Title: Impact of the ICAL on the treatment of acute leukemia

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Abstract

The *International Consortium on Acute Promyelocytic Leukemia* (*IC-APL*) is an initiative of the *International Members Committee of the American Society of Hematology* (ASH) created in the spirit of international clinical and laboratory collaboration with the aim of reducing the difference in the outcomes of patients with APL treated in developed and developing countries. It congregates leaders of well-established cooperative groups in Europe and North America and hematologists in Brazil, Chile, Peru, Uruguay and Paraguay. APL was initially selected as a model disease to test the impact of networking on outcomes because it is a highly curable disease if early diagnosis and specific treatment are promptly established. The network includes more than 20 hospitals with 5 national coordinators and reference laboratories, common clinical record forms (CRF), and laboratory and data management training programs. To orchestrate clinical, laboratorial and educational activities, five subcommittees were created: Treatment Guidelines; Drug Availability; Laboratory and Diagnostic Guidelines; Web Registration and Auditing and, Funding Subcommittee. As treatment, the consortium adopted the combination of ATRA and anthracycline, using the same design of PETHEMA/HOVON LPA2005 protocol, except that idarubicin was replaced by daunorubicin. Compared to historical controls, networking increased the overall survival (OS) from approximately 50% to 80% and reduced the induction mortality rate by half. The outcomes of patients enrolled in the IC-APL were similar to those observed in developed countries, including the tween protocol conducted in Europe. Based on the improvement observed in the outcome of patients with APL, the Consortium expanded its activities to projects involving patients with acute myeloid leukemia categorized as favorable or

intermediate risk according to the European LeukemiaNet proposal. To reflect this change, the cooperative group is now called the International Consortium on Acute Leukaemia (ICAL) and is planning to expand its activities to regions other than Latin America.

In 1957 Hillestad[1] reported three cases of acute myeloid leukemia characterized by a very rapid fatal course of only a few weeks' duration, with a white blood cell (WBC) picture dominated by promyelocytes and a severe bleeding tendency. This is considered to be the first description of acute promyelocytic leukemia (APL) and was followed by the report of an additional 20 cases described in 1959 by Bernard et al[2] in 1959. The exquisite sensitivity of APL to anthracyclines was described more than 10 years later in 1973 also by Bernard et al.[3] The next milestone for the understanding of the pathogenesis and establishment of a successful treatment of APL was the identification by Rowley et al. of its association with translocations involving chromosomes 15 and 17 [t(15;17)] in more than 95% of patients in 1977. [4] The progress in molecular biology methodologies in the subsequent decade allowed the identification of the breakpoints involved in the t(15;17), which lie within the *Retinoic Acid Receptor Alpha* (*RARA*) gene locus on chromosome 17 and the *Promyelocytic Leukemia* (*PML*) locus on chromosome 15.[5-8] As consequence of the t(15;17) the *PML-RARA* fusion gene is generated and the expression of corresponding fusion protein is necessary but not sufficient to induce leukemia as demonstrated by studies using

transgenic mouse models. [9-13] Importantly, studies *in vivo* demonstrated that the degradation of PML-RARA is essential to eradicate APL.[14,15]

There are currently two strategies to treat *de novo* APL: the combination of all-*trans* retinoic acid (ATRA) with anthracyclines and the combination of ATRA with arsenic trioxide (ATO). ATRA and ATO trigger PML-RARA degradation through distinct mechanisms, with ATRA acting through the proteasome pathway, and ATO functioning through the PML-transformation-related protein 53 (Trp53) axis.[14,16] Different cooperative groups have demonstrated the clinical efficacy of both therapies, which result in complete hematologic remission (CHR) rates exceeding 90%. In the LPA99 trial of the Programa Español para el Tratamiento de las Hemopatias Malignas del Adulto (PETHEMA) group, the use of ATRA and anthracycline for induction, consolidation, and low-dose chemotherapy maintenance resulted in a 5-year overall survival (OS) of 82%. Favorable long-term outcome with an ATRA and chemotherapy regimen was also observed by the European APL group that reported a 10-year survival rate of 77% in patients treated in the APL93 trial. Two phase 3 prospective randomized trials have compared the outcomes of patients with *de novo* APL treated with ATRA+chemotherapy regimens versus ATRA+ATO combinations as first line therapy,[17-19] Both studies showed that ATRA+ATO treatment resulted in significantly improved outcomes compared with ATRA+chemotherapy. Moreover, as expected, ATRA+ATO combination was associated with considerably less hematological toxicity.[19]

