT2A*-rearrangement (*KMT2A*-r) in infants <1 year is a high-risk childhood ALL subtype, with consistently poor event-free survival (EFS) of approximately 35% when treated with intensive chemotherapy with or without hematopoietic stem cell transplant. Infant ALL blasts are characterized by DNA hypermethylation, which is hypothesized to contribute to chemoresistance by altering transcriptional regulation of gene expression. In preclinical studies of *KMT2A*-r blasts, epigenetic priming with DNA methyltransferase inhibitors improved the *in vitro* cytotoxicity of chemotherapy. Azacitidine, a pyrimidine nucleoside analog of cytidine and hypomethylating agent, has been used in combination with chemotherapy in children with leukemia. We previously reported that azacitidine was safe and well tolerated in AALL15P1 (ASPHO 2021) and herein we report survival outcomes.

Methods

The Children's Oncology Group (COG) trial AALL15P1 (NCT02828358) was a single arm, open label, groupwide pilot trial. The primary aim of the trial was to evaluate the tolerability of azacitidine in addition to Interfant-06 standard chemotherapy in infants with newly diagnosed *KMT2A*-r ALL. **Estimation of 5-year EFS was an exploratory aim, given the small sample size.**

Eligibility criteria included B-ALL or acute leukemia of ambiguous lineage with ≥50% B-lymphoblasts, <366 days of age at diagnosis, and >36 weeks gestational age at enrollment. Exclusions included Down syndrome, secondary ALL, and prior cytotoxic therapy, except intrathecal chemotherapy or corticosteroids.

Following an Interfant-based induction, infants with *KMT2A*-r received 4 courses of azacitidine, 2.5 mg/kg/dose intravenously over 10-40 minutes daily for 5 consecutive days in each course, preceding the start of a chemotherapy course on day 6.

Treatment failure was defined as failure to achieve M1 marrow status with resolution of extramedullary leukemia by the end of consolidation. EFS and overall survival (OS) were measured from the time of enrollment.

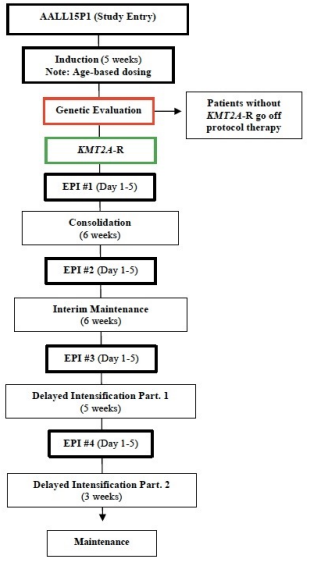
Patients

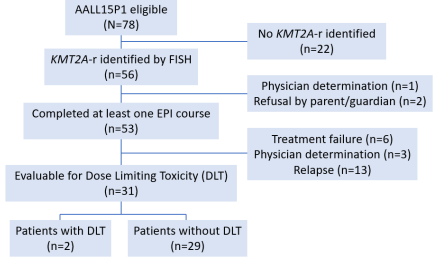
The study accrued from March 2017 to December 2019 and all protocol- directed treatment concluded in December 2021.

Of the 78 infants enrolled, 56 had *KMT2A*-r (72%), and 53 completed induction therapy and received at least 1 course of azacitidine. No patients were ineligible.

Highest risk diagnostic clinical characteristics of infants with *KMT2A*-r included four infants age <7 days (7%), 13 age <90 days (23%), 18 with white blood cell count ≥300,000/µL (32%), 32 CNS2 (57%), and four CNS3 (7%).

Experimental Design & Dose Limiting Toxicity





Evaluable Patients (n)	Toxicity Boundary (n)
6	3
7-10	4
11-16	5
17-21	6
22-28	7
29-30	8

152 azacitidine (EPI) courses completed in 53 patients

2 patients with DLT reported
- 1 delayed neutrophil recovery in Consolidation
- 1 delayed neutrophil recovery in DI Part 1

No deaths due to toxicity

DLT rate below toxicity boundary

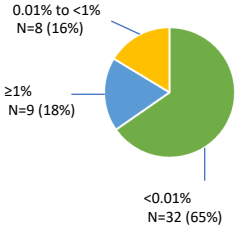
KMT2A-r Infant Response & Survival

Data cutoff (06/30/2022). Median follow-up is 3.8 years.

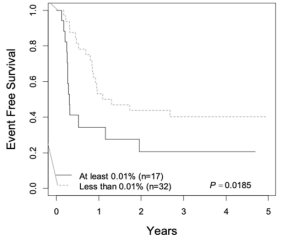
The majority (65%) of infants with flow cytometry minimal residual disease (MRD) reported were negative (<0.01%) after induction. Six infants experienced treatment failure.

3-year EFS (SE) and OS (SE) rates are 34.2% (+/- 8%) and 63.8% (+/- 8%), respectively.

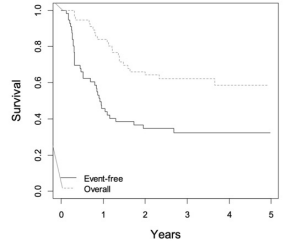
MRD at End of Induction N=49 Infants with *KMT2A*-r



AALL15P1 *KMT2A*-r EFS by MRD at End of Induction



AALL15P1 *KMT2A*-r Survival



Conclusions

Epigenetic priming with azacitidine prior to standard chemotherapy was well tolerated in infants with *KMT2A*-r ALL, but the EFS was consistent with the poor survival of historical outcomes. Positive flow MRD at the end of induction predicted a higher risk of treatment failure, relapse, or death, in comparison to negative MRD, but EFS was still unacceptably low for MRD- negative patients. There remains an urgent need for improved therapies for infants with *KMT2A*-r ALL.

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