MOLECULAR EPIDEMIOLOGY OF PEDIATRIC ACUTE PROMYELOCYTIC LEUKEMIA IN BRAZIL

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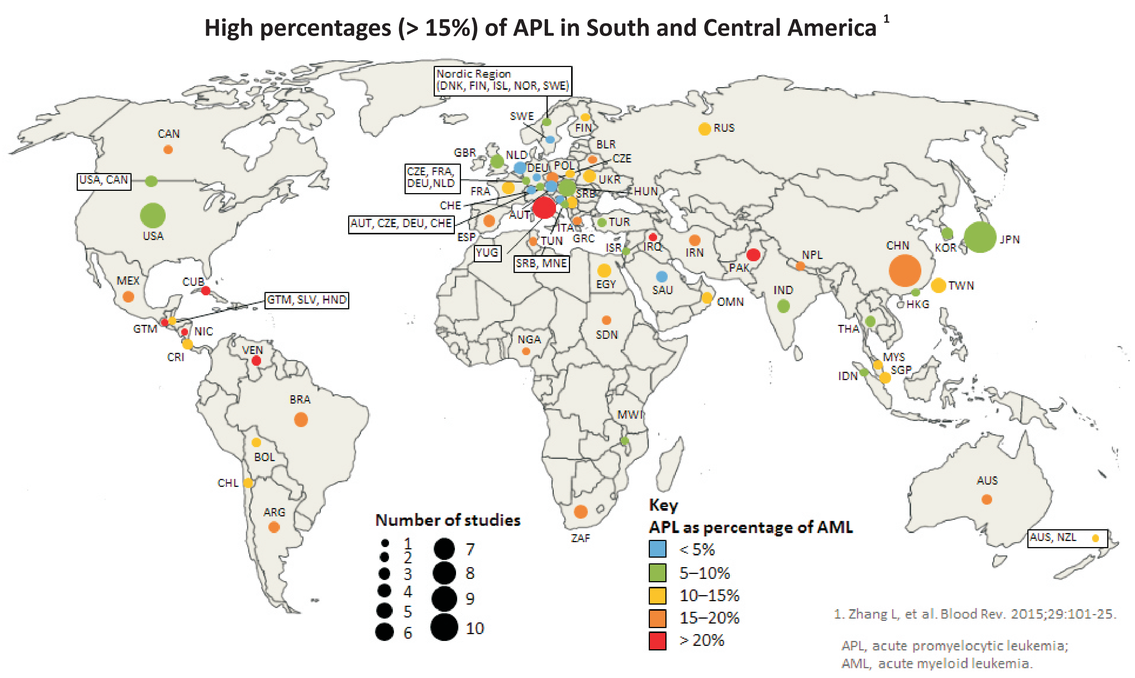
Background

- Acute promyelocytic leukemia (APL) is characterized by a defining chromosomal aberration [t(15;7)(q24;q21), which creates a chimeric *PML-RARα* fusion gene] and a distinctive cytopathology.
- Incidence rates of pediatric APL differ markedly among certain ethnic groups and geographical regions. High proportions of APL were reported in countries from South and Central America and in the Latino population (Figure 1).
- The causes of this variance are unknown - potentially genetic factors associated with ancestry may play a role; alternatively, exposures to environmental agents may impact regional variation.

High percentages (> 15%) of APL in South and Central America [1]



1. Zhang L, et al. Blood Rev. 2015;29:101-25.

APL, acute promyelocytic leukemia; AML, acute myeloid leukemia.

Aim

- To establish the incidence rate of APL among children and adolescents according to hospital- based and population-based cancer registries (PBCR) in Brazil.
- To describe the molecular features of APL to provide insight into molecular epidemiology potentially associated with APL development.

Material and Methods

Study Population, data sources and extraction.

Population-based cancer registries (PBCR). Incidence and mortality data on Brazilian children (age 0-14 years) and adolescents (age 15-19 years) diagnosed with myeloid malignances were obtained from databases of 15 PBCR (2000-2009). The information of patients was collected according to standardized criteria recommended by International Agency for Research in Cancer to Cancer Registries. Cases were classified according to the third edition of the International Classification of Diseases for Oncology (ICD-O-3).

Hospital-based cancer registry (PHOP, INCA). APL cases (<19 years old) were assessed from a dataset of hospital-based registry from a central laboratory (PHOP, INCA) that is a reference for leukemia diagnostic assistance (2002-2017). Diagnostic algorithm included morphology, immunophenotyping, and molecular biology (FISH/RT-PCR) for identification of *PML-RARα*. 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. This study was approved by the ethics and scientific committee of National Cancer Institute (INCA) (#186.688), and the ethics committee of all collaborating Brazilian institutions

Statistical analysis.

Population-based cancer registries (PBCR). Incidence rates were calculated as the annual number cases per million person-years, geographical regions and four groups of age (< 1year, 1-4 years, 5-9 years, and 10-19 years), based on the period of 10 years of available information for each PBCR (2000-2009). Age-stardardized incidence per million person-years and confidence intervals (CI) of 95% were calculated.

Hospital-based cancer registry (PHOP, INCA). Descriptive analyses were performed through continuous variables in order to measure central tendency and dispersion, as well as categorical variables to determine the frequency distribution. χ^2 or Fisher's exact test was used to compare proportions between groups. The non-parametric Mann-Whitney U test was used for continuous variables. Age was considered a categorical variable with three groups for analysis, comprising cases who were ≤ 2 years old, 2-10 years old and >11 years old.

Results

In the PBCR, 45 out of 1.421 (3.2%) myeloid malignances (MM) were diagnosed with APL (Table 1), while in the PHOP-based registries, 149 patients out of MM (20.3%) were APL (Table 2). The incidence rate based on PBCR showed that APL was highest in Southeast/South (1.60 per million) compared with other Brazilian regions (0.9 per million). MM rate of unspecified cell-type in PBCRs was about 50% and the coverage of PHOP, which was estimated to cover 95% of PBCRs.