Unfortunately, the previously-reported treatment outcome for patients with APL in developing countries is significantly inferior to that reported in Europe and United States. Jacomo et al.[20] reported a death rate of 32% during

induction and of 10% during consolidation among Brazilian patients treated with ATRA+chemotherapy. High induction death rates were also reported in Pakistan[21] (61.5%), Korea[22] (23.9%), Iraq[23] (24%) and Central America[24]. Most of the deaths that occur during induction are caused by hemorrhage. ATRA has the ability to reverse the coagulopathy associated with APL, but the risk of severe bleeding remains high during the first two weeks of ATRA administration.[25] Therefore, several guidelines have highlighted the importance of considering APL as a medical emergency that requires the immediate commencement of ATRA therapy, prompt genetic diagnosis, and measures to counteract the coagulopathy (hence the relevance of ongoing medical education). [26]

The *International Consortium on Acute Promyelocytic Leukemia* (*IC-APL*) was created in the spirit of international clinical and laboratory collaboration with the aim of reducing the difference in the outcomes of patients with APL treated in developed and developing countries.[27] *IC-APL* was an initiative of the *International Members Committee of the American Society of Hematology* (ASH) and was established in 2005. It congregates leaders of well-established cooperative groups in Europe and North America and hematologists in Brazil, Chile, Peru, Uruguay and Paraguay. To foster regional development and exchange of experiences not only between developing and developed countries but also amongst developing countries, the Consortium decided to work with national networks rather than with multiple independent institutions. The project includes 5 national coordinators and reference laboratories, common clinical record forms (CRF), and laboratory and data management training programs. To orchestrate clinical, laboratorial and educational activities, five subcommittees were created: the Treatment Guidelines Subcommittee was responsible for the

study design and CRF elaboration; the Drug Availability Subcommittee was responsible to ensure that drugs were available at all times; the Laboratory and Diagnostic Guidelines Subcommittee was responsible for the standardization of diagnostic and minimal residual disease (MRD) methods and for the control of biobanking; the Web Registration and Auditing Subcommittee oversaw the quality of the data in the web database and the infrastructure for the web meetings; the Funding Subcommittee was responsible for obtaining financial support from private and public sources. Minimum criteria for national networks to join the Consortium were established, including: i) prompt availability of ATRA in all centers; ii) pre-existing transfusion medicine services and hematology labs capable of performing basic fluorescence microscopy, iii) ability to report data and participate in meetings using web tools and iv) identification of one national coordinator and one person responsible for molecular studies. [27]

ATRA treatment was initiated immediately in all cases in which the diagnosis of APL was suspected based on morphology.[27] As many patients were first admitted in emergency rooms or intensive care units in one of the 22 hospitals in the 5 countries, the Consortium established small stocks of ATRA in these sites and developed educational material for hematologists and non-hematologists (guidelines). To assure prompt diagnosis with a minimum of laboratory infrastructure, the IC-APL adopted the anti-PML immunofluorescence as a genetic screening test for all cases. Cytogenetic analysis for t(15;17) and/or polymerase chain reaction (PCR) analyses for PML/RARA rearrangements were then performed on bone marrow (BM) samples shipped to the national reference laboratories; the detection of one or the other was required for confirmation of the diagnosis of APL and enrollment in the protocol, upon which daunorubicin

was combined with ATRA.[27] CRF were common to all countries and the Pediatric Oncology Network Database (POND) was used for online collection of clinical and laboratorial data during the first six years of the study then, due to regulatory issues, moved to the Research Eletronic Data Capture (RedCap) system.

