Published OnlineFirst March 9, 2010; DOI: 10.1158/1535-7163.MCT-09-0078

Molecular Cancer Therapeutics

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.

Iñigo Santamaria
Ana S. Pitiot
Milagros Balbin
Molecular Oncology Laboratory, Hospital Universitario Central de Asturias-Instituto Universitario de Oncologia del Principado de Asturias, Oviedo, Spain

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Lee TS, Ma W, Zhang X, et al. BCR-ABL alternative splicing as a common mechanism for imatinib resistance: evidence from molecular dynamics simulations. Mol Cancer Ther 2008;7:3834–41.
2. Laudadio J, Deininger MW, Mauro MJ, Druker BJ, Press RD. An intron-derived insertion/truncation mutation in the BCR-ABL kinase domain in chronic myeloid leukemia patients undergoing kinase inhibitor therapy. J Mol Diagn 2008;10:177–80.
3. Quigley NB, Henley DC, Hubbard RA, Laudadio J, Press RD. ABL kinase domain pseudoexon insertion is not uncommon in BCR-ABL transcripts. J Mol Diagn 2008;10:475–6.
4. Sung-Chao C, Jih-Luh T, Chi-Cheng L. Dasatinib in chronic myelogenous leukemia. N Engl J Med 2006;355:1062–3.

Published OnlineFirst 03/02/2010.
©2010 American Association for Cancer Research.
doi: 10.1158/1535-7163.MCT-09-0078

Downloaded from mct.aacrjournals.org on October 23, 2021. © 2010 American Association for Cancer Research.

Published OnlineFirst March 9, 2010; DOI: 10.1158/1535-7163.MCT-09-0078

AACR American Association for Cancer Research

Molecular Cancer Therapeutics

ABL Alternative Splicing Is Quite Frequent in Normal Population - Letter

Iñigo Santamaria, Ana S. Pitiot and Milagros Balbin

Mol Cancer Ther 2010;9:772. Published OnlineFirst March 9, 2010.

Updated version	Access the most recent version of this article at: doi:10.1158/1535-7163.MCT-09-0078

Cited articles	This article cites 4 articles, 1 of which you can access for free at: http://mct.aacrjournals.org/content/9/3/772.1.full#ref-list-1
Citing articles	This article has been cited by 3 HighWire-hosted articles. Access the articles at: http://mct.aacrjournals.org/content/9/3/772.1.full#related-urls

E-mail alerts	Sign up to receive free email-alerts related to this article or journal.
Reprints and Subscriptions	To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.
Permissions	To request permission to re-use all or part of this article, use this link http://mct.aacrjournals.org/content/9/3/772.1. Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.

Downloaded from mct.aacrjournals.org on October 23, 2021. © 2010 American Association for Cancer Research.