Characteristics and outcomes of newly diagnosed pediatric acute myeloid leukemia patients who were removed from standard regimens and received alternative therapy

Acute myeloid leukemia (AML) accounts for 20% of childhood leukemia.[1] The 5-year event-free survival (EFS) and overall survival (OS) are 46% and 60% respectively, with particularly dismal outcomes for patients with high-risk (HR) disease.[2] In the US, many AML patients start treatment enrolled on or following a standardized Children's Oncology Group (COG) study regimen, but are then taken off and offered alternative therapy because of either persistent disease or toxicity. There are limited data about these patients given the minimal centralized data collection once these patients are removed from COG study protocols. We sought to determine when and why patients deviated from the standard COG-based AML therapy, what alternative treatments they received, and what their outcomes were. Our goal is to provide information that will support future evidence-based decision-making regarding alternative up-front AML treatment options. This study provides additional evidence of the potential value of giving fludarabine-based regimens to pediatric patients with *de novo* AML.

In the last two decades, COG conducted three major up-front-randomized phase III trials for patients with newly diagnosed AML (*clinicaltrials gov. Identifier: NCT04293562, NCT01371981* and *NCT00372593*); the chemotherapy backbones were similar and included three to five courses of intensive chemotherapy, and HSCT in first complete remission (CR) for the HR group.[3-6] These studies have resulted in more refined risk assessment, incorporation of a FLT3 inhibitor for patients with a *FLT3*-internal tandem duplication (ITD) mutation, and standard use of gemtuzumab ozogamicin (GO) in induction. Nevertheless, improvements in survival rates have been incremental.[3,7] Approximately 40% of AML patients who achieve CR after intensive chemotherapy relapse, with limited curative options.[2-5] Achieving early minimal residual disease (MRD) negativity is a consistent and powerful prognostic factor across different treatment regimens.[8-11] On COG regimens, induction II has less intensive chemotherapy compared to induction I, and so clinicians may feel pressured to deviate from the standard chemotherapy cycle sequence to an alternative regimen for patients with persistent disease at the end of induction I. Additionally, patients who experience toxicity may need to receive alternative regimens.

We retrospectively identified consecutive patients aged 0-21 years with newly diagnosed AML who were treated between January 2012 and December 2022 at Texas Children's Cancer Center or MD Anderson Cancer Center. AML was diagnosed per standard World Health Organization criteria. For the purposes of this analysis, risk assignment was made according to the schema for the protocol on which the patient was treated, recognizing that criteria differed between studies. The institutional review boards of both institutions approved this project.

OS was defined as the time from diagnosis until death. EFS was defined as the time from diagnosis until death, or relapse of any type, whichever occurred first. Patients who remained alive (OS) or alive and relapse-free (EFS) were censored at the last follow-up date. Refractory disease was defined as the persistence of central nervous system (CNS) disease after induction I, or the presence of morphologic bone marrow blasts ≥5% or any extramedullary disease at the end of induction II. MRD was assessed by flow cytometry. Patients with secondary malignancy or with myeloid sarcoma and no marrow disease or whose first treatment cycle was based on adult protocols were excluded. Kaplan-Meier analyses were used to estimate the distribution of OS and EFS from the date of diagnosis. Differences between groups were assessed by log-rank (Mantel-Cox). Statistical analysis was conducted using GraphPad Prism version 10.2.1 for Windows (Boston, MA, USA).

We included 144 consecutive patients in the analysis. Most patients began treatment enrolled on or treated according to COG trials AAML0531, AAML1031, or AAML1831. Three patients began treatment according to St. Jude trials AML02 or AML16. Ninety-five patients followed the standard sequence ("followed") and 49 were removed from the standard sequence ("deviated"), because of either persistent disease (N=45) or chemo-toxicity (N=4). Of those who followed the standard sequence, 33 were high risk (HR) and 62 were low risk (LR). As expected, most of the patients who deviated were HR (38/49). Of those who deviated, 30% deviated after induction I, 57% after induction II, and 10% after intensification I (Figure 1). Cytomolecular features and CNS status at diagnosis for the HR group who followed the standard sequence and the deviated group are reported in *Online Supplementary Table S1*. The median EFS was 672 days for the deviated group compared to 412 and 1,815 days for HR and LR patients who did not deviate, with 3-year EFS 26.5% *versus* 34.3% *versus* 40.3%, respectively (P=0.043). The median OS was 1,425 days for the deviated group compared to 832 days for HR patients who did not deviate, with a hazard ratio of 0.64 (95% confidence interval [CI]: 0.34-1.23) and 3-year OS 36.7% *versus* 39.4%

