

## The results of the International Consortium on Acute Promyelocytic Leukemia: a ‘proof of concept’ of networking as a strategy to improve the outcome of treatment of hematological malignancies in developing countries

Eduardo Magalhães Rego

Faculdade de Medicina de Ribeirão Preto,  
Universidade de São Paulo - USP, Ribeirão  
Preto, SP, Brazil  
International Consortium on Acute  
Promyelocytic Leukemia

On January 14th 2013, the results of the International Consortium on Acute Promyelocytic Leukemia (IC-APL)<sup>(1)</sup> were published online in the journal *Blood*. Eight Brazilian institutions participated in the IC-APL: the Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo (USP) as coordinator, the Hematology Divisions of the Universidades Federal do Rio Grande do Sul (UFRGS), do Paraná (UFPR) and de Minas Gerais (UFMG), the Hematology and Transfusion Medicine Division of the Universidade Federal de São Paulo (UNIFESP), Hematology and Hemotherapy Center of the Universidade Estadual de Campinas (UNICAMP), the Hematology Division of Santa Casa de São Paulo (SCSP) and Fundação Hemocentro de Pernambuco (HEMOPE). The IC-APL was developed under the auspices of the American Society of Hematology and gathered specialists from Latin America, the United States and Europe with the aim of improving the cure rates of patients with acute promyelocytic leukemia (APL) in developing countries through the establishment of an international clinical network. Four developing countries were selected to participate in the IC-APL: Brazil, Chile, Mexico and Uruguay; 183 adult patients with suspected diagnosis of APL were enrolled in this registered trial between June 2006 and September 2010.

In order to participate in the IC-APL, countries had to fulfill minimum requirements, which included availability of drugs, pre-existing transfusion medicine services, a hematology lab capable of performing basic fluorescence microscopy and ability to report data and participate in meetings using web tools. APL was selected as a model disease to test the hypothesis that networking is an effective strategy to improve the outcome of patients with hematological malignancies in developing countries. The main reasons that guided this choice were: a) APL has become a highly curable disease since the introduction of combination therapy with all-trans retinoic acid (ATRA) and anthracycline-based chemotherapy, b) ATRA is of relatively low cost and available in the four developing countries, and c) the prompt diagnosis and immediate introduction of therapy can revert the coagulation abnormalities common in the disease and associated with high mortality rates due to bleeding.

In order to perform a prompt diagnosis and the immediate introduction of ATRA, the IC-APL adopted the anti-PML immunofluorescence staining test which was developed by Falini et al.<sup>(2)</sup> and requires minimal infrastructure. This test is based on the molecular pathogenesis of APL, which is characterized by its association with chromosomal translocations involving the loci of the *Promyelocytic Leukemia (PML)* and *Retinoic Acid Receptor Alpha (RARA)* genes on chromosomes 15 and 17, respectively. The PML-RARA fusion protein retains most of the functional domains of the parental proteins and interacts with several proteins in the nucleus, in particular with the native PML causing its delocalization from the nuclear body<sup>(3)</sup>. As a consequence, in APL cells, the PML protein is dispersed throughout the nucleus and generates a microspeckled pattern identifiable by the immunofluorescence staining test using the anti-PML (PG-M3) antibody (Figure 1).

Conflict-of-interest disclosure:

