

Letter to the Editor

ABL Alternative Splicing Is Quite Frequent in Normal Population - Letter

In the article by Lee et al. (1), an alternative splicing of *BCR-ABL* is proposed as a mechanism for imatinib resistance in chronic myeloid leukemia (CML) patients. This splicing (2), which inserts 35 bp between exons 8 and 9 of *ABL* (35INS), results in a truncated BCR-ABL protein that the authors compare dynamically with the native protein. We found their work very relevant, especially the finding on the conformational change and its similarity with tertiary structures due to resistance mutations. We were nonetheless surprised by the high proportion of patients who became resistant to imatinib with the alternative splicing; however, the authors did not present data on the presence of the 35-bp insertion in other populations or native *ABL* mRNA.

Using a similar experimental approach to the one described in their article, we analyzed 18 samples from CML patients treated with kinase inhibitors and 24 samples from a normal population. The analysis of the normal population may serve as an estimation of the alternative splicing frequency of the *ABL* gene. The results showed that 27% of the patients with CML and 41.6% of the normal population expressed 35INS in different degrees (only those with >5% alternatively spliced were considered positive, as described by Lee et al.). In the samples from CML patients, we were unable to correlate either the presence or relative levels of expression of INS35 to tyrosine kinase inhibitor resistance. Several patients who had suboptimal responses to imatinib and an absence of *ABL* mutations were negative for INS35. One patient, who was marginally positive (5.1%) for INS35 and have a F359V mutation, presented a *BCR-ABL/GUS* ratio of 22.3%; after being switched to dasatinib treatment, his *BCR-ABL* ratio decreased to 0.08% in 4 months, but showed an INS35 presence of 24%, which indicates that the splicing was occurring in non-mutated Ph+ cells. The *BCR-ABL* ratio of the patient, however, further decreased to undetectable levels in the

following 4 months. Another patient, who failed to achieve a complete molecular response, was negative for INS35 or *ABL* mutation at that point; previous samples showed the presence of the alternative splicing in 48.4% of the *BCR-ABL* mRNA, which indicates that the splicing has decreased over time while the resistance has endured.

All these data seem to confirm that INS35 may just be a pseudo-exon not uncommon in the *ABL* gene processing (3) and therefore unrelated to resistance or sensitivity (4) to inhibitors in CML treatment.

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No potential conflicts of interest were disclosed.

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