ally have lower bone marrow cellularity and myeloid/erythroid ratios compared to CML-BC.

Mutations in signaling pathways: Mutations in FLT3 receptor can lead to constitutive activation that in turn can lead to decrease in apoptosis and increase in leukemia proliferation and survival. Patients with FLT3/ITD mutations typically have high white cell counts at disease presentation and have normal or intermediate risk karyotypes. FLT3/TKD mutations tend to confer slightly better prognosis. NPM1 mutations usually occur in exon 12 in the C-terminus of the protein and can lead to cytoplasmic localization of NPM1 protein. Studies have shown that NPM1 mutations usually carry a favorable prognosis in the absence of FLT3-ITD and mainly in the presence of IDH1-2.

Other gene mutations in AML: ASXL1 gene encodes a chromatin binding protein, which in turn enhance or repress gene transcription in localized areas by chromatin structure modification. The overall frequency of ASXL1 mutations in AML is approximately 3–5% but its incidence is higher in patients with intermediate risk AML. DNMT3A is a DNA methyltransferase that regulates epigenetic alterations through DNA methylation. DNMT3A mutations are frequently found with FLT3-ITD, NPM1, IDH1-2 mutations though rarely associated with t (15; 17) and CBF leukemia's. IDH1 and IDH2 are two enzymes that play an important role in DNA methylation and histone modification and affect the active isocitrate binding site and lead to increased level of 2-hydroxyglutarate. IDH2 mutations occur in 8–12% of adult AML. 2-HG can be detected in vast excess in the serum and BM of AML patients with IDH1/2 mutations, suggesting that it may serve as a biomarker for this genetically defined subset of AML patients and as a measure of residual disease after AML therapy.

Mutations in cohesion complex members; BCOR, PHF6;

Mutations in splicing machinery: The most common splicing factor gene abnormalities involved in AML are SF3B1, U2AF1, SRSF2, and ZRSR2. These mutations are mutually exclusive and can be defined as founder mutations or associated with certain phenotype in a subset of patients such as SF3B1 mutations in MDS patients with ring sideroblasts and SRSF2 in chronic CMML.

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How clinical networking may be a powerful strategy to face the challenges faced by hematologists treating acute leukemias in the developing world. The experience of the International Consortium on Acute Leukemia (ICAL)

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The International Consortium on Acute Promyelocytic Leukemia (IC-APL), later renamed as International Consortium on Acute Leukemias (ICAL), was founded in 2004 as an initiative of the International Members Committee of the American Society of Hematology (ASH). Its goal was to create a network of institutions in developing countries that would exchange experience and data and receive support from well-established cooperative groups, bringing together clinical investigators from Europe, North America and Latin America. The Consortium selected acute promyelocytic leukaemia (APL) as a model disease to test the impact of networking on the outcome of patients treated in developing countries, because it is a highly curable disease, if early diagnosis and specific treatment are promptly established. By the end of the 1990's, European and American groups reported complete remission (CR) and long-term disease-free survival (DFS) rates of approximately 90% and 85%, respectively, in studies of cohorts of APL patients who were treated with all trans retinoic acid (ATRA) and anthracyclines (Soignet et al., 1997; Sanz et al., 1999). In contrast, a retrospective analysis of 134 Brazilians patients with APL treated between 2003 and 2006 reported a death rate of 32% during induction, with most of the deaths caused by APL-associated coagulopathy (Jacomo et al., 2007). In this study the long-term overall survival (OS) rate at 2 years was less than 60%, indicating a clearly unmet medical need. The consortium adopted the combination of ATRA and anthracycline, using the same design of the PETHEMA/HOVON LPA2005 protocol (Sanz et al., 2010, 2015), except that idarubicin was replaced by daunorubicin at a ratio of 1:5. Importantly, medical educational activities, centralized laboratory diagnosis and monitoring and specific guidelines for supportive treatment were adopted. Here we will present the analysis of 306 Brazilian patients treated according to the IC-APL protocol and discuss the achievements and pitfalls that the group has faced during its 16-year experience. In total Number of screened patients: 374 patients were screened and 306 were considered elegible with an average of 25.4 pts/year. The main reasons of ineligibility were PML/RARA was not detected (36%); previous chemo or radiotherapy (12%), drug unavailability (10%); age >75 y (8%); pregnancy (7%). One case of ZBTB16/RARA rearrangement was detected. The median time of follow up was of 50 months. The Complete Hematological Remission was of 88.9% and the number of deaths during induction among eligible patients was of 33 (10.7%). The Cummulative Incidence of Relapse was 13% (35/265 pts) and most relapses occurred during maintenance relapse (21 pts). Monitoring was successfully performed by RT-qPCR and conventional RT-PCR. With discrepant results in only 7 patients (in whom relapse was first detected by RT-qPCR). The 10-year overall survival rate was of 75% (95% CI: 68–80%) and the 10-year disease free survival was of 82% (95% CI: 75–87). The ICAL experience confirmed that the establishment of clinical networks involving developing and developed countries may be a powerful strategy to face the challenges faced by hematologists treating acute leukemias in the developing world.

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SP 26

Novel approaches to the treatment of polycythemia vera

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Since the times of Vaquez and Osler over one hundred years ago phlebotomy has been has been a mainstay of treatment in Polycythemia vera (PV) and for more than fifty years, cytore-