are at odds with the claims on the company's website (http://www.upstate.com) that this antibody was raised against amino acids 27-37 of human β-catenin. As published previously, the 8E7 epitope mapped directly C-terminal to amino acid 35.[3]

It is unfortunate that these antibodies with such similar names, commercialized by the same company, have strikingly different specificities. Our observations imply that the 8E4 antibody does not possess the advertised specificity for the dephosphorylated regulatory region of β-catenin and should not be used to study activity of the Wnt pathway, for instance, on cytospin preparations of cells suspected for hematologic malignancies.

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References

1. Guo Z, Dose M, Kovalovsky D, et al.Beta-catenin stabilization stalls the transition from double-positive to single positive stage and predisposes thymocytes to malignant transformation. Blood. 2007;109:5463-5472.
2. Roman-Gomez J, Cordeu L, Agirre X, et al. Epigenetic regulation of Wnt-signaling pathway in acute lymphoblastic leukemia. Blood. 2007;109:3462-3469.
3. van Noort M, Meeldijk J, van der Zee R, Destree O, Clevers H. Wnt signaling controls the phosphorylation status of beta-catenin. J Biol Chem. 2002;277:17901-17905.
4. Staal FJ, Noort Mv M, Strous GJ, Clevers HC. Wnt signals are transmitted through Nterminally dephosphorylated beta-catenin. EMBO Rep. 2002;3:63-68.
5. Gottardi CJ, Gumbiner BM. Distinct molecular forms of beta-catenin are targeted to adhesive or transcriptional complexes. J Cell Biol. 2004;167:339-349.
6. Derksen PW, Tjin E, Meijer HP, et al. Illegitimate WNT signaling promotes proliferation of multiple myeloma cells. Proc Natl Acad Sci U S A. 2004;101:6122-6127.
7. Diks SH, Hardwick JC, Diab RM, et al. Activation of the canonical beta-catenin pathway by histamine. J Biol Chem 2003;278:52491-52496.
8. Jamieson CH, Ailles LE, Dylla SJ, et al. Granulocyte-macrophage progenitors as candidate leukemic stem cells in blast-crisis CML. N Engl J Med. 2004;351:657-667.

To the editor:

Interferon-α or homoharringtonine as salvage treatment for chronic myeloid leukemia patients who acquire the T315I BCR-ABL mutation

We report here the clinical outcome for 2 chronic myeloid leukemia (CML) patients who acquired the T315I mutation while on imatinib, both of whom were treated successfully, one with recombinant interferon-alpha (rIFN) and the other with semisynthetic homoharringtonine (HHT).

Patient 1 was a 75-year-old man with CML diagnosed in October 2003 who started imatinib 400 mg daily. After 4 months he achieved a complete cytogenetic remission (CCyR) with low BCR-ABL transcript numbers (0.3%) quantified by real-time quantitative polymerase chain reaction (RQ-PCR).[1] He maintained a good response for 12 months but then BCR-ABL transcripts started to increase progressively and a T315I mutation was identified. The earlier samples were then analyzed retrospectively. Thirty months after starting imatinib, cytogenetics revealed loss of CCyR (2% Philadelphia chromosome [Ph]–positive cells) and the patient started rIFN 9 MU/week. Ten months later the patient was still in complete hematologic remission (CHR) with low BCR-ABL transcripts (3%), a level that is just consistent with CCyR. Interestingly, on rIFN, the percentage of mutant transcripts measured by quantitative single-nucleotide polymorphism pyrosequencing[1] decreased from 100% to 30% (Figure 1A).

The second patient was a 60-year-old woman diagnosed with chronic-phase CML in 1997. She received rIFN and thereafter imatinib 400 mg daily from October 2002. She achieved a major cytogenetic response (15% Ph-positive cells) at 12 months but lost her response 2 years later. Bone marrow examination then revealed myelofibrotic transformation with 100% Ph positivity. Imatinib was increased to 600 mg/day, but she went into accelerated phase at 40 months, and thus received dasatinib 70 mg twice a day. Four months later a bone marrow aspirate still showed accelerated-phase leukemia, and a T315I mutation was identified. The earlier samples were then analyzed and the mutated clone was detected before starting dasatinib. The patient started on HHT at 1.25 mg/m^2 subcutaneously twice daily for 5 consecutive days every month. Five months later she achieved a CHR. The marrow showed a minor cytogenetic response, and at 10 months the percentage of the mutant clone had decreased from 100% to 27% (Figure 1B).

