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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SP 25

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)

Eduardo M. Rego

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

Martin H. Ellis

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-

ductive agents have been added to achieve hematocrit control in patients at high risk for thrombosis. Thus PV has lagged behind other hematologic malignancies in the implementation of novel and targeted drug therapy. This has changed recently with the development of novel therapies for this disease, a number of which have received regulatory approval internationally.

Ruxolitinib has been approved as second line therapy for PV patients intolerant of or resistant to hydroxyurea on the basis of the RESPONSE trial. In this study 222 patients were randomized to receive ruxolitinib or best available therapy (BAT) in the second line setting. At 5 years 60% of the ruxolitinib patients versus 19% of the BAT patients maintained hematocrit control without need for phlebotomy. Reduction in spleen volume was also more frequent among ruxolitinib patients (89 vs. 49%). There were decreases in *JAK2* V617F allele burden in both groups but complete molecular remissions were rare. Importantly, herpes zoster infections occurred among ruxolitinib treated patients.

Interferon has become an important drug in the treatment of PV with the publication of interim and final results of a number of studies of pegylated versions of interferon. The Myeloproliferative Disorders Research Consortium (MPD-RC) 112 and MPD-RC 111 randomized studies previously treated and untreated patients respectively. Good clinical responses with manageable toxicity were attained and further follow up is awaited. The 3 year results of the combined PROUD-PV and CONTINUATION-PV, randomized, phase 3 trials comparing ropeginterferon (a novel, long-acting, mono-pegylated proline interferon) to hydroxyurea in newly diagnosed PV patients show improved complete haematological response and reduced *JAK2* V617F allele burden with ropeginterferon. The drug is also under study in patients with low-risk PV in whom hematocrit levels at or below 45% compared with those who received monthly phlebotomy alone were more common according to interim findings from the ongoing LOW-PV trial.

Novel agents for PV include MDM2 inhibitors, nutlins. MDM2, an inhibitor of *TP53* is up-regulated in PV CD34+ cells and exposure to a nutlin induced *TP53* and selective stem cell depletion in preclinical models. Early trials of idasanutlin, an oral MDM2 antagonist demonstrated a 58% overall response rate and median duration of response of 16.8 months in high-risk PV patients after failing prior therapy. Idasanutlin is being evaluated in a multinational phase 2 trial.

A unique approach to controlling the hematocrit in PV by targeting iron metabolism is currently in early testing. Hepcidin is the major physiologic regulator of iron metabolism. PTG-300 is a first-in-class synthetic hepcidin mimetic that is in phase 2 clinical trial development. The agent reduces iron available for erythropoiesis and in a preliminary study was able to maintain the hematocrit at <45% without need for phlebotomy in a small number of PV patients all of whom were previously phlebotomy dependent.

These novel agents and others will likely change treatment paradigms in PV.

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SP 27

New drugs for low grade lymphoproliferative diseases

Argiris Symeonidis

For asymptomatic patients with low-grade lymphoproliferative disorders and low tumor burden, watchful waiting represents a rational approach. For symptomatic patients or for those with high tumor burden, initial treatment is usually chemoimmunotherapy with an anti-CD20 monoclonal antibody (mo-Ab), most commonly Rituximab or Obinutuzumab plus an alkylator, such as bendamustine or chlorambucil and/or a pourine analog, such as fludarabine or cladribine. For the Refractory/Relapsed (RR) setting treatment options depend on patient's background, initial PFS and on various prognostic parameters. Newer anti-CD20 mo-Abs, such as Ublituximab appear equally effective, but have not yet been tested comparatively with the previous ones. Radioconjugates such as 90Y-ibritumomab tiuxetan and 131I-tositumomab are no more in broad use due to unpredicted myelotoxicity. The newer 90Y-epratuzumab tetratexan appears safe as consolidation following R-CHOP in DLBCL patients. Polatuzumab vedotin, Pinatuzumab vedotin and Tafasitamab targeting CD19 have mainly been used, combined with an anti-CD20 mo-Ab to treat RR-DLBCL with success, which render them candidates for indolent lymphomas also. BTK inhibitors represent one main treatment option, either as initial treatment or in the RR setting. Ibrutinib, the first in class drug, is used either alone or in combination with Mo-abs and/or alkylators. Acalabrutinib, already approved for CLL/SLL and MCL, is now being tested for other B-cell malignancies. Zanubrutinib, a newer analog not exhibiting some of ibrutinib's AE, has been approved for RR-MCL and is currently being evaluated alone or in combination with Mo-Abs, lenalidomide and other agents. Idelalisib, the first PI3K-inhibitor, the second family of highly used targeted agents, has been approved for CLL/SLL and FL. Duvelisib, Copanlisib and Umbralisib are newer agents coming up and are currently being tested usually in combination with mo-Abs or other agents. Bimiralisib, a dual PI3K/mTOR inhibitor is a promising agent still in phase I. Hepatotoxicity, the major AE of this class, is reversible and dose-dependent. The BCL2 inhibitor venetoclax, alone or combined with mo-Abs and/or bendamustine (BRVen) or with Ibrutinib (ongoing trial), is a breakthrough approach, being tested in several disease entities with impressive results. Bispecific antibodies engaging CD19 (Blinatumomab) or CD22 (Inotuzumab ozogamycin) to a T/NK-cell surface antigen have received approval for more aggressive B-cell lymphomas. Lenalidomide combined with Rituximab (R2) has demonstrated impressive results as initial treatment in FL and the newer cereblon-modifier Avadomide is now being tested in combination with Obinutuzumab in RR B-cell lymphomas of all types. Lenalidomide with Blinatumomab is also tested in an ongoing study. mTOR/NF-κB inhibitors (temsirolimus, everolimus) are not so effective as single agents but can be combined with various targeted and/or cytotoxic agents and construct synergistic regimens. Tazemetostat a novel EZH2 inhibitor recently received accelerated approval by FDA for patients with RR-FL and EZH2 gene mutations, following the