

factor-alpha concentrations and outcome of patients with severe sepsis. *Crit Care Med.* 1996; 24:381-384.

- Schroder NW, Hermann C, Hamann L, Gobel UB, Hartung T, Schumann RR. High frequency of polymorphism Arg753Gln of the Toll-like receptor-2 gene detected by a novel allele-specific PCR. *J Mol Med.* 2003;81:368-372.

## Der9q deletions in CML: the next chapter in the story

The classic Philadelphia chromosome giving rise to *Bcr-Abl* is associated with a certain additional cytogenetic abnormality in a significant minority of patients. A number of groups have previously investigated the significance of large deletions adjacent to the translocation breakpoints in patients with chronic myeloid leukemia (CML). These deletions have been reported in between 10% to 15% of patients; they typically span the translocation breakpoint and often involve both chromosomes 9 and 22. The deletions can be many megabases in length and are presumably formed at the time of the Philadelphia translocation. Such deletions are associated with a poor prognosis in terms of shorter length of chronic phase, earlier disease transformation, and shorter survival. Previous analyses were largely confined to patients who had been treated with interferon-alpha (IFN- $\alpha$ ), although interestingly the effect was still evident in patients treated by allogeneic transplantation. However, does the "poor-prognosis" effect still stand up in imatinib-treated patients?

In this edition of *Blood*, Huntly and colleagues (page 2205) present new data addressing the question of whether therapy with imatinib overrides the deletion effect. The answer seems to be that deletions still seem to confer a somewhat poorer prognosis in certain settings but that the effect is clearly "diluted" by the use of imatinib in comparison to groups of patients treated with IFN. For example, in 122 chronic-phase patients, significant differences in progression-free survival, but not overall sur-

vival, were seen among patients with (n = 15) and without (n = 107) deletions. In successive cohorts of analyzed patients it seems evident that as there is a greater proportion treated with imatinib so the prognostic impact of deletions diminishes.

Finally, why these deletions should confer a poor prognosis remains far from clear. The data presented in this article would suggest that the molecular abnormalities present in patients with deletions in some way cooperate with, but are not entirely dependent upon, *Bcr-Abl*. It would seem that this evolving story is far from complete: the prospective analysis of deletions in future clinical studies will not only allow confirmation of the initial observations of this study, but will also allow a long-term analysis of the true impact on survival. Furthermore, it is not inconceivable that elucidation of the molecular aberrations underlying this effect may allow further improvements in the therapy of CML in due course.

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## Location matters. . .

Molecular therapy of chronic myeloid leukemia (CML) since the advent of imatinib mesylate (Gleevec, Glivec) is a developing paradigm for oncology in general and for hematologic malignancies in particular. Our understanding of the basic biology of the disease, and the availability of high-throughput drug screens, arms us with small-molecule drugs that inhibit the key steps in the genesis, maintenance, and proliferation of the tumor. However, imatinib, at the vanguard, has shown that responses to single specific inhibitors alone may be short-lived and relapse is most often associated with a loss of drug binding caused by the exquisitely powerful selection of random cells carrying mutations in the *Bcr-Abl* tyrosine kinase domain that render them resistant to imatinib. Even as it becomes increasingly likely that imatinib does confer long-

term benefit in the treatment of CML, the addition of other drugs will have an important role in improving clinical responses to imatinib used as a single agent or in managing resistance to this drug.

In addition to *Bcr-Abl*, other downstream proteins essential for transducing the oncogenic signal are good candidates for targeted therapy. For example, a key player is the oncoprotein Ras, known to be active only when tethered to the cytoplasmic membrane. This attachment depends on a specific posttranslational modification (called prenylation, usually of the farnesylation type) of Ras, although the exact mechanism underlying this location-dependent activity, and the cast of other proteins that behave similarly, is only partly understood. An important observation is that mutagenesis of one specific cysteine residue in oncogenic Ras, whereby farnesylation and localization to the cell membrane cannot occur, prevents transformation of fibroblasts via loss of Ras/MAPK (mitogen-activated protein kinase) signaling.<sup>1</sup> Therefore, Ras signaling might represent an excellent target for intervention in many areas of oncology.

At present, clinical trials of inhibitors of the farnesyl transferases (known as FTIs) in CML are underway, and the in vitro data for these drugs are encouraging, even where responses to imatinib are poor.<sup>2</sup> However, it appears that when Ras farnesylation is prevented, other lipid modifications such as geranylgeranylation may be possible, leading to restoration of Ras/MAPK signaling and the loss of the therapeutic effect.

In this issue, Kuroda and colleagues (page 2229) present in vitro and in vivo data describing the cytotoxic effects on