Table 1. Coverage by Brazilian contributing registries and constitution of datasets by region, 2000-2009

	Coverage			AML				Age		
	Registry	Population covered (%)	Range	Non-APL	APL, N	M, %	F, %	0-4 years	5-9 years	10-19 years
Region										
North	Capital and County	30	2000-2009	106	03	33.3	66.7	0 (0.0)	00 (0.0)	3 (100.0)
Northeast	Capital city	21	2000-2009	145	04	100.0	00.0	1 (25.0)	02 (50.0)	1 (25.0)
Midwest	Capital and County	23	2000-2009	55	02	100.0	00.0	0 (0.0)	01 (50.0)	1 (50.0)
Southeast	Capital and County	24	2000-2009	387	11	45.5	54.5	1 (9.1)	03 (27.3)	7 (63.6)
South	Capital city	14	2000-2009	77	15	46.7	53.3	0 (0.0)	04 (26.7)	11 (73.3)
Brazil	Capital and County	23	2000-2009	770	35	54.3	45.7	2 (5.7)	10 (28.6)	23 (65.7)

AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; F, female; M, male; n, number cases. Registries by region: North (Belém and Manaus); Northeast (Aracaju, Fortaleza, João Pessoa, and Recife); Midwest (Cuiabá and Goiânia); Southeast (Barretos, Belo Horizonte, Jahu, Espírito Santo, and São Paulo); South (Curitiba and Porto Alegre).

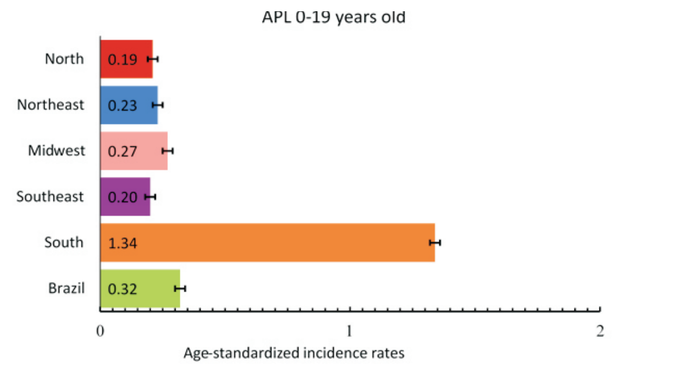


Figure 1. Age-standardized incidence rates per million for acute promyelocytic leukemia among children and adolescents according geographical region, Brazil 2000-2009. Error bars represent 95% confidence intervals.

Table 2. Features of pediatric APL, Brazil, 2002–2017

	Frequency, n (%)
Brazilian locality	
Northeast	65 (43.6)
South	2 (1.3)
Southeast	44 (29.5)
Midwest	36 (24.2)
North	2 (1.3)
Age, years	
≤ 2	5 (3.4)
> 2–10	68 (45.6)
≥11	76 (51.0)
Sex	
Female	65 (43.6)
Male	84 (56.4)
Race	
Black	13 (8.7)
Non-Blacks	136 (91.3)
WBC count at diagnosis (x10^9/L)	
≤10	72 (48.3)
>10	77 (51.7)
Total	149 (20.3)

N, number of cases; WBC, white blood cell count

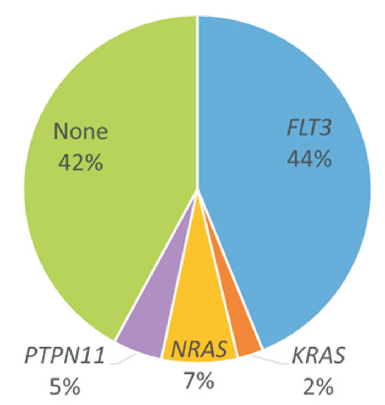


Figure 2. Frequency of *RAS* pathway mutations in pediatric APL

Table 3. Features of APL according to *FLT3* mutations , Brazil, 2002–2017

	FLT3 ^{mut}, n (%)	*FLT3* ^{wt}, n (%)	p
Median of age at diagnosis (years)	11.2	9.3	0.294
Age (years)			0.136
≤ 2	0 (0.0)	3 (4.9)	
> 2–10	19 (39.6)	30 (49.2)	
≥ 11	29 (60.4)	28 (45.9)	
Sex			0.120
Female	16 (31.2)	2 (45.9)	
Male	33 (68.8)	33 (54.1)	
Median of WBC at diagnosis (x10^9/L)	22.850	7.000	0.003
WBC count (x10^9/L)			0.001
≤10	14 (29.2)	37 (60.7)	
>10	34 (70.8)	24 (39.3)	
Median of platelets count (×10^9/L)	21.000	30.000	0.127
Platelets (×10^9/L)			0.053
≤40	35 (81.4)	37 (63.8)	
>40	8 (18.6)	21 (36.2)	
Morphological subtype			0.057
Hypergranular	38 (79.2)	56 (91.8)	
Microgranular	10 (20.8)	5 (8.2)	
Breakpoint cluster region in *PML*			<0.0001
Bcr 1	2 (10.5)	10 (58.8)	
Bcr 2	0 (0.0)	4 (23.5)	
Bcr 3	17 (89.5)	3 (17.6)	
Total	49 (58.3)	35 (41.7)	

Bcr, breakpoint cluster region; mut, mutated; n, number of cases ; wt, wild type.

Conclusion

APL is the most frequent subtype of myeloid malignance and is highly associated with *FLT3* mutations, reflecting the profile of the disease in Brazil. Future studies should explore these association with environmental exposures.

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

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