Gastrointestinal stromal tumor (GIST) represents one of the most prevalent sarcoma subtypes and is the most common mesenchymal neoplasm of the gastrointestinal tract. Most GISTs harbor activating oncogenic "driver" mutations in the receptor tyrosine kinase (RTK) KIT, or, less frequently, platelet-derived growth factor receptor alpha (PDGFRA). Among GISTs with wild-type KIT and PDGFRA, the majority possess loss-of-function defects in the mitochondrial succinate dehydrogenase (SDH) complex, a component of the Krebs cycle. Imatinib mesylate inhibits KIT and PDGFRA kinase activity and represents the first-line drug for the treatment of unresectable and advanced GISTs, achieving a partial response or stable disease in about 80% of patients with metastatic disease (1). KIT mutation status has a significant impact on treatment response, with GIST now a leading paradigm for genotype-driven targeted therapy. Patients with GIST containing a KIT exon 11 mutation have a partial response rate of 84% compared with 0% among patients without a KIT or PDGFRA mutation (2). Despite a high initial overall disease control rate, within 2 to 3 years of treatment the majority of patients develop imatinib resistance (3), which almost never occur in untreated GISTs. Notably, the primary and secondary mutations were always located on the same allele. Consistent with a secondary clonal evolution, the primary mutation was detectable in all metastases from an individual patient.

The mechanisms of imatinib resistance in GIST are complex and heterogeneous and based on the primary genotype and duration of clinical response to the drug. About 15% to 20% of patients exhibit primary or early resistance to imatinib (continuous growth or growth within 6 months of therapy), including those with BRAF, RAS, or NFI mutations or SDHB deficiency. Our study showed that secondary KIT mutations are rare in primary and early resistance, but are found in 50% to 67% of patients with secondary (i.e., acquired) resistance (3, 4). Most second-site KIT mutations are identified in GISTs with a mutant KIT exon 11 genotype, and these patients generally experience prolonged clinical responses. Thus, secondary mutations are found in 73% to 86% of imatinib-resistant patients harboring KIT exon 11 primary mutations, compared with only 19% to 33% of patients with KIT exon 9 mutations (3, 5, 6). Our study highlighted that the pattern of second-site mutations in the setting of acquired imatinib resistance was exclusively substitutions, distributed between the first and the second KIT kinase domains, which almost never occur in untreated GISTs. Notably, the primary and secondary mutations were always located on the same allele. Consistent with a secondary clonal evolution, the primary mutation was detectable in all metastases from an individual patient.

Two possible mechanisms have been proposed to explain how acquired resistance to imatinib therapy may develop. First, second-site mutations may specifically interfere with imatinib binding without affecting the overall KIT kinase conformation, as happens with the T670I gatekeeper mutation (exon 14) that disrupts an important H-bond to imatinib. The other explanation is that activation loop mutations (exon 17) specifically stabilize the active conformation of the KIT kinase and prevent imatinib binding, which occurs only in the inactive conformation.

Regardless of the primary genotype or whether resistance is primary or secondary, most resistant tumors remain addicted to the initial driver oncogene and show reactivation of KIT phosphorylation. The fact that resistance occurs at the level of KIT and not by additional mutations in downstream components or other signaling pathways is the most stunning illustration of the specificity of oncogene addiction and underscores the unique role of KIT as a therapeutic target in these tumors. In addition, our study ruled out the possibility of KIT gene amplification as a common mechanism of oncogene reactivation in imatinib-resistant GIST with or without second-site mutations. We also found that KIT activation, as measured by phosphorylation, was heterogeneous and did not correlate with histologic or clinical response to
imatinib; surprisingly, most nonresistant GISTs showed reactivation or persistent activation of KIT protein by Western blotting. KIT activation was also variable in the subset of patients with second-site mutations, with uneven phospho-KIT expression among patients with similar primary and secondary genotypes or within different nodules of individual patients, regardless of the type of second-site mutation. Additional complexity for targeting imatinib-resistant GIST results from the intratumor and intertumor heterogeneity of secondary KIT mutations. Long-term imatinib therapy can lead to polyclonal acquired resistance, whereby different tumor nodules acquire different secondary mutations and progress independently (7). This genetic complexity of acquired resistance supports an argument against second-site mutations and progress independently (7). This genetic complexity of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit of acquired resistance supports an argument against second-line tyrosine kinase inhibitor monotherapy providing durable benefit.


CCR 20th Anniversary Commentary: A Genetic Mechanism of Imatinib Resistance in Gastrointestinal Stromal Tumor—Where Are We a Decade Later?

Cristina R. Antonescu and Ronald P. DeMatteo


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