The finding of a T315I mutation in the BCR-ABL gene characteristic of CML is associated with clinical resistance to imatinib, nilotinib, and dasatinib.[2-4] The only established salvage option for patients harboring this mutation is allogeneic stem cell transplantation (allo-SCT)[5]; the role of the aurora kinase inhibitor MK-0457 is not yet clear.[6] Because the mechanisms of action of rIFN and HHT differ from that of tyrosine kinase inhibitors (TKIs), we evaluated their effect in these 2 patients with a predominant T315I clone.[2,7,8] Although longer follow-up is needed, both patients

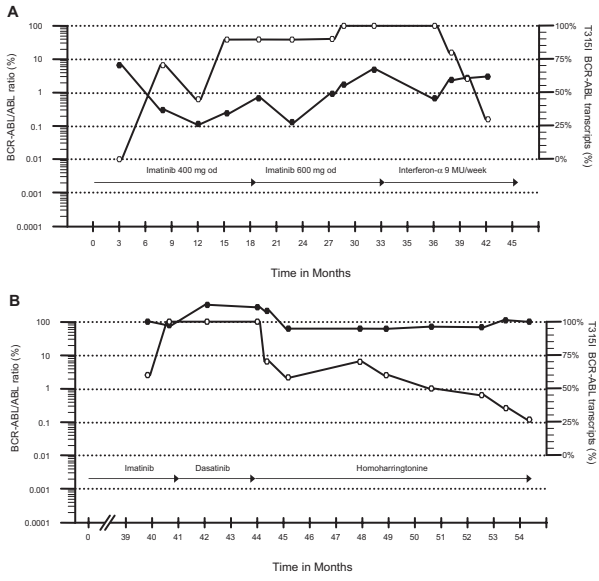

Figure 1. Total and T315I BCR-ABL in vivo kinetics. The figure shows BCR-ABL transcript levels measured by RQ-PCR and the relative size of the mutant clone. ● and ○ represent the total BCR-ABL transcripts and the percentage of the mutant clone, respectively. The type and duration of therapy are represented by the arrows.

showed a significant decrease in the percentage of the mutated clone along with a continuing disease response for a follow-up of 10 months. The question whether T315I-expressing CML cells are more "aggressive" than cells expressing native protein is still debated.[9,10] However, it is possible that the decrease in size of the mutant subclone was a consequence of removing the selection pressure by stopping TKI. Thus rIFN or HHT should be considered for CML patients harboring the T315I mutation.[2]

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Contribution: H.d.L. collected and analyzed clinical data and wrote the manuscript; J. S. Khorashad performed the molecular studies, assembled the molecular data, and commented on the manuscript; H.P.D. recruited the first patient, provided clinical care, and commented on the manuscript; D. Milojkovic provided clinical care and commented on the manuscript; J. S. Kaeda supervised the day-to-day running of the Minimal Residual Disease laboratory and commented on the manuscript; J.M.G. commented on and revised the manuscript; J.F.A. was responsible for coordinating the CML program and commented on the manuscript; and D. Marin supervised patient care and revised the manuscript.

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References

1. Khorashad JS, Anand M, Marin D, et al. The presence of a BCR-ABL mutant allele in CML does not always explain clinical resistance to imatinib. Leukemia. 2006;20:658-663.
2. Legros L, Hayette S, Nicolini FE, et al. BCR-ABL(T315I) transcript disappearance in an imatinib-resistant CML patient treated with homoharringtonine: a new therapeutic challenge? Leukemia. In press.
3. Nicolini FE, Corm S, Le QH, et al. Mutation status and clinical outcome of 89 imatinib mesylate-resistant chronic myelogenous leukemia patients: a retrospective analysis from the French intergroup of CML (Fi(phi)-LMC GROUP). Leukemia. 2006;20:1061-1066.
4. Shah NP, Tran C, Lee FY, et al. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science. 2004;305:399-401.
5. Jabbour E, Cortes J, Kantarjian HM, et al. Allogeneic stem cell transplantation for patients with chronic myeloid leukemia and acute lymphocytic leukemia after Bcr-Abl kinase mutation-related imatinib failure. Blood. 2006;108:1421-1423.
6. Giles FJ, Cortes J, Jones D, et al. MK-0457, a novel kinase inhibitor, is active in patients with chronic myeloid leukemia or acute lymphocytic leukemia with the T315I BCR-ABL mutation. Blood. 2007;109:500-502.
7. Angstreich GR, Matsui W, Huff CA, et al. Effects of imatinib and interferon on primitive chronic myeloid leukaemia progenitors. Br J Haematol. 2005;130:373-381.
8. Marin D, Kaeda JS, Andreasson C, et al. Phase I/II trial of adding semisynthetic homoharringtonine in chronic myeloid leukemia patients who have achieved partial or complete cytogenetic response on imatinib. Cancer. 2005;103:1850-1855.
9. Miething C, Feihl S, Mugler C, et al. The Bcr-Abl mutations T315I and Y253H do not confer a growth advantage in the absence of imatinib. Leukemia. 2006; 20:650-657.
10. Griswold IJ, Macpartlin M, Bumm T, et al. Kinase domain mutants of bcr-abl exhibit altered transformation potency, kinase activity, and substrate utilization, irrespective of sensitivity to imatinib. Mol Cell Biol. 2006;26:6082-6093.