LOCALITY OF TREATMENT IS ASSOCIATED WITH OUTCOME OF ACUTE MYELOID LEUKEMIA IN EARLY CHILDHOOD

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Background

- Acute myeloid leukemia (AML) diagnosed in the first years of life displays unique features that have provided important insights into the mechanisms of eukemogenesis once the first genetic hit arises before birth, when he ematopoietic progenitors are more sensitive to enotoxicvents Figure 1).
- Our aim was to described he frequency of recurrent molecular abnormalities in infants, toddlers and young children (≤ 5 years of age) with AML and investigated the association of demographic and molecular features with the outcome.

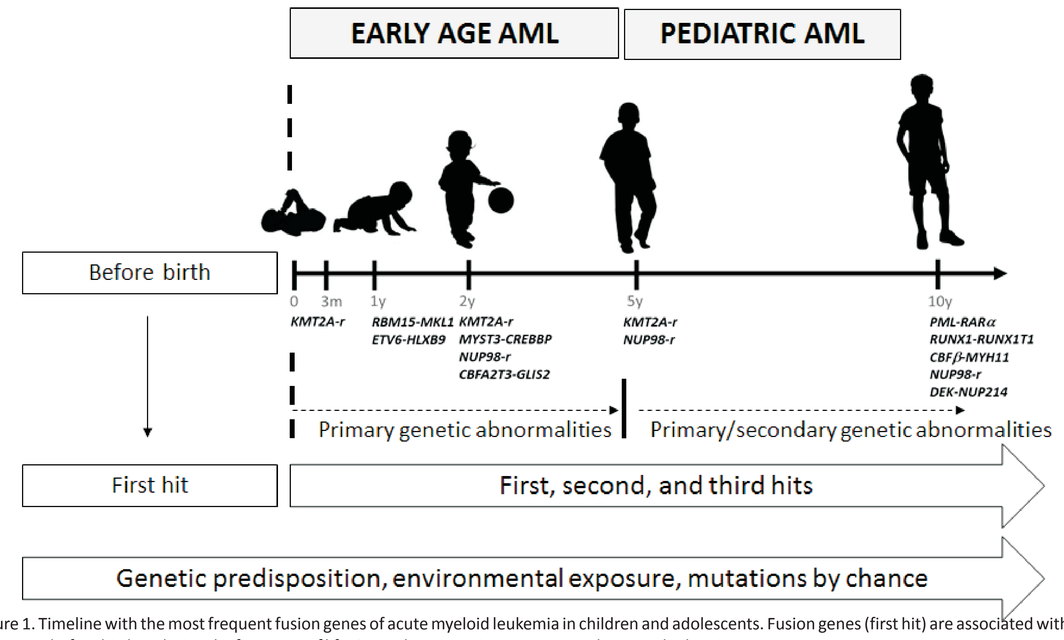

Figure 1. Timeline with the most frequent fusion genes of acute myeloid leukemia in children and adolescents. Fusion genes (first hit) are associated with age and may occur before birth or during the first years of life. Secondary mutations are required to overt leukemia.

Material and Methods

Patients. We analyzed a cohort of 221 cases of *de novo* AML (≤ 5 years-old) referred to the Pediatric Hematology-Oncology Research Program, INCA, Rio de Janeiro, that is a reference for leukemia diagnostic assistance. Cases included were forwarded from public Brazilian medical institutions of oncological care.

Molecular alterations. Mutations in hotspot regions of RAS pathway signaling genes (*FLT3*, *NRAS*, *KRAS*, and *PTPN11*) were analyzed by direct sequencing. Briefly, *FLT3* mutations were examined at the tyrosine kinase domain (TKD) in codon 835 and juxtamembrane domain in exons 11/12 as internal tandem duplications (ITD). *NRAS*/*KRAS* status was determined by searching mutations in exon 1 (codons 12/13), and *PTPN11* mutations were screening in exon 3.

Fusion genes associated with childhood AML were screened by RT-PCR and/or FISH [*MLL*/*KMT2A* rearrangements (*KMT2A*-r), *RUNX1-RUNX1T1*, *CBFb-MYH11*, *PML-RARa*, *NUP98* rearrangements (*NUP98*-r), *CBFA2T3-GLIS2*, *MYST3-CREBBP*, and *RBM15-MKL1*].

Survival analysis. Patients were treated according to BFM-AML2004 guidelines, not formally enrolled in treatment protocols. Patients with acute promyelocytic leukemia (APL) were excluded from the survival analysis. Categorical variables were compared using ^{2} test analysis or Fisher's exact test. An estimate of overall survival (OS) was determined using the Kaplan–Meier and log-rank tests in order to verify the association of one genetic alteration in the patients' outcome. OS was defined as the time from study entry to death from any cause. Patients lost to follow-up were censored at their date of last known contact.

