Ibrutinib: targeting the hidden CLL

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In this issue of Blood, Herman et al elucidate the in vivo effects of ibrutinib (a BTK inhibitor) in various disease compartments of patients with chronic lymphocytic leukemia (CLL).1

The study validates the differential impact of ibrutinib in various tumor compartments of patients treated on a small but well-designed and well-conducted clinical trial. In their study, the authors provide a link between the extent of on-target drug effects and the magnitude of clinical responses. They demonstrate rapid and sustained inhibition of the B-cell receptor (BCR) signaling pathway and progressive inhibition of the dependent NF-κB pathway in circulating CLL B cells over the first few weeks of therapy with ibrutinib. This effect was also observed in matched lymph node and bone marrow resident CLL B cells obtained at serial time points in the trial. Similarly, significant reductions were observed in the expression of activation markers CD69 and CD86, and the proliferation marker Ki-67. This provides evidence for simultaneous pathway targeting and inhibition in tumor compartments of peripheral blood, bone marrow, and lymph nodes.

The authors did not observe significant correlation in nodal responses among patients in various prognostic subgroups. A previously validated specific BCR gene signature score5 was also observed to correlate with nodal responses, regardless of risk factors, only from B cells obtained from lymph node biopsies rather than circulating B cells. However, no definite explanation was provided for the dramatic tumor reductions seen with ibrutinib other than a combination of reduced proliferation, inhibition of survival mechanisms, and slightly increased apoptosis observed in circulating cells.

The BTK gene is located on the long arm of the X chromosome at the Xq21.33-q22 locus and encodes the BTK protein that is part of the Tec family of kinases. BTK is located downstream of the BCR that has been established as the primary CLL tumor cell survival signal. It is essential for the activation of several constitutively active pathways of CLL cell survival including Erk, Akt, PLCγ2, and NF-κB along with those involved in chemokine-mediated homing and adhesion of B cells.3,4 In vivo mouse studies using various CLL models have established the significance of BTK in disease establishment and progression. Moreover, ibrutinib demonstrated significant reduction in development and progression of disease in these models.5 Together, these studies laid the foundation for further investigation of BTK targeting as a therapeutic strategy for patients with CLL.

The recent Food and Drug Administration approval of ibrutinib for the management of M-CLL. However, even if anergy is more evident in M-CLL, it is also present in U-CLL, and in both types of CLL the critical point may be represented by the balance between cell lethargy and cell proliferation.3 It is plausible to postulate that anergy is reverted and proliferation starts when antigen-triggered CLL B cells encounter T cells. This encounter likely occurs within the tissue microenvironment, especially in the proliferative clusters known as pseudofollicles (and perhaps might even give rise to their development).6 As most CLL studies have been performed using cells from peripheral blood, the results may be a pale reflection of the events that occur in the tissues where the proliferation rate has been found to be much higher than anticipated.2,3 As anergic cells can be recruited in the proliferation process both in M- and in U-CLL, they might represent a major clonal reservoir of indecisive, hesitant cells that are persuaded to proliferate by the proper T-cell encounter. The pool of anergic cells likely gives shelter to subclones harboring dangerous mutations, and these subclones may be expanded by subsequent rounds of proliferation.

The implication is that CLL anergic cells are a potentially important therapeutic target. When the anergic state has been experimentally reverted, the leukemic cells were found to undergo apoptosis.9 This brings in another interesting finding of this paper. By investigating both DNA methylation and histone modifications associated with PRDM1 transcriptional control elements, the authors find that the transcriptional inactivity of the PRDM1 gene is due to transcriptional repression and failure to facilitate gene transcription.1 The observation that anergy and the differentiation block are linked by epigenetic modifications may open a novel therapeutic avenue. Conceivably, the anergic state might be reverted by means of epigenetic-interfering drugs. This leads us to envisage the possibility of a combination treatment policy, whereby epigenetic-interfering or other drugs able to modify the anergic status might be added to those that efficaciously target BCR signaling.10

