The apparent excess of acute promyelocytic leukemia in infant acute leukemias in brazil

Haematologica 2004; 89:(11)e135

Acute promyelocytic leukemia (APL) is an uncommon variant of acute myelogenous leukemia (AML) in childhood. This subtype of leukemia is distinguished by balanced reciprocal translocations between chromosomes 15 and 17 resulting in a *PML/RARα* fusion transcript, which plays a crucial role in their pathogenesis.[1] Epidemiological studies have reported a 5% to 10% incidence of APL between AML in adulthood. APL patients are referred to as having bimodal age distributions; however, this occurs seldomly in children less than 2 years of age. A high frequency of APL in Latino AML patients have been reported recently, and led to the hypothesis that APL could be related to ethnic background and/or exposure to distinct environmental factors.[2-6] With this letter we add more information about the increased prevalence of APL in Latino children raising questions about earlier environmental exposures. We also suggest the *in utero* origin of the *PML/RARα* fusion gene based on the short period of environmental exposure of the cases reported herein. Since June 1999 a non-population based registry, called The Brazilian Group for Infant Acute Leukemias Studies was created with the following aims: i) to conduct an immunophenotypic and molecular study in children under 2 years of age with acute leukemia, in order to determine the associations with selected risk factors in acute infant leukemias (AIL) from different regions of Brazil; ii) to characterize the more frequent chromosomal abnormalities detected by molecular markers in AIL in Brazil. All children included in this study were newly diagnosed and previously untreated. The genotype was characterized by cytogenetics and molecular analysis with well-established techniques such as RT-PCR and FISH. In a preliminary evaluation of the dataset, a high prevalence of MLL rearrangements (85%) was found as expected;[7] however, an unusually high frequency of APL (5 out of 45, 11% of AML cases) was found amongst other chromosomal abnormalities. The mean age of the AIL cases was 16 months (ranged 14 to 21 months). The mean leukocyte count was 10.900/mm^3 and in four cases the t (15; 17)(q22; q21) was identified by conventional cytogenetics and/or by RT/PCR and in one case the karyotype was characterized by add^{15} i^{17} that is a rare variation of the classical translocation. They were treated with All-trans Retinoic Acid and Idarubicin according to the AIDA protocol.[8] One patient lacks follow-up, three are dead after 3 years since diagnosis and one is alive after 3 years since diagnosis. Enquiries on maternal behaviour demonstrated that living in rural towns and being exposed to agricultural products (pesticides and/or herbicides) was a common factor among the mothers. Furthermore, the frequencies of APL in a series of 392 children's AML (0-16 years of age) in our laboratory 51 (13.0%) were APLs.

Since the first report using molecular markers in identical twins with concordant leukemia and retrospectively with Gutherie cards, several authors have demonstrated that gene fusions such as *AF4/MLL, TEL/AML1, AML1/ETO, CBFH/MYHII* and *PML/RARα* in acute leukemia arose before birth.[9,10] However, only the most common translocation in infants that involves *MLL* gene fusions has been associated with maternal transplacental exposure.[11] The former study investigated the effects of selected exposures [medicines, tobacco, alcohols, pesticides, chemical solvents and herbicides] *in utero* in children who developed AIL, demonstrated a specific association of exposure to pesticides with AMLs (OR 5.08; 95% CI 1.84-14.04).

The present data support the previous results related to the high frequency of APL in Latino AML. The apparent excess of APL in a Brazilian series of IAL could be potentially related to distinct environmental factors rather than to ethnic background. The apparent *PML/RARα* fusion gene arousing early in life should be evaluated in an extended cooperative study, since limited epidemiological study is available worldwide to support the apparent associations with environmental exposure.

References

1. Grignani FR, Ferruci PF, Testa U et al. The acute promyelocytic leukemia specific PML/RARα fusion protein inhibits differentiation and promotes survival of myeloid precursor cells. Cell. 1993; 74: 423-
2. Biondi A, Rovelli R, Canti-Raynoldi A, et al. Acute promyelocytic leukemia in children: experience of the Italian Pediatric Hematology and Oncology Group (AIEOP). Leukemia. 1994; 8: 1264-66.
3. Douer D, Preston-Martin S, Chang E, et al. High frequency of acute promyelocytic leukemia among Latinos with acute myeloid leukemia. Blood. 1996; 87:308-13.
4. Tomas JF, Fernandez-Ranada JM. About the increased frequency of acute promyelocytic leukemia among Latinos: the experience from a center in Spain. Blood. 88:2357-8, 1996.
5. Otero JC, Santillana S, Fereyros G. High frequency of acute promyelocytic leukemia among Latinos with acute myeloid leukemia. Blood. 1996; 88:377.
6. Ruiz-Arguelles GJ. Promyelocytic leukemia in Mexican Mestizos. Blood 1997; 89:348.
7. Pombo-de-Oliveira MS, Silva M.L.M., Salles T.J. Infant leukemia with chromosomal abnormalities and exposure risk factors in Brazil. Medical & Pediatric Oncology. 2000; 53:172.
8. Breccia M, Diverio D, Noguera NI, et al. Clinico-biological features and outcome of acute Promyelocytic leukemia patients with persistent polymerase-chain reaction detectable disease after AIDA front-line induction and consolidation therapy. Haematologica 2004; 89; 29-33.
9. Gale KB, Ford AM, Repp R, et al. Backtracking leukemia to birth: identification of clonotypic gene fusion sequence in neonatal blood spots. Proc Natl Acad Sci USA 1997; 94:13950-54.
10. McHale CM, Wielmels JL, Zhang L, et al. Prenatal origin of childhood acute myeloid leukemias harboring chromosomal rearrangements t(15;17) and inv (16). Blood 2003; 101: 4640-46.
11. Alexander FE, Patheal SL, Biondi A et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Cancer Res 2001; 61:2542-46.

*Wellington Luiz Mendes, Virginia Maria Coser, Gilberto Ramos, Waldir Pereira, Luiz Fernando Lopes, Maria S Pombo de Oliveira **

Correspondence: Maria S Pombo de Oliveira, MD, PhD
Instituto Nacional de Câncer-Centro de Pesquisa
Rua André Cavalcanti, 37 CEP 20 231050 Rio de Janeiro
E-mail: mpombo@inca.gov.br