Polyclonal Resistance in Gastrointestinal Stromal Tumor Treated with Sequential Kinase Inhibitors

To the Editor: We read with interest the article by Wardelmann et al. (1) describing the evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors (GIST) associated with resistance to treatment with imatinib mesylate. We have witnessed a similar emergence of multiple secondary KIT mutations conferring “polyclonal resistance” in a patient with GIST treated with imatinib and subsequently with the newer multi-targeted kinase inhibitor sunitinib malate (Pfizer, La Jolla, CA), which inhibits VEGFR1, VEGFR2, VEGFR3, PDGFRα, and PDGFRβ in addition to KIT.

A 51-year-old female with a duodenal GIST metastatic to the liver was treated with 400 mg of imatinib orally once daily. After a partial response lasting 14 months, she developed progressive disease while continuing imatinib and underwent debulking surgery. She was then enrolled on a trial evaluating sunitinib in imatinib-resistant GISTs. Follow-up with serial computed tomography measured five intra-abdominal tumors that were all defined as measurable index lesions using conventional methodology (Response Evaluation Criteria in Solid Tumors). There was a transient period of disease stability, which lasted 2 months, before progression of the largest index lesion sampled at autopsy (Fig. 1).

All samples revealed a primary exon 11 mutation (del569_574). Analysis of the debulked imatinib-refractory tumor before sunitinib exposure identified an additional exon 17 point mutation (D816H). This D816H mutation was identified in one of the eight samples tested from autopsy material. Five autopsy samples had an additional exon 13 point mutation (V654A), which was not demonstrable in either sample taken before sunitinib treatment. The six autopsy samples that revealed secondary KIT mutations were all taken from different areas within the three largest index lesions, all of which had progressed on sunitinib. Samples from the two smallest index lesions showed only the primary exon 11 mutation. Although all samples exhibited the fundamental exon 11 mutation, no sample showed secondary mutations in both D816H and V654A, indicating that these resistant lesions arose in different subclones of the original tumor.

The most common cause of imatinib resistance in GIST is the acquisition of secondary KIT mutations involving kinase domain I or II (exon 13, 14, or 17; refs. 1–3). This case shows with radiological, autopsy, and molecular correlation the emergence of multiple progressive GIST tumor clones from within a background of controlled disease, caused by the acquisition of secondary KIT kinase domain mutations. Such “polyclonal resistance” to imatinib has been previously described by Shah et al. in patients with chronic myeloid leukemia (4). In our case, sunitinib therapy initiated after the onset of imatinib resistance produced only limited benefit. The transient clinical response to sunitinib and the relative infrequency of the secondary D816H mutation within autopsy samples suggests that the D816H mutation may retain some sensitivity to inhibition by sunitinib, but the emergence of the sunitinib-resistant V654A mutation was associated with further disease progression and ultimately death.

The complexity of KIT mutational profiles in imatinib-resistant GIST makes it unlikely any single next-generation kinase inhibitor will effectively inhibit all mutant clones. However, the limited number of different mutations that are associated with imatinib resistance suggests that the use of multiple conformationally distinct kinase inhibitors will likely be better than any single agent. Using monotherapy, a single genetic event conferring resistance on an individual tumor cell can lead to clinical progression and indeed can be looked on as an inevitable consequence of a selection process under pressure of individual drugs, similar to the rationale for combination antibacterial or antiretroviral therapies. A better outcome will likely be achieved using combinations of targeted agents initially, in a manner analogous to that employed in treating HIV infection, to prevent rather than wait for treatment following the development of drug resistance (5, 6).

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Fig. 1. Schematic diagram representing five intra-abdominal GIST index lesions and their KIT mutational profiles in a patient who was treated with imatinib and subsequently sunitinib, was followed up with serial computed tomography while on sunitinib, and who underwent autopsy examination. Lesion A, top right quadrant; lesion B, bottom right quadrant; lesion C, central pelvis; lesion D, within residual liver tissue (previous partial hepatectomy); lesion E, left anterior abdominal wall. Only the three largest lesions (A–C) increased in size on sunitinib. A primary KIT exon 11 del569_574 mutation was identified in all samples tested, and one of two secondary KIT kinase domain mutations (V654A or D816H) was identified in samples from three progressive tumors (A–C). Two samples tested from lesion B showed different mutational profiles. The two smallest index lesions (D and E) harbored no secondary KIT mutations and were nonprogressive on imaging.

References


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