MOLECULAR ALTERATIONS IN PEDIATRIC ACUTE MEGAKARYOBLASTIC LEUKEMIA

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Background / Objectives

Acute megakaryoblastic leukemia (AMkL) represents about 15% de novo acute myeloid leukemia (AML). This subtype is divided into two distinct entities: i) AMkL arising in the context of Down syndrome (DS-AMkL) and ii) de novo AMkL (AMkL-nonDS). Our aim was to compare biological features of pediatric AMkL with and without Down syndrome (DS) and evaluate the outcome according to leukemia subtype.

Design /Methods

We have analyzed 163 cases of AMkL, with age ≤ 21 years-old. The most frequent genetic alterations in AMkL [*KMT2A* rearrangements (*KMT2A*-r), *NUP98* rearrangements (*NUP98*-r), *CBF2AT3-GLIS2*, and *RBM15-MkL1*] were identified by FISH, RT-PCR, and RT-PCR multiplex. Mutations in *GATA1* were identified by Sanger sequencing in cases with DS. The overall survival (OS) was analyzed by Kaplan Meier method, and differences between groups were compared by log rank test.

Results

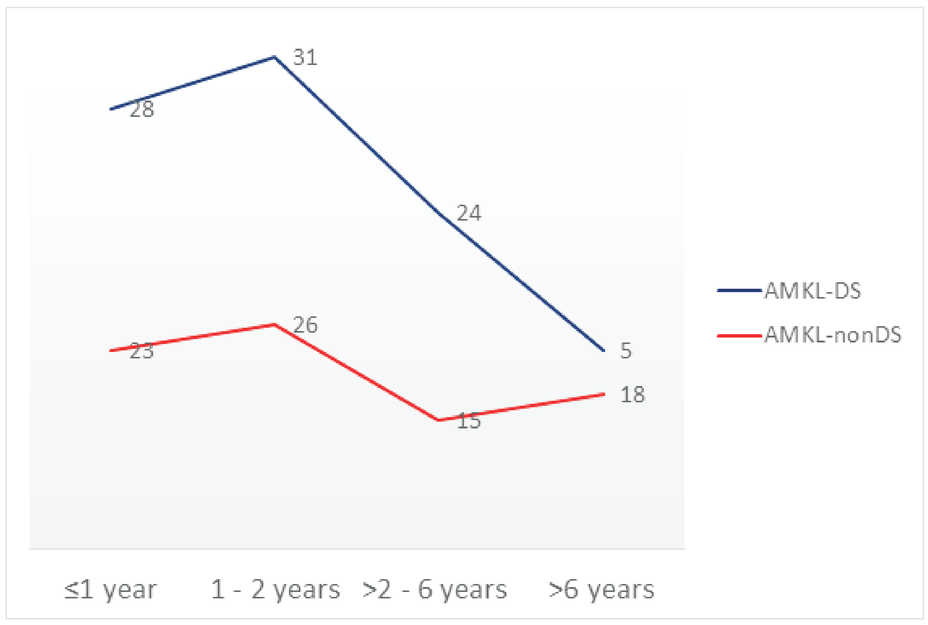

Figure 1. Frequency of patients with AMkL according to age. AMkL-DS, Acute megakaryoblastic leukemia with down syndrome. AMkL-nonDS, Acute megakaryoblastic leukemia without down syndrome .

The most frequent age was <25 months of age (67.1%; p<0.001)

Age (years)		AMkl-DS	AMkL-nonDS	p-Value
	≤1	28 (54,9%)	23 (45,1%)	
	1 - 2	31 (54,4%)	26 (45,6%)	0.002
	>2-6	24 (75%)	8 (25%)	
	>6	5 (21,7%)	18 (78,3%)	
Sex				
	Male	45 (54,9%)	37 (45,1%)	
	Female	43 (53,1%)	38 (46,9%)	0.471
WBC				
	<20.000	39 (46,4%)	45 (53,6%)	0.25
	>20.000	45 (63,4%)	26 (36,6%)	

White blood cell (WBC) count at diagnosis ≤50x10^9 cell/L (88.4%; p<0.001). The median of WBC count and age at diagnosis in patients with AMkL-nonDS was 9.2x10^{9}cell/L and 18 months, respectively. In patients with AMkL-DS the median of WBC count and age was 12x10^{9}cell/L and 19 months, respectively.