As treatment, the consortium adopted the combination of ATRA and anthracycline, using the same design of the *Programa Español de Tratamiento en Hematologia / Dutch-Belgian Haemato-Oncology Cooperative Group* (PETHEMA/HOVON) LPA2005 protocol[28,29], except that idarubicin was replaced by daunorubicin at a ratio of 1:5. This change aimed to reduce cost and to assure the availability of the required drugs in all centers. The detailed protocol has been described elsewhere.[27] Treatment response was confirmed by morphological analysis and by RT-PCR at the end of the 3 consolidation cycles. MRD was monitored at national reference laboratories by RT-PCR every 3 months during maintenance and for 2 years after completion of the treatment. The IC-APL used web meetings and presentations during national meetings (with the support of local hematology societies) to increase the awareness of the disease and to publicize supportive measures guidelines, which were based on the European LeukemiaNet guidelines for APL patients.[26] In particular, educational efforts reinforced the importance of platelet transfusions to maintain the platelet count above 30,000 to 50,000/μL, and of cryoprecipitate to maintain the fibrinogen level above 150 mg/dL.

The first interim analysis of the IC-APL study was performed in December 2011, evaluating 183 enrolled patients with a median follow up among survivors of 28 months.[27] The majority of the patients (52%) were categorized according

to the risk of relapse as intermediate risk, using the PETHEMA/GIMEMA classification guidelines.[26] Thirty-two percent were categorized as high and 16% as low risk. Compared to studies conducted in US and Europe there was a significantly higher number of patients deemed as high risk in the IC-APL study.[30,31]

The complete hematologic remission (CHR) rate was 85%. Twenty-seven (15%) of the patients died between diagnosis and the first morphologic evaluation of BM. Compared to historical controls (patients treated between 2003 and 2006 in the same Brazilian institutions that after 2006 participate in the IC-APL study), there was a reduction of approximately 50% (32% to 15%) in the mortality during induction. [20,27] The 2-year OS and DFS were 80% (95% confidence interval [CI]: 73% to 85%] and 91% (95% CI: 86% to 95%), respectively. The 2-year cumulative incidence of relapse (CIR) was 4.5% (95% CI: 1.8% to 9.2%). Currently, there are more than 500 patients enrolled in the study and death during induction is approximately 12% and the 5-year OS is 77% (unpublished data). The DFS and OS of patients enrolled in the IC-APL study are comparable to those from trials conducted in developed countries, despite the relatively high proportion of high-risk patients.[28,30,32]

When the outcomes of patients enrolled in the IC-APL and in the PETHEMA/HOVON LPA2005 studies were compared (using matched-pair analysis) CHR rate was significantly higher (94% *versus* 85%, P=0.02) in the PETHEMA/HOVON than in the IC-APL cohort.[28] Nevertheless, the cumulative incidence of relapse and DFS rates were similar.[28] Therefore, although the Consortium continues to work to further reduce mortality during induction, the experience has shown that it is feasible to decrease the gap between countries

with lower or upper middle income and high income economies with regard to the quality of care and treatment outcomes using available resources, networking and medical education.

IC-APL has expanded its activities to other subtypes of leukemia and the cooperative group is now called the International Consortium on Acute Leukemia (ICAL). In 2016, we initiated a new study called *'Feasibility Study of the Use of Intermediate Doses of Cytarabine Associated with Autologous Hematopoietic Stem Cells as Consolidation Treatment of Young Adults with Low- or Intermediate-risk de Novo Acute Myeloid Leukaemia (ICAML2015)'*, which aims to improve the outcome of adult patients with AML of good or intermediate prognosis according to the European LeukemiaNet proposal[33] through the development of a clinical network that will speed diagnosis. We propose to make available the full range of cytogenetic and molecular methods so that the best treatment choice (based on best practice) may be offered to patients soon after diagnosis, develop a method based on flow cytometry to monitor disease response, and promote guidelines for supportive care. In addition, based on the existing evidence that autologous SCT transplantation presents lower myelotoxicity in comparison with multiple cycles of chemotherapy, and is therefore associated with a lower frequency of infectious complications, a second aim of this study is to test the viability of consolidation treatment using autologous SCT for patients with good (excluding APL cases) or intermediate (without HLA matched sibling donor) prognosis.

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