Chronic myeloid leukemia (CML) originates in the hematopoietic stem cell because of a reciprocal translocation of chromosomes 9 and 22. This translocation juxtaposes the \textit{ABL} proto-oncogene with \textit{BCR}, which translates into a constitutively active BCR-ABL kinase that drives expansion of leukemic progeny. Treatment of CML with ABL kinase inhibitors such as imatinib is very effective and brings about complete cytogenetic response in more than 80% of newly diagnosed patients.

CML is a celebrated model disease because of its stem cell origin, straightforward oncogene, targeted therapy, easy monitoring, and high odds of remission.

I remember treating patients with CML in the pre-imatinib era. Interferon-\(\alpha\) was the standard of care, and the patients were miserable because of feverish side effects and frequent injections. When we opened our first clinical trial of imatinib in the late 1990s, one particular Veterans Health Administration (VA) patient whose CML responded wonderfully on study was distraught because he faced the possibility of being cured of his disease and that meant a possible loss of his VA health benefits. To mixed fortune, we continued imatinib in this patient out of fear of relapse.

Since that time, we’ve learned that despite low to undetectable levels of BCR-ABL transcripts, discontinuing imatinib results in CML relapse in a majority of patients, indicating that disease-causing leukemic cells persist below limits of detection. Because of this risk of recurrence, the clinical standard is to continue imatinib lifelong, even at high cost and potential for severe side effects.

One of the most pressing issues in leukemia, and possibly all of oncology, is how a model disease with such fantastic response to a targeted therapy can exhibit such recalcitrance. Our reductionist tendencies have brought us as far as they can with CML, and it is now time to admit that our model disease is much more tangled than a single oncogene.

Several hypotheses have been proposed to explain how CML evades ABL kinase inhibition. Possibilities include minor populations of BCR-ABL kinase domain mutants (eg, T315I), increased expression of BCR-ABL, and sanctuary sites in the microenvironment. Alterations of imatinib influx and efflux appear less likely as explanations for resistant disease. The fact that minimal residual CML cells can persist despite years of imatinib therapy argued for a cancer stem cell hypothesis and led to the discovery that the imatinib-resistant CML population resides in a small subset of slow-cycling, self-renewing leukemia stem cells (1).

Another basic yet critical question was whether imatinib resistance was dependent or independent from BCR-ABL. Should we keep hammering away at BCR-ABL or should we look elsewhere for cooperating lesions? In CML stem cells, chronic suppression with ABL kinase inhibitors did not eradicate the leukemic clones (2), which supported the search outside of the BCR-ABL oncoprotein for more definitive treatment.

In this issue of the Journal, Chen et al. (3) present a rationally designed combination treatment for eliminating CML stem cells: ABL inhibition plus Janus kinase 2 (JAK2) inhibition. Leading up to this report were four important discoveries by this group and others (4–7): 1) the BCR-ABL kinase is stabilized by another oncoprotein, Abelson helper integration site-1 (AHI-1); 2) AHI-1 stabilizes BCR-ABL by linking it with JAK2; 3) this stabilized complex results in resistance to imatinib; and 4) CML stem cells overexpress AHI-1. Together, these findings implicated JAK2 as not only a downstream target of BCR-ABL but also an accomplice.

In this study (3), the investigators provide more clarity on the AHI-1 oncoprotein in CML. They demonstrate that uncoupling AHI-1 from BCR-ABL and JAK2 improved sensitivity of CML stem cells to imatinib. Whereas disconnecting AHI-1 from BCR-ABL was most potent, separating AHI-1 from JAK2 also improved responsiveness to imatinib albeit to a lesser extent. AHI-1 may not be the whole story to imatinib resistance. JAK2 is known to interact directly with BCR-ABL, and results from this study support previous findings. Therefore, the investigators decided to focus on JAK2 inhibition to block both direct and AHI-1–mediated interactions with BCR-ABL. They used an investigational JAK2 inhibitor, TG101209, to demonstrate that combination treatment with imatinib is more effective at eliminating CML stem cells than either agent alone. Importantly, they confirmed CML cell line results with a small number of primary specimens from patients who failed with imatinib treatment.

These results are exciting because they advance our understanding of CML persistence in the face of imatinib monotherapy and they also provide the basis for a promising combination treatment strategy. But a couple of considerations should be made before translating these results into a clinical trial. The first consideration is hematologic toxicity. Our clinical experiences with ABL kinase inhibitors and JAK2 inhibitors, separately, have shown us clinically significant cytopenias in our patients that necessitated dose reductions and sometimes discontinuation of treatment altogether. Combining inhibitors could bring about treatment-limiting hematological toxicities.

Another consideration is the off-target effects of JAK2 inhibitors. All JAK inhibitors—including the two already approved by the US Food and Drug Administration and the cornucopia in development—suppress more than JAKs. For example, the agent used in this study also targets FLT3, RET, and, to a lesser extent, other JAKs (8). The investigators present a clear illustration of the importance of AHI-1 in CML, but results from use of the JAK2 inhibitor should be interpreted with multiple kinases in mind.
Experience with JAK2 inhibitors in patients with myeloproliferative diseases has also taught us that cytokines are important. As a case in point, clinical improvement with ruxolitinib in patients with myelofibrosis appears to be related to a reduction in proinflammatory cytokines (eg, interleukin 6, tumor necrosis factor α, and macrophage inflammatory protein 1β), rather than reduction in mutant JAK2 allele burden (9). This clinical experience attests to the importance of the microenvironment in myeloproliferative diseases and urges us to appreciate the knotted ecology of cancer.

Even with these considerations, this study provides a strong preclinical basis for inhibiting JAK2 in combination with imatinib for CML.

References


Notes

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