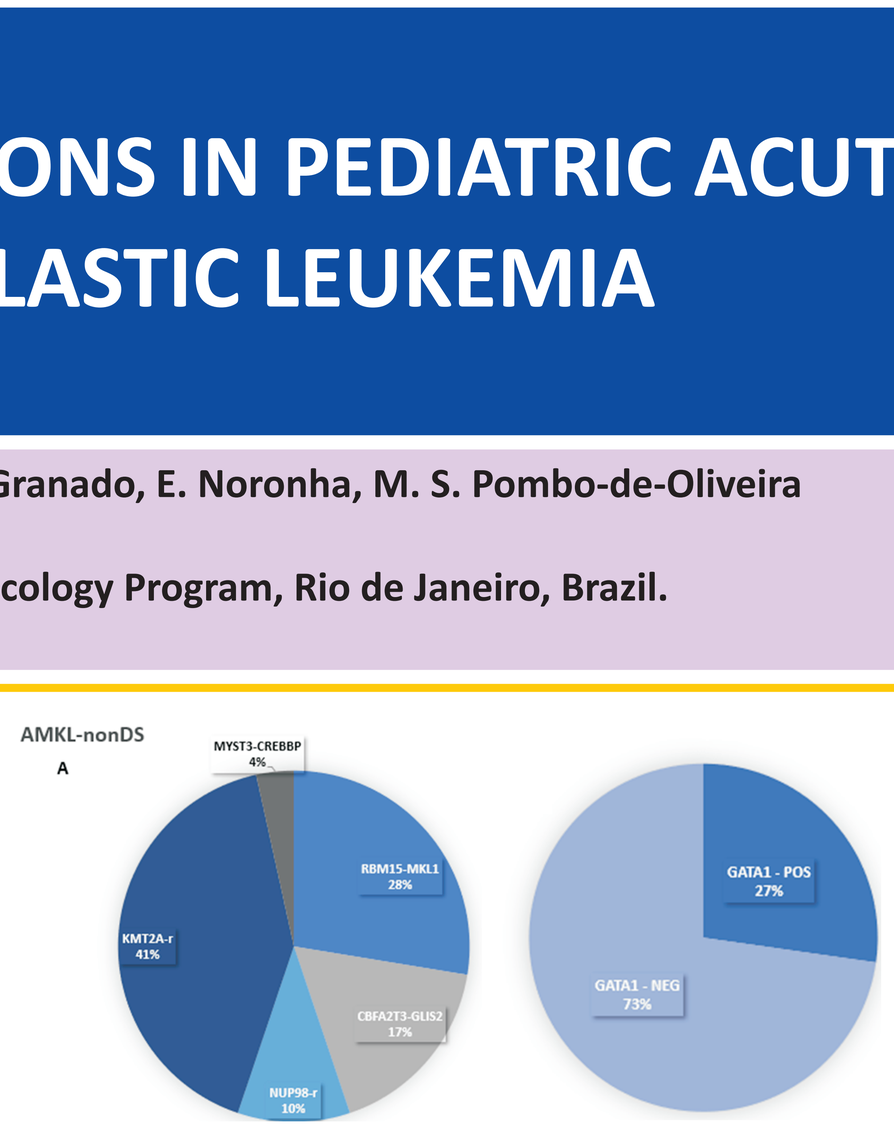

Figure 2. Frequency of molecular alterations in AMkL. **(A)** The frequency of major molecular alterations in AMkL-non DS in the cases studied. **(B)** The frequency of major molecular alterations in AMkL-DS in the cases studied.