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of relapsed CLL is a landmark event that heralds a new era of targeted therapies for the management of this disease. The drug is generally well tolerated with mostly mild side effects that frequently resolve despite continuation of therapy. Interestingly, results were also seen in the current study. However, progression-free survival (PFS) has been shown to be inferior in patients with deletion 17p or 11q.6 Interestingly, the redistribution lymphocytosis and its persistence in some patients also do not appear to correlate with PFS. In addition, minimal residual disease negative state, which could potentially be used as a surrogate for PFS, is rare with single-agent use.6

A small percentage of patients treated with ibrutinib develop progressive disease or resistance to therapy, the mechanisms of which are currently being investigated and can at least be partially attributed to specific mutations in the BTK protein itself or downstream targets. With the expected rapid increase in the use of ibrutinib, similar well-designed trials are desperately needed to study not only the mechanisms of action and resistance, but also to obtain better understanding of its off-target effects. Studying the various disease compartments simultaneously will also enable us to evaluate the differential effects of these agents and tumor escape mechanisms, and will enable us to devise rational combination strategies that will hopefully result in the eventual cure of CLL.

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Comment on Taskesen et al, page 3327

Splicing factor mutations in AML

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In this issue of Blood, Taskesen et al propose a novel subset of myeloid neoplasms that encompasses splicing factor (SF) mutation-positive refractory anemia with excess blasts (RAEB) and acute myeloid leukemia (AML), which is composed of 2 molecularly and clinically distinct subgroups.1

Myeloid neoplasms comprise a wide variety of clinically and pathologically distinct entities commonly characterized by neoplastic proliferation of myeloid lineage cells with deregulated differentiation.2 Although straightforward for typical cases, distinction among different subtypes of myeloid neoplasms may not be unambiguous, complicating the diagnosis of and the therapeutic choice in borderline cases. According to the current World Health Organization (WHO) classification system, for example, distinction between AML with low blast counts (AML-LBC) and the RAEB subtype of myelodysplastic syndromes (MDS) is made only by the presence or absence of ≥20% bone marrow blasts.2 However, these criteria, based on the blast counts, would lead to a diagnosis of AML for some patients who might be biologically/clinically more properly classified as RAEB or vice versa. In this regard, during the past 10 years, our knowledge about the molecular pathogenesis of myeloid neoplasms has been substantially improved by the identification of major driver mutations causally related to these neoplasms,3-6 which may help better understanding, classification, diagnosis, and management of different entities of myeloid neoplasms.

Taskesen et al focused on pre-messenger RNA SF mutations and tested their hypothesis that SF mutations could define a novel subset of myeloid neoplasms that includes SF mutation–positive RAEB and AML as well as AML–LBC. SF mutations are a novel class of driver mutations recently identified through whole exome sequencing of myeloid dysplasia.7,8 Affecting at least 8 different components of the pre-messenger RNA splicing machinery, including SF3B1, SRSF2, U2AF35, ZRSR2, U2AF65, SF1, SF3A1, and PRPF40B, SF mutations represent among the most frequent genetic lesions in MDS (45% to 85% of MDS depending on their subtypes) and other related myeloid neoplasms with myelodysplasia but much less common (5% to 10%) in de novo AML and classical myeloproliferative neoplasms.3,4 In the current study, authors investigated 47 RAEB, 29 AML–LBC, and 325 other AML patients for predominant hot-spot mutations in SF3B1, U2AF35, and SRSF2, and found that patients with RAEB and AML–LBC showed significantly higher SF mutation rates compared with other AML and, except for white cell counts and bone marrow blast counts, shared a highly similar clinical, cytological, and molecular profile. Also, SF-mutated patients among RAEB, AML–LBC, and other AML categories had similar clinical phenotypes, including lower blast counts, older age, lower white cell counts, and higher erythroblast counts in bone marrow compared with SF-unmutated cases, indicating that SF–mutated cases comprised a distinct entity among MDS/AML. In accordance with this, a hierarchical clustering of AML/AML–LBC/RAEB cases based on combined, but not separate, gene expression (GEP) and DNA-methylation profiles (DMP) identified...
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