Unraveling CML phase by phase

John Goldman Imperial College London

Dasatinib induces hematologic and cytogenetic responses in both myeloid and lymphoid blastic phase of CML regardless of the presence of BCR-ABL kinase domain mutations, and these responses are durable at least in the short term. Blastic transformation or blastic crisis of chronic myeloid leukemia (CML) is one of the most aggressive and intractable of leukemias, and it is therefore very encouraging to learn from the report by Cortes and colleagues published in this issue of Blood that dasatinib, one of the so-called second-generation tyrosine kinase (TK) inhibitors that includes also nilotinib, can induce major hematologic responses in about one third of patients treated previously with imatinib and complete cytogenetic responses in a similar proportion. These results are much better than might have been expected with classical cytotoxic drug combinations and shed some light on at least 4 questions that have fascinated CML aficionados over the years. First, do residual Ph-negative stem cells routinely survive in the marrow of patients after the onset of blastic transformation? The evidence here suggests that even in blastic transformation a significant number of presumably normal stem cells do survive and can reconstitute hematopoiesis if given the chance.

Second, what role does the BCR-ABL fusion gene play in causing or maintaining the blastic subclone? It might have been assumed that the BCR-ABL fusion gene set the scene for progression of leukemia to blastic phase but then became operationally irrelevant. This seems not to be the case. The fact that some patients respond to dasatinib even after failing imatinib suggests (but does not prove) that the BCR-ABL gene still plays some crucial cooperative role in maintaining the blastic phase (though studies that showed resumption of the capacity of Bcr-Abl in vitro to phosphorylate Crkl might have been definitive). This would mean either that dasatinib, at least in this setting, is generally a much more powerful BCR-ABL inhibitor than imatinib, perhaps because of its less stringent binding requirements, or that other activated TKs, such as SRC or other SRC family kinases, which are targeted by dasatinib but not by imatinib, have substituted for BCR-ABL in maintaining the transformed leukemia.1

Third, why do some of the responses seem to be durable, although the follow-up is still relatively short? If dasatinib-resistant subclones were already present when the drug was started, one would have expected to see resistance developing quite quickly; if, however, resistant subclones had not yet developed and dasatinib completely or near-completely suppressed the whole population in which they would have been expected to occur, then the drug should control the leukemia for some time. One hopes this proves to be the case.

And finally, what is the role of kinase domain mutations in “causing” resistance to TK inhibitors? An increasing body of evidence suggests that whereas some mutations are indubitably the cause of imatinib resistance, others seem merely to be epiphenomena.2 Dasatinib actually controls almost all mutant subclones,3,4 though not the notorious T315I. One might speculate therefore that it might for this reason be slightly more effective than imatinib for treating chronic-phase disease, but in “late” blastic phase disease resistance seems often to be due to mechanisms other than BCR-ABL kinase domain mutations. The challenge now must be to identify activated signal transduction pathways that maintain the blastic phenotype even when the BCR-ABL kinase remains fully suppressed.

The author declares no competing financial interests.

REFERENCES

Inside-out, outside-in: what’s the difference?

Edward F. Plow and Yan-Qing Ma Cleveland Clinic

Zou and colleagues use retrovirus infection and fetal liver transplantation to engineer platelets in mice expressing αIIbβ3 and use point mutations to dissect inside-out and outside-in signaling in vivo. As if integrin nomenclature were not complicated enough, with all its alphas and betas, we must now be cognizant of the subtleties of an additional layer of terminologies, “inside-out” and “outside-in” signaling. There is, of course, a logic to integrate these additional terms into our integrin vocabulary: they define distinct and biologically important aspects of integrin-mediated cellular responses. αIIbβ3 is the integrin that mediates platelet aggregation, and its ability to form a stable thrombus in vivo depends upon both inside-out and outside-in signaling. Engagement of fibrinogen or von Willebrand factor by the extracellular domain of αIIbβ3 is necessary for platelet aggregation and requires a conformational transition, the consequence of inside-out signaling. As platelets aggregate, occupied αIIbβ3 integrins cluster and trigger outside-in signaling that
Unraveling CML phase by phase

John Goldman