KIT, PDGFRA, and BRAF Mutational Spectrum Impacts on the Natural History of Imatinib-naive Localized GIST: A Population-based Study

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The mutation status of *KIT* or *PDGFRA* notoriously affects the response of advanced gastrointestinal stromal tumors (GISTs) to tyrosine kinase inhibitors. Conversely, it is currently still unclear whether mutation status impinges on the prognosis of localized, untreated GISTs. Hence, at present, this variable is not included in decision making for adjuvant therapy.
AIMS

• a well-characterized preimatinib population-based series of localized, surgically resected primary GISTs was investigated to shed light on the clinical impact of mutation status on the natural history of GIST.
• A series of 451 primary localized GISTs were analyzed for *KIT*, *PDGFRA*, and *BRAF* mutations. Univariable and multivariable analyses and a backward selection procedure were used to assess the impact of mutation status on overall survival and to identify prognostically homogenous groups.

• The authors have previously proposed a nomogram to predict overall survival (OS) on the basis of patients’ age, tumor location, size, and mitotic index. In their series, OS represented a valid surrogate of disease-specific survival in the below-65 age stratum (Rossi S. et al., Am J Surg Pathol, 2011;35:1646-1656). Thus, the OS of the 5 major genotypes (*KIT* vs. *PDGFRA* vs. *BRAF* vs. triple-negative/SDH-positive, and triple-negative/SDH-negative) were compared. As there was no significant difference in the OS of triple-negative/SDHB-proficient and triple-negative/SDHB-deficient cases in our series (P=0.56), these cases were taken as a whole (triple-negative tumors) in subsequent analyses.
RESULTS

• Significant heterogeneity (P<0.001) was observed at univariable Kaplan-Meier analysis: KIT-mutated patients displayed a lower OS than did PDGFRA-mutated and triple-negative patients, who showed comparable rates.

• Specifically, 120-month OS (95% confidence interval [CI]) was: 100% for BRAF, 67.5% (58.1%-78.3%) for PDGFRA, 62.5% (50.5%-77.5%) for triple-negative, and 46.3% (40.6%-52.9%) for KIT. Among the KIT-mutated cases, KIT W557_K558del displayed a trend toward worse survival.
RESULTS

The inclusion of mutation data in a multivariable Cox model, together with conventional clinicopathologic variables (size, mitotic index, site), led to the identification of mutation patterns with similar OS through a backward selection procedure.

This approach enabled to distinguish 3 molecular prognostic: group I, the group with the best outcome, included a limited number of patients carrying either PDGFRA exon 12, BRAF, or KIT exon 13 mutations; group II, with an intermediate prognosis, included triple-negative GISTs, KIT exon 17, PDGFRA exon 14-mutated cases, and PDGFRA D842V cases (group II vs. group I: hazard ratio=3.06; 95% CI: 1.09-8.58); the worst outcome was observed in group III, comprising the canonical KIT mutations (exons 9 and 11) and PDGFRA exon 18 mutations other than D842V, hereafter named exon 18-non842 (group III vs. group I: hazard ratio=4.52; 95% CI: 1.65-12.37) (Fig. 1A).
• The mutation status was an independent significant prognostic factor (P=0.001), and its inclusion resulted in a slight improvement in the discriminative ability of the model previously proposed by the authors (Rossi S. et al., Am J Surg Pathol, 2011;35:1646-1656).
RESULTS

Notably, ex-post analysis of the investigated tumor series highlighted the potential prognostic ability of the molecular signature to further stratify patients within the low-moderate or high categories according to AFIP/Miettinen criteria (Miettinen M, Lasota J, Semin Diagn Pathol 2006;23:70-83):

• FIGURE 1B and C. Patient stratification according to the molecular signature. B, OS according to the proposed molecular prognostic groups in the set of patients classified as low-moderate risk on the basis of the AFIP/Miettinen criteria. C, OS according to the proposed molecular prognostic groups in the set of patients classified as high risk on the basis of the AFIP/Miettinen criteria.
• The correlations between clinical course and mutation status were further confirmed within anatomic GIST subgroups. OS in *KIT* exon 9 and *KIT* exon 11-mutated GISTs was similar, even among small intestinal GISTs (P=0.742; Fig. 2A). This is in contrast with the alleged unfavorable effect exerted by exon 9 mutations.
RESULTS

• The molecular categorization was integrated into a nomogram developed from the multivariable Cox model through a backward selection procedure. In this nomogram, the mitotic index appeared to make the greatest contribution to survival prediction, followed by molecular risk group, tumor size, and tumor site. Of course, these inferences are preliminary and need to be validated in an independent tumor series of primary imatinib-naive GISTs to draw definitive conclusions.
CONCLUSIONS

• Overall, the results highlight the prognostic impact of mutation status on the natural course of GIST and confirm that triple-negative and most PDGFRA-mutated GISTs are relatively indolent tumors. Conversely, in contrast to common belief, both KIT exon 9 and KIT exon 11 mutations, as well as PDGFRA exon 18-non842 mutations, appear as unfavorable prognostic factors.
TAKE HOME MESSAGES

• The molecular prognostic stratification may complement the portfolio of clinicopathologic information and support the clinician in decision making for adjuvant therapy. This may be particularly important for the gray area of GIST classified as intermediate risk according to conventional clinicopathologic parameters.