Polyclonal Resistance in Gastrointestinal Stromal Tumor Treated with Sequential Kinase Inhibitors

In response: We thank Loughrey et al. for supporting our observation of polyclonal resistance to treatment with tyrosine kinase inhibitors in patients with gastrointestinal stromal tumors. They present another interesting case in which a patient developed several different new KIT mutations under therapy with both imatinib mesylate and subsequently with sunitinib, the latter also inhibiting the vascular endothelial growth factor receptor–linked tyrosine kinases. As in our series, all samples from the patient exhibited the same primary mutation, and furthermore, different new KIT mutations in several different metastatic lesions.

Their observation and our own results underline the importance of a continuous monitoring of patients under treatment with tyrosine kinase inhibitors by functional imaging such as positron emission tomography, computed tomography as well as by molecular studies on tissue samples of functionally active lesions. Concerning future treatment strategies, our observations have implications on possible therapy options. First, metastatic or recurrent gastrointestinal stromal tumors should be characterized molecularly prior to treatment to choose the right dosage of tyrosine kinase inhibitors, and in the future, with new upcoming inhibitory substances to select the most appropriate treatment regimen. Very recently, it has been shown in a large European Organization for Research and Treatment of Cancer study that patients with a primary exon 9 mutation had a longer progression-free survival when treated daily with 800 mg compared with 400 mg of imatinib mesylate (1). An insufficient dosage might be one reason for the development of resistant subclones due to surviving tumor residues (2) and could be prevented with the appropriate dosage of imatinib from the onset of therapy, at least in tumors with exon 9 mutations. During treatment, single progressive lesions with proven acquired KIT mutations could be resected surgically, while continuing the targeted treatment to control lesions still responding (3). The future will show if the combination of different “small molecules” will be able to prevent secondary polyclonal resistance by targeting different molecules in the signal transduction pathway of one tyrosine kinase or even inhibiting different tyrosine kinases activated in the same tumor synchronously.

In summary, we should learn to develop individualized treatment regimens for different patients dependent on the primary underlying molecular event(s) and on secondary genomic changes induced or accelerated by the treatment such as secondary polyclonal resistance in gastrointestinal stromal tumors.

Eva Wardelmann
Katharina Biermann
Sabine Merkelbach-Bruse
Hans-Ulrich Schildhaus
Nadja Thomas

Reinhard Büttner
Department of Pathology,
University of Bonn Medical Center,
Bonn, Germany

Torsten Pietsch
Department of Neuropathology,
University of Bonn Medical Center,
Bonn, Germany

Thomas Heinicke
Department of Internal Medicine,
University of Bonn Medical Center,
Bonn, Germany

Nicola Speidel
Department of Surgery,
University of Bonn Medical Center,
Bonn, Germany

Daniel Pink
Peter Reichardt
Department of Internal Medicine,
Hematology, and Oncology,
Robert Rössle Hospital and Tumor Institute,
Max Delbrück Center for Molecular Medicine,
Berlin-Buch, Germany

Peter Hohenberger
Department of Surgery,
Division of Surgical Oncology and Thoracic Surgery,
Faculty of Clinical Medicine Mannheim,
University of Heidelberg,
Heidelberg, Germany

References

©2006 American Association for Cancer Research.
doi:10.1158/1078-0432.CCR-06-1749
Polyclonal Resistance in Gastrointestinal Stromal Tumor Treated with Sequential Kinase Inhibitors

Eva Wardelmann, Katharina Biermann, Sabine Merkelbach-Bruse, et al.


Updated version  Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/12/20/6206

Cited articles  This article cites 3 articles, 2 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/12/20/6206.full.html#ref-list-1

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, contact the AACR Publications Department at permissions@aacr.org.