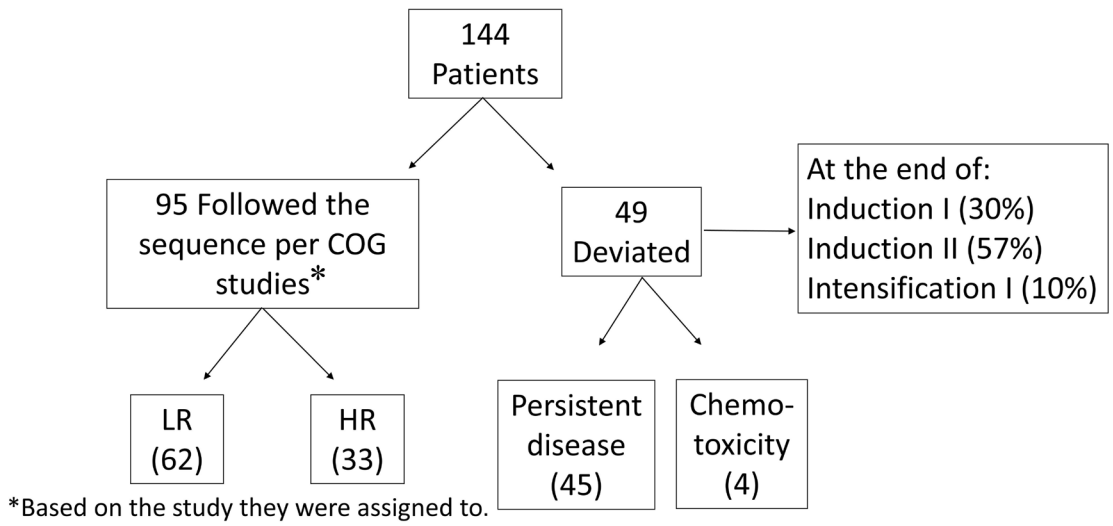

Figure 1. Overview of the patients included in the study. LR: low risk; HR: high risk; COG: Children's Oncology Group.

respectively (*P*=0.18) (Figure 2). Restricting the analysis to patients enrolled or treated according to AAML1031 showed a trend toward better OS for the AAML1031 deviated group compared to the AAML1031 HR followed group, although the difference was not statistically significant (*P*=0.16) (*Online Supplementary Figure S1*).

Outcomes were equivalent whether patients deviated after the first or second cycle (*Online Supplementary Figure S2*). We noticed a trend toward poorer outcomes for HR patients who followed the AAML 1031 regimen and got mitoxantrone and AraC as induction II (*Online Supplementary Figure S2)*. This suggests that there may have been some additional benefit from the deviated cycles, though the *P* value did not reach significance.

Median MRD was 1% for the followed group and 2.5% for the deviated group, respectively. There is no statistically significant difference in OS and EFS based on MRD status at end of induction I between followed and deviated groups (*Online Supplementary Figure S3*).

Twenty-five (51%) of the deviated group had MRD <1% and 24 patients (49%) had MRD equal or more than 1% at the time of deviation. OS was comparable between both groups but EFS favored MRD <1 group (*P*=0.01) (*Online Supplementary Figure S3*). The median time from the end of induction I bone marrow evaluation to HSCT date was used as an indication of treatment toxicity. Serious infections, prolonged cytopenias, and other complications of intensive alternative regimens would be expected to delay the time to HSCT. However, the median time to transplant was similar between the deviated group and HR patients who did not deviate (112 days compared to 110 days, respectively).

Forty-five percent of the patients who followed the standard sequence relapsed (40.3% for LR and 54.5% for HR) compared to 42.9% for the deviated group. Twenty percent of the deviated group had refractory disease before deviating, of whom 50% achieved CR and 30% received transplant. Most of the HR patients who followed the standard sequence and subsequently relapsed died (83%) compared to 40% and 57% for the LR and deviated groups, respectively (Table 1).

Eighteen relapsed patients of the followed group (15 LR and 3 HR) achieved CR2 with 11 patients surviving for more than 2 years, while nine relapsed patients in the deviated group achieved second complete remission (CR2), four of whom survived more than 2 years. The median time from relapse to death was 91 days for the HR followed group compared to 444 days for the deviated group.

