CLINICAL TRIALS

Comment on Efficace et al, page 4554

CML: live long and prosper

Richard A. Larson  UNIVERSITY OF CHICAGO

Chronic myeloid leukemia provides one of the outstanding success stories in hematologic oncology. Thousands of patients have been able to continue their lives because of a remarkably effective, genetically targeted therapy.

Within the lifespan of most hematologists practicing today, CML has gone from a uniformly fatal disease to a chronic, subclinical disorder that can be managed with a once- or twice-per-day oral medication. CML is the poster child for targeted therapy in oncology. Indeed, this year the American Society of Hematology is honoring Dr Janet Rowley and Dr Brian Druker with the Beutler Lecture and Prize for their pioneering work in translating basic science into a highly effective treatment.

In clinical trials, investigators typically focus on severe or life-threatening toxicities and develop management strategies for minimizing them or avoiding them altogether. Particularly in oncology, low-grade, treatment-related toxicities are generally considered to be the price that patients must pay to prolong their survival. But what about CML patients who now expect to live out their normal lifespan? Are there chronic, cumulative, or late effects from these TKIs that impact on patients' activities of daily life and feelings of well-being, and thus might also interfere with their adherence to daily dosing?

In this issue of Blood, Efficace and colleagues report on a survey measuring the health-related quality of life (QOL) reported by 400 CML patients in Italy. These patients had been taking imatinib for 3-9 years. Although patients older than 60 years had QOL profiles very similar to those reported by the general population, younger patients, and women in particular, reported marked impairments due in part to physical and emotional problems. Fatigue was the most frequently reported symptom, followed by muscle cramps, pain, and edema (see figure). Remarkably, over one-quarter of all respondents stated that these symptoms bothered them “quite a bit or very much,” despite a median of 5 years on imatinib treatment. Because lack of adherence to daily dosing appears to be one of the major causes of imatinib treatment failure, it is important for hematologists to appreciate the frequency and severity of these on-going adverse effects in their patients.

Percentage of CML patients reporting the symptom by level of severity (N = 422).
is a necessary adjunct to prolonged, life-saving antileukemia therapy.

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES


Lymphoid Neoplasia

Comment on Barquem-Vrieze et al, page 4646

Sleeping Beauty: does ETP-ALL awaken later?

Marei Dose and Fotini Gounari

In the hope of identifying key events that drive malignant transformation, researchers have been aiming to compare tumor cells with the corresponding pre-transformed cell population of origin. This approach is attractive because, once established, such key events can then become the focus of new therapies that inter- fere with the transformation process as it happens, thus preventing it.

Different Cre transgenes initiate Sleeping-Beauty (SB) transposon-mutagenesis at distinct stages during T-cell development, causing T-ALL in mice. Distinct combinations of common insertion sites (CISs), equivalent to driver mutations, are selected for in the tumors, depending on when mutagenesis is initiated. Surprisingly, if mutagenesis is initiated late during development, at the DP stage, the resulting tumors show features of human ETP-ALL, raising the possibility that this high-risk leukemia originates from more mature cells that revert to an immature immune phenotype on transformation.

In this issue of Blood, Berquam-Vrieze et al directly show that the biologic state at which a population of cells first experiences oncogenic mutations strongly influences the type of driver mutations selected for in the resulting tumor in a mouse model of T-cell acute lymphoblastic leukemia (T-ALL). T-ALL is a malignant clonal expansion of immature T cells that accounts for 10% to 15% of pediatric and 25% of adult ALL cases. While 80% of patients with T-ALL can currently be cured with intensive chemotherapy, a subset of cases has a poor prognosis. A recent study found early T-cell precursor (ETP) leukemia to be a high-risk subset of T-ALL characterized by an immature surface immune-phenotype, increased genomic instability, a high frequency of remission failure or hematologic relapse, and a distinct gene expression profile. Because of its ETP-like immune-phenotype and gene expression profile, ETP-ALL was proposed to originate from very early thymic immigrants. However, the current work of Berquam-Vrieze and colleagues introduces an alternative scenario.

The authors designed a forward-genetic screen, using a Sleeping-Beauty (SB)-based transposon system that allows Cre-dependent activation of the SB transposase. This allows transposon-induced mutagenesis to be initiated under the control of stage-specific Cre transgenes. Mutagenesis was induced either early in hematopoietic stem cells (Vav–SB) or at 2 subsequent developmental stages of thymocyte development: the CD4–CD8– double-negative (DN) compartment (Lck–SB), and the β–selected, CD4+CD8+ double-positive (DP) compartment (CD4–SB). Tumors develop as a result of transposon insertions into or near tumor suppressors or oncogenes, either activating or disrupting their expression. By mapping common insertion sites (CISs), that is, transposon insertion sites frequently selected for, one can thus identify bona fide driver mutations for T-ALL originating from different developmental states (see figure).

Berquam-Vrieze et al sequenced the insertion sites of 101 lymphomas and deduced a total of 94 driver mutations. As a proof of principle, 75% of these mutations have previously been described to cause cancer. On the other hand, 25% of these candidate driver mutations have no previous entry in the literature linking them to cancer development and thus invite follow-up studies.

Do differences or commonalities exist between the models as well as between mouse and human T-ALL? Interestingly, yes. When transposon-induced mutation was initiated in hematopoietic progenitors, under the control of Vav1–Cre, a large fraction (72%) of the resulting T-cell tumors had mutations in Notch1, a hallmark of human T-ALL. The second most common mutation affected the Ikaros locus encoding for the transcription factors Ikaros, which is a rare target for mutation in human T-ALL. However, Ikaros mutations have frequently been observed to cooperate with Notch1 in murine T-ALL models. Interestingly, loss of Ikaros function was recently...
CML: live long and prosper

Richard A. Larson