Results

Table 1. Characteristics of pediatric patients with AML, Brazil, 2000-2017

	Early AML, n (%) (≤ 5 years old)
Brazilian geographical regions	
North/Northeast	80 (36.2)
South	22 (10.0)
Southeast	56 (25.3)
Midwest	63 (28.5)
Age (months)	
Sex	
Males	110 (49.8)
Females	111 (50.2)
WBC count (x10^9/l)	
≤50	155 (71.1)
>50	63 (28.9)
DS	
Yes	71 (32.1)
No	150 (67.9)
Total	**222 (100)**

AML, acute myeloid leukemia; DS, Down Syndrome

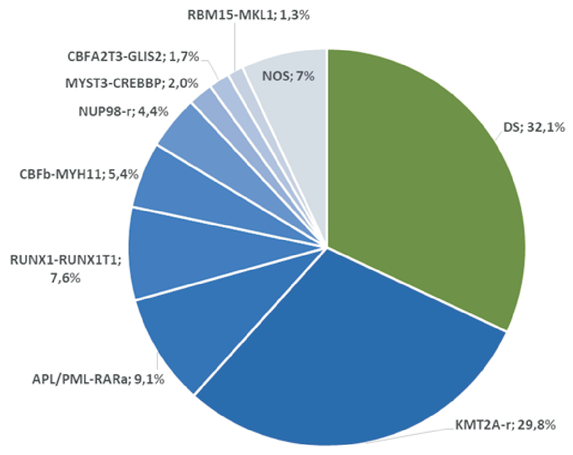

Figure 1. Frequency of genetic subtypes of pediatric acute myeloid leukemia. APL, acute promyelocytic leukemia; DS, Down Syndrome; NOS, not otherwise specified; r, rearragements.

Table 2. Association of mutations in *RAS* signaling pathway and demographical/laboratorial features, Brazil, 2000-2017

	Genes of RAS signaling pathway *		
	Mutated, n (%)	**Wild type, n (%)**	**p**
Age (years)			0.072
≤ 2	14 (41.2)	68 (58.6)	
>2	20 (58.8)	48 (41.4)	
Sex			0.456
Males	18 (52.9)	53 (45.7)	
Females	16 (47.1)	63 (54.3)	
WBC count (x10^9/L)			0.003
≤50	16 (47.1)	85 (74.6)	
>50	18 (52.9)	29 (25.4)	
Total	**34 (22.6)**	**116 (77.4)**	

**KRAS, NRAS, FLT3,* and *PTPN11*. AML, acute myeloid leukemia; WBC, white blood cell count

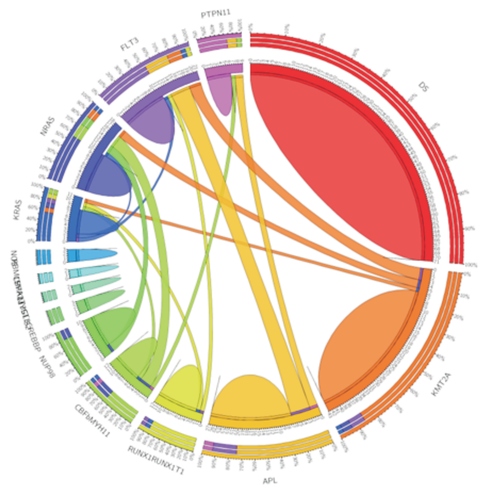

Figure 2. Distribution of molecular alteratios of pediatric acute myeloid leukemia. APL, acute promyelocytic leukemia; DS, Down Syndrome; NOS, not otherwise specified; r, rearragements. The circos plot depicts the co-occurrence of mutations in patients with *de novo* pediatric AML. The length of the arch corresponds to the frequency of the mutation, and the width of the ribbon with the percentage of patients with a specific mutation or a combination of mutations.

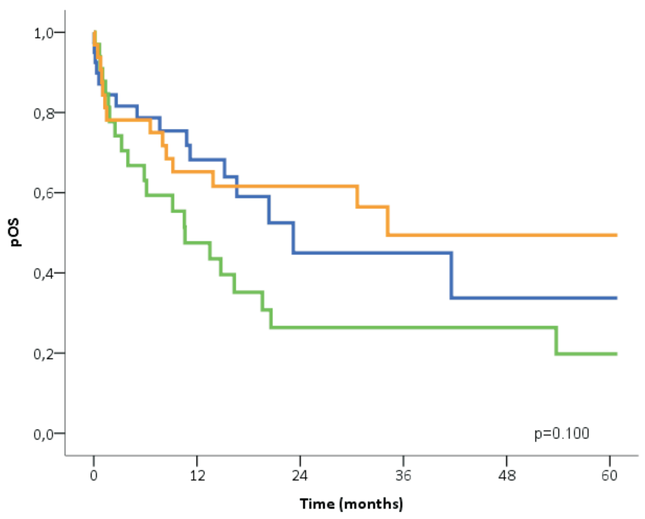

Figure 3. Survival analysis of the pediatric AML cases. Comparison of survival curves among geographic region* P values were calculated using log rank test. n, number of cases; pOS, probability of overall survival; SE, standard error.
*Excluding acute promyelocytic cases.

Conclusion

Collaborative efforts allowed the establishment of a network of diagnosis to characterize molecular subtypes AML. Differences in outcome were observed between Brazilian geographical regions, with the Midwest associated with low pOS.

Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA

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