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The impact of medical education and networking on the outcome of leukemia treatment in developing countries. The experience of International Consortium on Acute Promyelocytic Leukemia (IC-APL)

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Objectives: Several clinical trials conducted in Europe and US reported favorable outcomes of patients with APL treated with the combination of all trans retinoic acid (ATRA) and anthracyclines. Nevertheless, the results observed in developing countries with the same regimen was poorer, mainly due to high early mortality mainly due bleeding. The International Consortium on Acute Promyelocytic Leukemia (IC-APL) is an initiative of the International Members Committee of the ASH and the project aims to reduce this gap through the establishment of international network, which was launched in Brazil, Mexico and Uruguay.

Methods: The IC-APL treatment protocol is similar to the PETHEMA 2005, but changing idarubicin to daunorubicin. All patients with a suspected diagnosis of APL were immediately started on ATRA, while bone marrow samples were shipped to a national central lab where genetic verification of the diagnosis was performed. The immunofluorescence using an anti-PML antibody allowed a rapid confirmation of the diagnosis and, the importance of supportive measures was reinforced.

Results: The interim analysis of 97 patients enrolled in the IC-APL protocol showed that complete remission (CR) rate was 83% and the 2-year overall survival and disease-free survival were 80% and 90%, respectively. Of note, the early mortality rate was reduced to 7.5%.

Discussion: The results of IC-APL demonstrate the impact of educational programs and networking on the improvement of the leukemia treatment outcome in developing countries.

Keywords: Acute promyelocytic leukemia, Leukemia, Developing countries, All trans retinoic acid

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Acute promyelocytic leukemia (APL) is characterized by a massive infiltration of bone marrow by heavily granulated blasts that resemble promyelocytes and harbor balanced reciprocal translocations between chromosomes 15 and 17. The t(15;17) is detected in about 98% of patients with APL; it results in the formation of a fusion gene containing large sequences of the genes *RARalpha* and *PML*, localized on chromosomes 17 and 15, respectively. The expression of the oncoprotein PML–RARalpha is the basic leukemogenic event of APL.[1] Other chromosomal translocations, such as t(11;17) and t(5;17), are detected in less than 5% of cases of APL.[2] PML–RARalpha expression results in maturation arrest of myeloid cells in the promyelocytic phase. In short, PML–RARalpha forms homodimers that retain the functional domains of both proteins, bind to RARalpha targets, and repress their function by the recruitment of co-repressors. The end result is a block of cell differentiation and increased resistance to apoptosis.[1]

Douer *et al.*[3] were the first to report a higher incidence of APL in patients with 'Latino' and 'non-Latino' ancestry. Further studies based on hospital registries as well as population-based analysis suggested that the Latino population have shown that APL incidence ranged from 20% to 37.5% against 6–12% in Latino and non-Latino populations, respectively. We have reported that APL represents 28.2% of all acute myeloid leukemia (AML) cases in centers in Brazil,[4] a number that is very similar to the reported by Melo *et al.* (28%).[5] Similar results were reported by studies performed in Mexico (20%),[6] Venezuela (27.8%),[7] and Peru (22%).[8] Moreover, the higher APL frequency was also reported among children from Latin America, despite the fact that APL is less common in this age group.[9] The higher APL frequency may be due to the age distribution of the population, since APL is known to be more frequent among young adults, whereas the incidence of the other AML subtypes increases with age. In fact, an Italian study demonstrated that the incidence of APL in patients aging from 15 to 24 years was 27.7%, and among those older than 75 years, it was only 2.7%.[10] One may also argue that the difference in incidence between Latino and non-Latino populations is due to the lower frequency of APL in Northern Europe compared to Mediterranean countries, and consequently in their former colonies in America. In this regard, studies carried out in UK[11] and in Scandinavian[12] countries indicated that APL represented about 10% of all AML cases.

The introduction of the all-*trans*-retinoic acid (ATRA) in the treatment of APL changed one of the most lethal subtypes of leukemia into a highly curable disease.[13] But ATRA when used alone results in short lasting complete remissions in most cases, and the standard of care is considered to be the combination of ATRA and anthracyclines. This combination results in extremely high antileukemic efficacy, leading to complete remission (CR) in 90–95% of patients, and primary resistance has been only reported in just a few anecdotal cases.[14] The majority of centers in Latin America adopt protocols based on ATRA plus anthracyclines, similar to those reported by the Italian GIMEMA or the Spanish PETHEMA groups.[14–16] Nevertheless, the outcome of APL treatment in developing countries is poorer than that reported in the USA and Europe mainly due to high early mortality mainly due bleeding.[4,17] We have analyzed the outcome of 134 Brazilian patients treated with antracycline plus ATRA-based therapy between January 2003 and March 2006 at 12 institutions. The induction mortality was as high as 32.1% and bleeding was the cause of death in 60.5% of the cases. Even during consolidation, we observed a mortality rate of 10.5%, and mortality was mainly due to bleeding (21.4%), infection (28.6%), or their association (14.3%). The cumulative mortality was 44.7%.[4] In order to improve treatment outcome of APL patients in developing countries, the American Society of Hematology sponsored the creation of the International Consortium on Acute Promyelocytic Leukemia (IC-APL). The protocol is similar to the PETHEMA 2005,[18] but changing idarubicin to daunorubicin. Furthermore, the adoption of the immunofluorescence using an anti-PML antibody allowed a rapid confirmation of the diagnosis (<4 hours).[19] The importance of supportive measures was reinforced. These consisted mainly in the transfusion of fresh frozen plasma, fibrinogen, and/or cryoprecipitate and platelet transfusions to maintain the fibrinogen concentration and platelet count above 100–150 mg/dl and $30–50 \times 10^9$/l, respectively, which should be monitored at least once a day.[13] We recently reported preliminary data from 97 patients included in the IC-APL 2006 protocol.[20] There was a remarkable improvement in survival that reached 75% in 1 year and the disease-free survival in the same period was 95%. Furthermore, there was an improvement in early mortality which was reduced to 7.5%.[20] The results of IC-APL demonstrate the impact of educational programs and networking on the improvement of the leukemia treatment outcome in developing countries.