Patients received a wide range of chemotherapy combinations for their first deviated cycle (*Online Supplementary Table S2*). Twenty-two of 49 patients received a fludarabine-based salvage therapy and had variable outcomes. Nine patients received fludarabine/cytarabine +/- granulocyte colony-stimulating factor (FLA +/- G) and all became MRD negative after that first deviated cycle. Eleven patients received either FLA with idarubicin or azacitidine and half of them became MRD negative after the first deviated cycle. One patient received FLA with decitabine and vorinostat (T2016-003), four patients received idarubicin with cladribine for their first deviated cycle, and all remained MRD positive. Six patients with CNS refractory disease received high-dose cytarabine with asparaginase and one of them remained with active disease. One patient received azacitidine with venetoclax and achieved MRD negativity after that first deviated cycle.

In this study, we provide a comprehensive analysis of outcomes for patients who deviated from the standard COG-based AML therapy sequence. At our institutions 34% of patients overall and 54% of HR patients did not complete the intended treatment regimen, mostly because of persistent disease. In most cases, clinicians opted for alternative therapy after induction II. Patients who transitioned to alternative regimens had comparable outcomes to HR patients who followed the standard therapy sequence with no difference in time to transplant, indicating that significant toxicities were not different between the followed and deviated groups. Our finding of a trend toward better OS for patients receiving alternative regimens compared to the HR patients who followed the standard sequence is intriguing. One potential reason could be that patients receiving alternative regimens achieved a deeper remission prior to

HSCT, resulting in a longer duration of remission and fewer comorbidities at relapse.

AML therapy is evolving, and many agents that have shown efficacy or are being investigated in the relapsed setting could improve outcomes in *de novo* HR patients if given upfront. The combination of venetoclax plus decitabine achieved a

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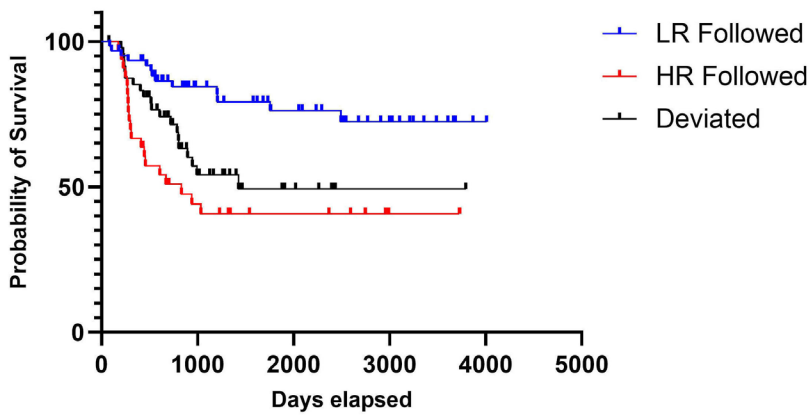

No at risk					
LR Followed	62	35	25	12	2
HR Followed	33	14	9	3	1
Deviated	49	19	7	2	1

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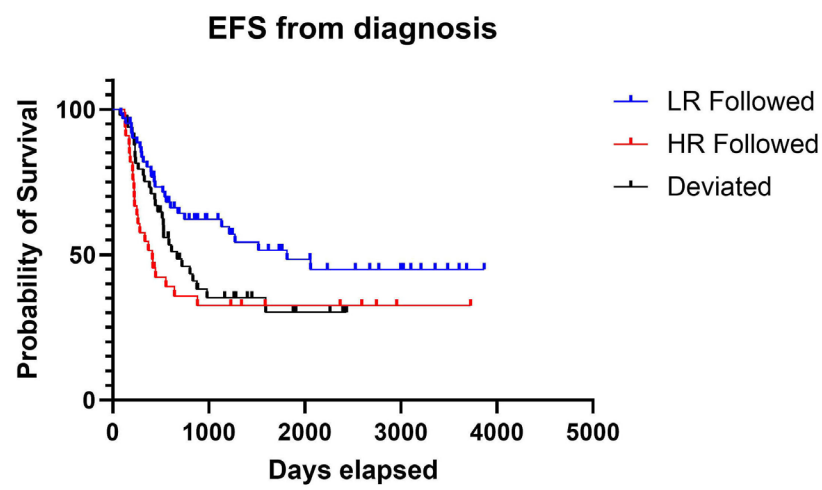

No at risk					
LR Followed	62	26	16	9	1
HR Followed	33	11	8	3	1
Deviated	49	13	5	1	0

