Cell Line Models Identify Different Sensitivity of Mutant Forms of c-KIT to Kinase Inhibitory Drugs and Predict the Response of Patients to Therapy

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Activating mutations in the receptor tyrosine kinase, c-KIT, were first described by Furitsu and colleagues (1) in a variant of the human mast cell line, HMC1. Two missense mutations resulting in single amino acid changes were observed: one in exon 11 leading to a V560G substitution in the intracellular juxtamembrane region, and the other in exon 17 causing a D816V substitution in the activation loop of the kinase domain. These substitutions individually caused constitutive kinase activation. Subsequently, various activating mutations have been reported in several human cancers arising in cell types that normally express c-KIT, notably gastrointestinal stromal tumors (GIST), systemic mastocytosis, testicular seminomas, core binding factor acute myeloid leukemia, and a subset of melanomas (reviewed in refs. 2 and 3). Different types of mutations are associated with different cancers. For example, at presentation GISTs most commonly have various mutations in exon 11 of KIT, with a lower frequency in exon 9, and rarely exon 17. In contrast, in systemic mastocytosis, mutations encoding substitutions at residue 816 in exon 17 (usually D816V) occur in most or all cases. The development of relatively specific tyrosine kinase inhibitors such as imatinib with activity on wild-type c-KIT raised the possibility of their use to treat tyrosine kinase inhibitors such as imatinib with activity on most or all cases. The development of relatively specific mutations or wild-type KIT mutations profoundly affect sensitivity to imatinib. Using factor-dependent murine early myeloid cells (FDC-P1) transduced to express wild-type, V560G or D816V mutant human KIT, we showed that the V560G substitution confers almost 10-fold enhanced sensitivity to imatinib, whereas the D816V substitution resulted in almost complete resistance. At the same time, another group also showed resistance to imatinib of D816V mutant KIT (4). These results can be explained by analysis of the structure of the KIT intracellular domains. Our molecular modeling analysis (5) showed that the D816V substitution strongly favors the activated conformation of the kinase domain to which imatinib cannot bind. A crystallographic study of KIT in an inactive conformation showed that the negative regulatory juxtamembrane region encoded by exon 11 partially blocks access of imatinib to its binding site (6); hence, activating mutations in that region enhance the affinity for the drug.

These observations in the FDC-P1 cell line model proved to be predictive of responses to imatinib therapy in patients. In GIST, patients with exon 11 mutations in KIT responded better to a standard therapeutic dose of imatinib than did patients with exon 9 (extracellular) mutations or wild-type KIT (7), whereas an increase in the drug dose improved responses in those with exon 9 mutations (8). As predicted, mastocytosis patients with D816V mutant KIT fail to respond to imatinib therapy (9). More recently we have extended our studies to examine secondary KIT mutations that arise in acquired resistance to imatinib and to evaluate alternate kinase inhibitors for activity against different mutant forms of KIT (10). Overall, the original study led to appreciation of the importance of specific mutation analysis in individual patients being considered for imatinib treatment and provided a model system for preclinical evaluation of newer KIT inhibitors.

Disclosure of Potential Conflicts of Interest

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