References

1 Rego EM, Pandolfi PP. Analysis of the molecular genetics of acute promyelocytic leukemia in mouse models. Semin Hematol. 2001;38:54–70.

2 Grimwade D, Biondi A, Mozziconacci MJ, Hagemeijer A, Berger R, Neat M, *et al*. Characterization of acute promyelocytic leukemia cases lacking the classic t(15;17): results of the European Working Party. Groupe Francais de Cytogenetique Hematologique, Groupe de Francais d'Hematologie Cellulaire, UK Cancer Cytogenetics Group and BIOMED 1 European Community-Concerted Action 'Molecular Cytogenetic Diagnosis in Haematological Malignancies'. Blood.2000;96:1297–308.

3 Douer D, Preston-Martin S, Chang E, Nichols PW, Watkins KJ, Levine AM. High frequency of acute promyelocytic leukemia among Latinos with acute myeloid leukemia. Blood. 1996;87:308–13.

4 Jacomo RH, Melo RA, Souto FR, de Mattos ER, de Oliveira CT, Fagundes EM, *et al*. Clinical features and outcomes of 134 Brazilians with acute promyelocytic leukemia who received ATRA and anthracyclines. Haematologica. 2007;92:1431–2.

5 Melo RA, de Vasconcellos JF, Melo FC, Machado CG, Lacerda TM, Souto FR. PML–RARalpha fusion gene transcripts and biological features in acute promyelocytic leukemia patients. Clin Lab Haematol. 2006;28:126–9.

6 Ruiz-Arguelles GJ. Promyelocytic leukemia in Mexican mestizos. Blood. 1997;89:348–9.

7 de Salvo L, Weir Medina J, Gomez Sanchez O, de Baena ES, de Ramos BU, Guevara J, *et al*. [Acute promyelocytic leukemia in the west of Venezuela]. Sangre (Barc). 1989;34:329–31. Spanish.

8 Otero JC, Santillana S, Fereyros G. High frequency of acute promyelocytic leukemia among Latinos with acute myeloid leukemia. Blood. 1996;88:377.

9 Mendes WL, Coser VM, Ramos G, Pereira W, Lopes LF, de Oliveira MS. The apparent excess of acute promyelocytic leukemia in infant acute leukemias in Brazil. Haematologica. 2004;89:ELT16.

10 Pulsoni A, Stazi A, Cotichini R, Allione B, Cerri R, di Bona E, *et al*. Acute promyelocytic leukaemia: epidemiology and risk factors. A report of the GIMEMA Italian archive of adult acute leukaemia. GIMEMA Cooperative Group. Eur J Haematol. 1998;61:327–32.

11 Moorman AV, Roman E, Cartwright RA, Morgan GJ. Patients entered into MRC AML trials are biologically representative of the totality of the disease in the UK. Clin Lab Haematol. 2002;24:263–5.

12 Lehmann S, Ravn A, Carlsson L, Antunovic P, Deneberg S, Möllgård L, *et al*. Continuing high early death rate in acute promyelocytic leukemia: a population-based report from the Swedish Adult Acute Leukemia Registry. Leukemia. 2011;25:1128–34.

13 Sanz MA, Grimwade D, Tallman MS, Lowenberg B, Fenaux P, Estey EH, *et al*. Management of acute promyelocytic leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2009;113:1875–91.

14 Sanz MA, Montesinos P, Vellenga E, Rayon C, de la Serna J, Parody R, *et al*. Risk-adapted treatment of acute promyelocytic leukemia with all-*trans* retinoic acid and anthracycline monochemotherapy: long-term outcome of the LPA 99 multicenter study by the PETHEMA Group. Blood. 2008;112:3130–4.

15 Sanz MA, Lo Coco F, Martin G, Avvisati G, Rayón C, Barbui T, *et al*. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. Blood. 2000;96:1247–53.

16 Avvisati G, Lo Coco F, Diverio D, Falda M, Ferrara F, Lazzarino M, *et al*. AIDA (all-*trans* retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study. Blood. 1996;88:1390–8.

17 Ribeiro RC, Rego E. Management of APL in developing countries: epidemiology, challenges and opportunities for international collaboration. Hematology Am Soc Hematol Educ Program. 2006:162–8.

18 Sanz MA, Montesinos P, Rayon C, Vellenga E, Rayón C, de la Serna J, *et al*. Risk-adapted treatment of acute promyelocytic leukemia based on all-*trans* retinoic acid and anthracycline with addition of cytarabine in consolidation therapy for high-risk patients: further improvements in treatment outcome. Blood. 2010;115:5137–46.

19 Falini B, Flenghi L, Fagioli M, Lo Coco F, Cordone I, Diverio D, *et al*. Immunocytochemical diagnosis of acute promyelocytic leukemia (M3) with the monoclonal antibody PG-M3 (anti-PML). Blood. 1997;90:4046–53.

20 Rego EM, Kim HT, Ruiz-Argüelles GJ, del Rosario Uriarte M, Jacomo RH, Gutiérrez-Aguirre H, *et al*. The impact of medical education and networking on the outcome of leukemia treatment in developing countries. The experience of International Consortium on Acute Promyelocytic Leukemia (IC-APL). Blood. 2009;114:116.