	LR Followed	HR Followed	Deviated
Median survival	Undefined	832	1425

	LR Followed	HR Followed	Deviated
Median survival	1815	412	672

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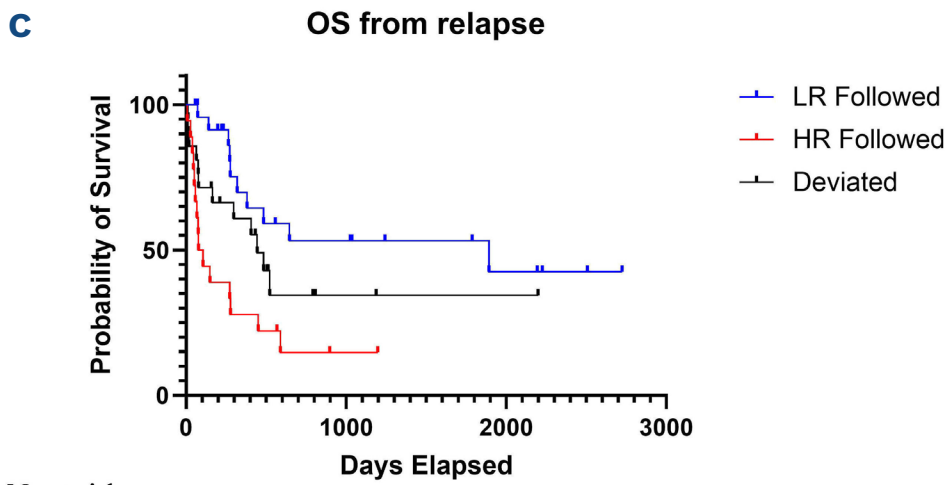

No at risk					
LR Followed	25	12	10	7	5
HR Followed	18	5	2	1	0
Deviated	21	8	3	2	1

	LR Followed	HR Followed	Deviated
Median survival	1893	91	444

Figure 2. Survival for newly diagnosed acute myeloid leukemia patients who followed the standard Children's Oncology Group-based sequence (low risk followed and high risk followed) and the deviated group. (A) Overall survival (OS) from diagnosis. (B) Event-free survival (EFS) from diagnosis. (C) Overall survival (OS) from relapse. LR: low risk; HR: high risk; COG: Children's Oncology Group.

Table 1. Patient outcomes for all patients who followed the standard sequence (followed), divided into low risk (low risk followed) and high risk (high risk followed), and the deviated group.

Outcome	Followed N=95	LR Followed N=62	HR Followed N=33	Deviated N=49
Relapse, N (%)	43 (45.3)	25 (40.3)	18 (54.5)	21 (42.9)
Refractory disease, N (%)	0	0	0	10 (20.4)
Death, N (%)	32 (33.7)	13 (21)	19 (57.6)	20 (40.8) (12 relapsed + 8 refractory)
Death after relapse, N (%)	25 (58.1)	10 (40)	15 (83.3)	12 (57)
Achieved CR2 after relapse, N (%)	18 (41.9)	15 (60)	3 (16.7)	9 (42.9)
Survival >2 years after relapse, N (%)	11 (25.6)	9 (36)	2 (11.1)	4 (19)

CR2: second complete remission; LR: low risk; HR: high risk.

66% CR rate when given as frontline therapy for adults with newly diagnosed AML, but only 24% in the relapse setting.[12] The UK Medical Research Council (MRC) AML15 trial investigated the use of FLAG-Ida for induction I and II in adult *de novo* AML and showed that FLAG-Ida significantly improved EFS but not OS.[13] In a recent pilot trial that treated 30 pediatric patients with *de novo* AML per MRC AML15, 93% of the patients achieved MRD negativity after induction I and all 30 patients were MRD negative post-induction II.[14] UK NCRI AML17 trial investigated the use of FLAG-Ida for three courses starting with induction II for adult HR-AML; 72% of the patients achieved CR and 13% CR with incomplete count recovery.[15]

Results should be interpreted with caution given the retrospective design, the variability in protocols and practices across different institutions and relatively small number of patients. Despite these limitations, further research is essential to validate our findings and assess long-term outcomes. These results highlight the need for a multicenter randomized controlled trial to better investigate FLA-based regimens as a frontline therapy for *de novo* pediatric AML. Our proposed Texas Children's Hospital institutional AML trial offers Ida-FLA as induction II and venetoclax-containing cycle as intensification I for newly diagnosed HR AML.

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Disclosures

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Contributions

Conceptualization by AW and MR. Data collection by AW, SC, KN and SD. Data analysis by AW and MR. Writing/original draft preparation by AW and MR. Writing/review and editing by AW, AS, BC and MR. All authors have read and agreed to the published version of the manuscript.

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Data-sharing statement

All data are available on request from the corresponding author.

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