Infant Acute Leukemia – Clinical, Imunophenotypic and Molecular Profile of Patients Treated at Instituto Nacional de Câncer – INCA, a Single Center in Brazil

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CONTEXT

Infant acute leukemia (IAL) represents an uncommon and complex disease arising in patients less than one year. It accounts for 2,5 to 5% of the childhood leukemias. Leukemogenesis can occur earlier in prenatal period due to chromosome abnormalities. Most of patients presents rearrangements involving *Mixed Lineage Leukemia (MLL)* gene on chromosome band 11q23. The t(4;11)(q21:q23) with *MLL-AFF1* fusion is the most prevalent subtype of 11q23/*MLL* rearrangements.

There is evidence that *MLL* rearrangements in acute leukemias occur in utero as well as its association with maternal and fetal exposure to carcinogens during pregnancy.

Some of the clinical characteristics of this disease include patients less than 12 months of age, high initial leukocyte count greater than $300x10^9/L$ at diagnosis, hepatomegaly/splenomegaly, absence of CD10 expression, myeloid-associated antigen expression, poor prognosis, frequent early relapses, any 11q23/MLL rearrangement, central nervous system (CNS) infiltration and a poor response to therapy. Children less than or equal to 90 days of age at diagnosis and those with MLL experiencing a particularly poor outcome.

Intensive care strategies and allogeneic haematopoietic stem cell transplantation (allo-HSCT) in first complete remission are the choices to improve the results in these patients.

This is a rare and heterogeneous group of diseases and it still arises interest in understanding carcinogenesis.

OBJECTIVE

Show IAL characteristics and diagnostic relevance in a single institution, not exclusively pediatric.

DESIGN

We retrospectively evaluated clinical and laboratorial data from a subset of five IAL patients between january 2008-2013.

SETTING/PATIENTS

From 6 infants with IAL, 2 were boys and 3, girls. Age ranged 4 to 7 months and leukocyte count at diagnosis ranged 19500 to 360000. Three were acute lymphoblastic leukemia (ALL) and 2, acute myeloid leukemia (AML). One M1-AML, 1 immature T-ALL, 2 pre-B ALL without CD10 expression, and 1 M4-AML with retroorbitary chloroma. Cytogenetic abnormalities involving 11q23 region were detected in 3 cases. The first with t(13;9;11)(q?13;p22-;q23), the second with t(10;14)(p12;q32), t(11;21;19)(q23;q22;p13) and the third with a complex karyotype. One patient had no mitosis and FISH was *MLL*-negative.

INTERVENTIONS/MAIN OUTCOMES MEASURES/RESULTS

IAL diagnosis was made according to morphology and immunophenotyping classification, followed by conventional karyotyping and Multicolor Banding (MCB). Samples were screened using RT-PCR for the presence of specific fusion genes. FISH assay for *MLL* rearrangements was performed in cases with negative or inconclusive cytogenetic or PCR results.

60% of cases were *MLL*-positive (not available for 1 patient and negative also for 1) and 80% had CNS infiltration. Rearrangements involving 11q23 region were derived from uncommon and complex “three way“ translocations. 80% were classified as high risk and 20% as low risk, according to Interfant-99 protocol. Two patients were submitted to unrelated allogeneic hematopoietic stem cell transplantation and both of them are alive in complete remission (CR). One patient was submitted to haploidentical transplant. One death occurred due to refractory disease after the third rescue therapy and was not submitted to allo-HSCT, although he had one donor. The low risk patient, *MLL* negative, who was not submitted to allo-HSCT, is alive and in complete remission (CR).

Table 1. Clinical and laboratory characteristics

	SEX	AGE (months)	LEUKOCYTES (/mm3)	VISCEROMEGALY	IMMUNOPHENOTYPE	KARYOTYPE	MLL	CNS	RISK	BMT	STATUS
1	M	4	75000	N	AML M1	COMPLEX	NR	Y	HR	Y	CR
2	F	7	360000	Y	ALL T	COMPLEX	Y	Y	HR	Y	CR
3	M	5	136000	Y	ALL PRE B	t(13;9;11)	Y	Y	HR	N	DEATH
4	F	5	66000	Y	ALL PRE B	NO MITOSIS	N	N	LR	N	CR
5	F	7	19500	N	AML M4 (myeloid sarcoma)	COMPLEX	Y	Y	HR	Y	CR

CONCLUSIONS

IAL is a rare disease with poor outcome, mainly due to high frequency of early relapses. The disease occurs slightly more often in girls than in boys and allo-HSCT in high risk patients in first remission is the treatment of choice due to its aggressiveness. Our results, concerning patients' characteristics, prognostic factors and therapy choice, endorse literature data. Rearrangements involving 11q23 region were derived from uncommon and complex “three way“ translocations were a particularity in our study. Any new information as well as additional molecular findings help identify other risk factors, reinforcing that there are different etiologies for molecularly defined subtypes of IAL. Disease's rarity is the major obstacle for new data, even more in a single institution like ours, which is not exclusively pediatric.

Projeto Gráfico: Área de Edição e Produção de Materiais Técnico-Científicos / INCA