Commentary

Overcoming Resistance to Imatinib by Combining Targeted Agents

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Bcr-Abl, the causative molecular abnormality of CML is known to activate numerous intracellular signaling proteins and pathways. These include ras, raf, phosphatidylinositol 3-kinase, AKT, STAT (signal transducers and activators of transcription), and various antiapoptotic proteins (1). The activation of these pathways and proteins is dependent on the tyrosine kinase activity of the Bcr-Abl protein. Thus, targeting the Bcr-Abl tyrosine kinase with imatinib, a specific inhibitor, has been a highly successful clinical strategy (2).

Targeted Agents

In deciding whether it is rational to add an agent to imatinib that targets a downstream signaling pathway, one would first want to know if the relapse mechanism was Bcr-Abl-dependent or -independent. In the case of Bcr-Abl-independent relapse, the Bcr-Abl kinase would remain inhibited by imatinib as would all of the pathways activated by the Bcr-Abl kinase. Thus, resistance would be driven by molecular abnormalities other than Bcr-Abl. Therefore, targeting pathways downstream of Bcr-Abl would be predicted not to be of utility, unless the additional molecular abnormalities happened to activate similar pathways to Bcr-Abl. In CML blast crisis patients who do not respond to imatinib therapy, many of them have resistance mechanisms that are Bcr-Abl-independent and would fall into this category (11).

In the case of Bcr-Abl-dependent relapses, the Bcr-Abl kinase would have been reactivated as the cause of imatinib resistance. Thus, all of the Bcr-Abl pathways would also be reactivated. In this case, it would be anticipated that an agent targeting a downstream pathway would be useful. This is exactly the case as described by Nakajima et al. (9) and Hoover et al. (10). Bcr-Abl cells that are resistant to imatinib because of Bcr-Abl amplification or point mutation are sensitive to SCH66336. Whether or not adding this second agent to imatinib results in improved therapeutic benefit might depend on whether the Bcr-Abl kinase is partially inhibited by imatinib or not. In the case of Bcr-Abl amplification, it is presumed that the kinase is inhibited by imatinib but not sufficiently to inhibit proliferation. In this case, residual downstream signaling would be inhibited by SCH66336, resulting in an enhanced antiproliferative effect as was observed (9, 10). However, in the case of T315I, which is completely insensitive to imatinib, the effects of imatinib plus SCH66336 are completely due to the antiproliferative effects of SCH66336 (9, 10). In patients who respond to imatinib and then relapse, Bcr-Abl point mutations are the most common mechanism of imatinib resistance, and these mutants are variably sensitive to imatinib (12–14). From this discussion, it would be predicted that mutants that retain some sensitivity to imatinib would be ideal candidates for an agent that targets a downstream, Bcr-Abl-activated signaling pathway to be added to imatinib.

A second related issue is the mechanism of molecular persistence of leukemia. In newly diagnosed, chronic-phase CML patients, the majority obtain a complete cytogenetic response with imatinib therapy (15). This corresponds with an approximately two-log reduction in Bcr-Abl levels by quantitative reverse transcription-PCR for Bcr-Abl. However, <5% obtain a five-log or greater reduction in Bcr-Abl levels.
There is an obvious concern that patients who do not achieve a molecular remission could relapse over time. For these patients, the question is why do these cells persist or why is imatinib unable to completely eradicate the disease? The mechanisms of persistence of leukemic cells could again be divided into Bcr-Abl-dependent and -independent mechanisms. For example, stem cell quiescence has been postulated as a potential Bcr-Abl-independent mechanism of resistance to imatinib (17). However, mechanisms that are Bcr-Abl-dependent are also possible. This includes the possibility that low levels of Bcr-Abl kinase activity prevent cells from proliferating but are sufficient to protect cells from apoptosis. This could be because of imatinib not being capable of completely inhibiting the Bcr-Abl kinase or because stem cells express high levels of P-glycoprotein expression that result in efflux of imatinib. For these Bcr-Abl-dependent mechanisms of molecular persistence, it would be quite reasonable to expect that adding a second agent that targets a downstream pathway might increase the percentage of patients who achieve a molecular remission.

The foregoing discussion has assumed that the mechanisms of action of the various compounds that would be combined are well understood. Although farnesyl transferase inhibitors were developed as ras inhibitors, it has become increasingly clear that their mechanism of action is much more complex (18). For example, inhibition of Bcr-Abl-induced proliferation is more profound with a farnesyl transferase inhibitor than by expression of a dominant-negative ras (6). Given that there are numerous farnesylated proteins in a cell, it is possible that these compounds do not work through one specific protein or that the critical target has yet to be identified. There is also evidence that farnesyl transferase inhibitors function by altering the ratio of farnesylated to geranylgeranylated forms of RhoB having growth-suppressive properties (19). Unfortunately, the lack of a thorough understanding of the mechanism of action of farnesyl transferase inhibitors makes it difficult to predict where they would be best used. However, it is clear from the articles by Nakajima et al. (9) and Hoover et al. (10) that it would be reasonable to combine imatinib with a farnesyl inhibitor in imatinib-resistant patients, and this clinical trial is currently in progress at Stanford University (Stanford, CA) and Oregon Health and Science University.

References
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