The author declares no competing financial interest

Submitted: 2/18/2013

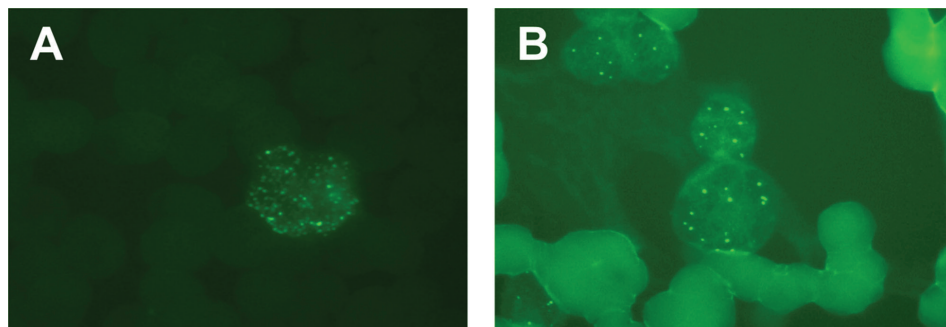
Accepted: 2/19/2013

### Corresponding author:

Eduardo Magalhães Rego  
Hematology/Oncology Division, Department  
of Internal Medicine, Faculdade de Medicina  
de Ribeirão Preto da Universidade de São Paulo  
Av Bandeirantes 3900  
14048-900 Ribeirão Preto, Brazil  
phone: +55 16 21019361  
emrego@hcrp.fmrp.usp.br

www.rbhh.org or www.scielo.br/rbhh

DOI: 10.5581/1516-8484.20130001



**Figure 1** - Photomicrographs of the immunofluorescence staining test using the anti-PML antibody showing: (A) the microspeckled pattern in an APL cell, (B) the nuclear bodies (fewer and larger dots compared to A) in an acute myeloid leukemia non-APL case. The green dots correspond to the PML protein.

Yet the introduction of a method for rapid diagnosis was only one of the items in the IC-APL strategy. By fostering collaboration between researchers, clinicians, and laboratory scientists from institutions in developing countries and well-established international cooperative groups based in the United States and in Europe, the IC-APL group generated guidelines, trained personnel, developed medical educational material, facilitated lab research and enforced requests to health authorities to guarantee ATRA availability.

The formulated treatment guidelines, based on the experience of the Spanish group, PETHEMA<sup>(4)</sup>, were adapted to local conditions and resources. An important change in the induction therapy protocol in the IC-APL study was the replacement of the commonly used anthracycline idarubicin with the less expensive and more readily available daunorubicin. The guidelines also covered standardized approaches for supportive care and disease follow-up measures. Throughout the trial, participating sites registered all cases using common clinical record forms in the Pediatric Oncology Network Database (POND) and collaborated with national clinical trial coordinators and reference laboratories to confirm the integrity and accuracy of treatment data.

The results of the study were remarkable, of 180 evaluable patients, 153 (85%) achieved complete hematological remission. Twenty-seven patients (15%) died during induction (early death). About 90% of all patients who achieved complete remission were alive at the time of analysis, five (2.6%) were lost to follow-up and ten (5.2%) died in complete remission. There was one case of molecular persistence of the PML/RARA rearrangement after consolidation and there were nine relapses, of which four were molecular relapses. The 2-year overall survival and disease-free survival were 80% (95% confidence interval: 73% - 85%) and 91% (95% confidence interval: 86% - 95%), respectively. The 2-year cumulative incidence of relapse was 4.5% (95% confidence interval: 1.8%-9.2%). The results are comparable to those reported in the US<sup>(5)</sup> and Europe<sup>(4,6)</sup> and represent a nearly 50% decrease in early mortality and a nearly 30% improvement in overall survival compared to historical controls<sup>(7)</sup>.

It is important to stress that there is a disparity between reported outcomes, particularly in hemorrhagic-related death rates, in clinical trials as compared to population based studies. In the study by Park et al.<sup>(8)</sup> the death rate within one month of APL diagnosis was 17.3%. Likewise, Lehmann et al.<sup>(9)</sup> reported the outcomes of APL patients registered in the population-based Swedish Adult Acute Leukemia Registry between 1997 and 2006 with calculated death rates of 26% and 29% within 14 and 30 days of diagnosis, respectively.

Taken together, the results reported by the IC-APL demonstrate that international networking is an effective strategy to change the reality of treatment of patients with hematological malignancies in developing countries. In addition, it was an

opportunity for Brazilian hematologists to strengthen ties, exchange experiences and consolidate the position of the country in the international scientific scenario.

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