Characterization of KRAS Mutation Variants and Prevalence of KRAS-G12C in Gastrointestinal Malignancies

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BACKGROUND

The KRAS G12C inhibitor sotorasib has shown promising anticancer activity in patients with advanced solid tumors harboring the KRAS G12C mutation, holding the potential for transforming clinical management of KRAS mutated solid tumors. The distribution of KRAS variants, including G12C in gastrointestinal (GI) cancers, has not been well described. Herein, we characterized the prevalence of the different KRAS variants, including G12C, its associated genomic alterations, and the relationship between G12C and immunotherapy (IO) biomarkers in GI cancers.

METHODS

A retrospective review of 17,009 patients with GI cancers that underwent Tempus xT or xF next-generation sequencing was performed. Logistic regression was used to analyze the association between cancer subtypes and KRAS variants, the association between KRAS variants and IO-biomarkers, and co-mutations between G12C and other oncogenes. False discovery rate-adjusted P-value (FDR P) was used for multiple testing. FDR P <0.05 was the cutoff for statistical significance.

RESULTS

In total, 7559 (44.4%) GI tumors harbored *KRAS* mutations, of which 325 were G12C. The most frequent *KRAS* variants observed in *KRAS*-mutated GI tumors were G12D (35.4%), G12V (23.5%), G12R (8.7%), G13D (8.0%), Q61H (4.6%), and G12C (4.3%). However, the distribution of *KRAS* variants significantly varied by cancer-type (FDR-P<0.001). In *KRAS* mutated pancreatic cancers (n=3,693), the most common variants were G12D (41.8%), G12V (31.6%), G12R (16.1%), Q61H (4.7%), and G12C (1.8%); in *KRAS* mutated colorectal cancers (CRC, n =2,971) the most frequent variants were G12D (29.9%), G12V (20.0%), G13D (15.8%), G12C (7.0%), G12A (4.9%), and Q61H (4.2%); and in *KRAS* mutated appendiceal cancers (n=136), the most prevalent variants were G12D (50.7%), G12V (25.7%), G12C (7.4%), G13D (7.4%), G12S (2.9%), and Q61H (2.2%).

In all GI cancers, G12C were most frequently observed in patients with appendiceal (11/279, 3.9%), colorectal (208/6586, 3.2%), small bowel (9/630, 1.4%), pancreatic (66/5029, 1.3%) and biliary (18/1481, 1.2%) cancers. There was no significant difference in the prevalence of G12C between colon (3.2%), rectal (3.1%), and rectosigmoid (3.5%) tumors (p=0.95).

G12C was infrequently observed in gastric cancers (9/1401, 0.6%), esophageal adenocarcinomas (3/686, 0.004%) and hepatocellular carcinoma (1/467, 0.2%). Furthermore, no G12C mutations were observed in squamous cell carcinomas (SCC) of the esophagus (0/205, 0%) and anal canal (0/195, 0%).

Significant differences in co-occurring genomic mutations with G12C compared to non-G12C in all GI cancers were observed in the following genes: *APC* (67.1% vs 39.6%); *CDKN2A* (9.2% vs 26.6%); *CTNNB1* (8.6% vs. 4.0%); *KEAP1* (4.0% vs 1.2%); and *KMT2D* (8.0% vs. 3.8%); FDR-P<0.05, respectively. However, in CRC, there were no significant differences in co-occurring mutations between G12C and non-G12C tumors. GI cancers harboring G12C were less likely to be associated with MSI-high status than non-G12C (OR, 0.63 [0.23-1.72]) and *KRAS*-wild-type (OR, 0.32 [0.12-0.87]) tumors (FDR-P <0.0001).

CONCLUSIONS

Our data suggest that G12D and G12V are the most common KRAS variants across GI malignancies; however, the distribution of KRAS variants significantly differed by cancer-type. G12C was most frequently observed in patients with appendiceal, colorectal, small bowel, biliary, and pancreatic cancers. G12C was not detected in SCC of the esophagus or anal canal.

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