We have witnessed remarkable gains in the biological understanding and treatment of acute lymphoblastic leukemia (ALL) over the past decade. Hence, it is a challenge to summarize even the key advances of recent ALL research. My intent here is to clarify and elaborate on a few of the topics discussed by Rabin and Poplack in their concise review.

**Epidemiology**
From data collected by the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, it is estimated that there were 5330 cases of newly diagnosed ALL (3150 in males and 2180 in females) in 2010 in the United States, approximately 60% of which were diagnosed in patients younger than 20 years of age.[1] Hence, while the total number of cases of leukemia (including acute and chronic myeloid leukemia as well as chronic lymphocytic leukemia) is 10 times higher in adults than in children, ALL is predominantly a childhood disease. This difference in prevalence, together with the fact that most cases of childhood ALL, but only a very small proportion of adult cases, are treated in clinical trials, readily explains why most research advances in ALL are made in children.

**Molecular Genetics**
Standard genetic studies can identify specific genetic abnormalities with prognostic and therapeutic implications in only about 75% to 80% of childhood ALL cases.[2] Moreover, these studies cannot identify the full repertoire of genetic alterations in individual patients. Recent global genome-wide analyses have revealed many new “driver” mutations in ALL, including *IKZF1* deletion, *CRLF2* overexpression, *JAK* mutations, *ERG* deletion, and *CREBBP* mutations. These analyses have clearly showed that cooperative mutations are necessary for malignant transformation and progression, and that such mutations account for the development of drug resistance.[3-7] Virtually all childhood ALL cases can now be classified according to specific genetic abnormalities.[8] Importantly, the presence of *JAK* mutations in cases with *IKZF1* deletion or *CRLF2* overexpression has led to a phase I trial of *JAK* inhibitors in relapsed ALL, and the identification of *CREBBP* mutations that affect transcriptional and epigenetic regulation as a mechanism of drug resistance raises the possibility of epigenetic treatment with a histone deacetylase inhibitor.[7]

**Pharmacogenetics**
Rabin and Poplack mention that a deficiency of thiopurine methyltransferase can lead to myelosuppression and increase the risk of second malignancies induced by treatment with a “standard dose” of mercaptopurine. It should be noted that a so-called standard dose varies from 50 mg/m² to 75 mg/m² per day according to the specific clinical trial. While all patients who are homozygous for this deficiency (~1 in 180 to 1 in 2500 individuals) are at risk for life-threatening myelosuppression and require a 10-fold reduction in the dose of mercaptopurine, 30% to 60% of heterozygous patients (~3% to 14% of the population) are at risk for only moderate toxicity.[9] Thus, heterozygous patients should be started on a lower dose (eg, 50 mg/m² per day), with subsequent doses adjusted according to the degree of myelosuppression. In this regard, in a Berlin-Frankfurt-Mnster (BFM) study featuring mercaptopurine at 60 mg/m² per day, patients who were homozygous wild-type (normal enzyme activity) had higher minimal residual disease levels after treatment than did patients with enzyme deficiency, and they would have benefited from a higher dose of mercaptopurine.[10] The risk of mercaptopurine-induced second malignancy (mainly acute myeloid leukemia or myelodysplastic syndrome) depends not only on the enzyme activity but also on the dose intensity of antimetabolite treatment. Thus, lower enzyme activity was related to a relatively high risk of secondary acute myeloid malignancies in the Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL-92 protocols, which featured intensive antimetabolite-based continuation treatment with a starting dose of mercaptopurine of 75 mg/m² per day;[11] however, this relationship was not found in the BFM protocols, in which a lower dose of...
mercaptopurine (50 mg/m² per day) was used during continuation treatment.[12] To my knowledge, all reported second malignancies related to mercaptopurine treatment occurred in patients who were heterozygous (not homozygous) for the thiopurine methyltransferase deficiency, mainly because of the rarity of the homozygous deficiency.

**Prognostic Factors**

Historically, age and initial leukocyte count have been two of the most important clinical prognostic factors. [13] However, with improved risk-directed chemotherapy and supportive care, as well as close attention to treatment adherence, older age and even leukocyte count are losing their prognostic impact, as demonstrated in the recently completed Total Therapy study XV at St. Jude Children's Research Hospital.[14,15] In fact, the 5-year event-free survival rates were comparable between the older adolescents (aged 15 to 18 years) and younger patients treated in the study (86.4% ± 5.2% [standard error] and 87.4% ± 1.7%, respectively).[15] It is well recognized that African Americans and especially those with Hispanic ethnicity have poorer outcomes than do European Americans or Asians in the United States. Our recent genome-wide germline SNP study, conducted in collaboration with investigators in the Children's Oncology Group, showed an extensive ancestral admixture in Hispanic patients, and a component of genomic variation that co-segregated with Native American ancestry was associated with an increased risk of relapse in Hispanic patients and even in patients self-reporting as white.[16] Importantly, ancestry-related differences in outcome could be abrogated by an additional phase of delayed intensification therapy,[16] demonstrating the overriding importance of treatment efficacy.

Currently, the most important prognostic factor in ALL is the early treatment response, as assessed by measurements of minimal residual disease (MRD); this is because early response reflects leukemic cell genetics, host pharmacodynamics and pharmacogenetics, effectiveness of treatment regimen, and treatment adherence.[13,14]. While MRD positivity is an indication for intensified therapy, I would advise caution regarding the use of MRD negativity to reduce treatment intensity, since even low-risk ALL requires a certain degree of intensified chemotherapy for cure. In this regard, omission of a delayed intensification treatment phase resulted in an inferior outcome in standard-risk patients treated in a BFM study.[17] Thus, any attempt to reduce the intensity of treatment should be done judiciously and weighed against the prevention of treatment-related mortality and serious late sequelae.

**Treatment**

The optimal dose and type of glucocorticoids used in the treatment of ALL are still uncertain. When bioequivalent doses (a dose ratio of prednisone and dexamethasone of 7 to 10) were used, both drugs resulted in comparable event-free survival rates; however, dexamethasone still appears to yield improved CNS control.[18] Dexamethasone is now used for postremission therapy in most pediatric protocols, but prednisone is still used in many protocols for remission induction, especially for older children and adults, to avoid excessive toxicity. It is not surprising that escalating doses of intravenous methotrexate without leucovorin (so-called Capizzi methotrexate) is superior to oral methotrexate in the treatment of ALL, not only because of increased systemic exposure and higher peak serum level (potentially better CNS control) but also because of improved treatment adherence with the use of intravenous methotrexate. In this regard, high-dose intravenous methotrexate could prove to be superior to Capizzi methotrexate. Finally, with effective systemic and intrathecal chemotherapy, prophylactic cranial irradiation can be safely omitted in all children and adolescents with ALL, regardless of their presenting features. In St. Jude Total Therapy study XV, which did not use prophylactic cranial irradiation in all patients, those who met previous criteria for treatment with cranial irradiation actually had significantly longer continuous complete remissions than did the historical controls.[14] The encouraging results of this study and those of the Dutch Childhood Oncology Group[19] have led several European and Asian study groups to abandon the use of prophylactic cranial irradiation in all patients.

Despite this progress, we must not forget that all treatments for ALL carry some risk of toxicity. In this regard, the emerging fields of functional genomics and proteomics promise to yield a full understanding of ALL pathophysiology. This, in turn, should provide an expanded repertoire of targeted therapeutics for clinical evaluation, with the long-term goal of “personalized medicine” that maintains high rates of cure with significant reductions in toxicity.

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