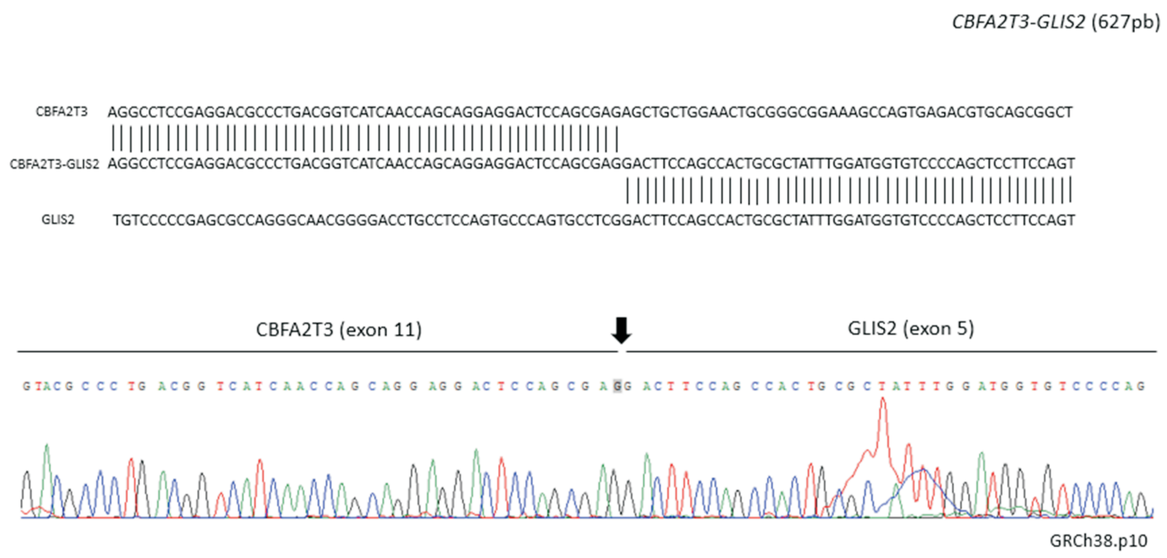

Figure 3. Description of the fusion transcript *CBFA2T3-GLIS2*. Sanger sequencing of a positive case for fusion *CBFA2T3-GLIS2*.

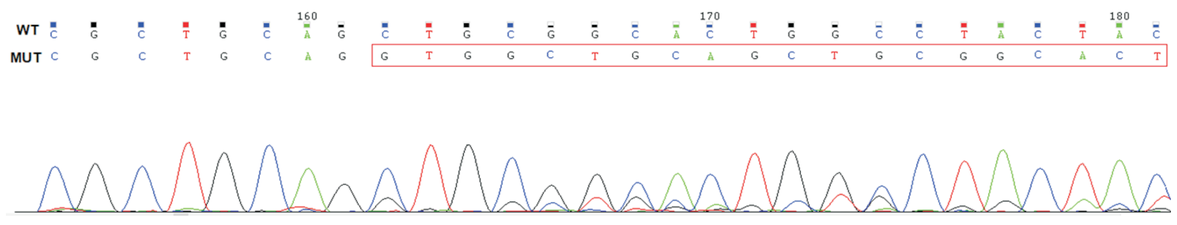

Figure 4. Mutation in *GATA-1*. The mutation is characterized by a frameshift insertion in codon 57 (c.169_170insGTGGCTGCAG), resulting in a stop at codon 70.

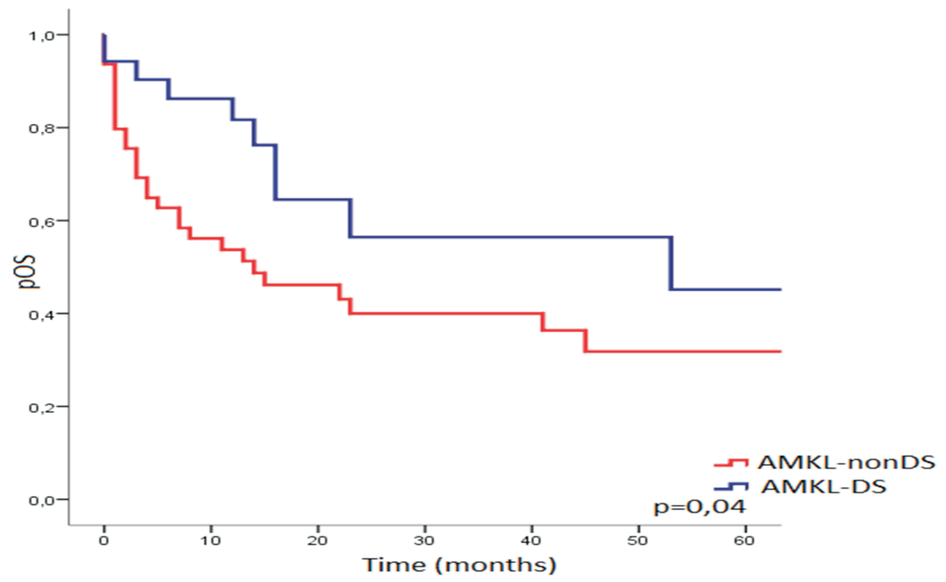

Figure 5. Overall survival in 5 years of patients with AMkL.

The cases of AMkL-DS (87 pacients, 13 events) presented higher probability of OS compared to patients with AMkL-nonDS (63 pacients, 30 events) (78.6%±11% and 23.7%±11.1%, respectively; p=0.04).

Conclusion

Fusion genes are frequent in AMkL-nonDS, which is genetically heterogeneous and associated with poor prognosis.

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