SO-13 KRAS-G12C mutations in a Nordic cohort of 1441 metastatic colorectal cancer patients

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Background: KRAS is mutated (mt) in nearly half of metastatic colorectal cancers (mCRC) and is a predictive marker for no benefit of anti-EGFR therapy. The KRAS-G12C mutation has a cysteine residue for which specific drugs have been developed. Current data on this specific mutation is limited and conflicting (Schirripa et al, Clin Colorectal Cancer 2020, Wong et al, Proc ASCO 2020).

Methods: Patients from the prospective real-life Finnish RAXO study, its population-based data collection substudy and the population-based Scandinavian SP/PRCRC cohorts were combined. Patients with incomplete RAS & BRAF testing were excluded. Demographics, treatments, and outcomes were compared with logistic and Cox regression models.

Results: The KRAS-G12C mutation frequency was 4%, 4%, and 2% in all tested patients in the above-mentioned cohorts, and 7%, 8% and 4% of all KRASmt patients in the cohorts, respectively. No differences according to age, sex, performance status, synchronous/metachronous presentation, number of metastatic sites, blood counts, alkaline phosphatase, or CEA between KRAS-G12C (n=91) and other KRASmt (n=658) patients were observed. For G12C vs. other KRASmt, primary tumour site was right colon in 29% vs. 34%, left colon in 37% vs. 33%, and rectal in 34% vs. 33%. Liver metastases were present in 65% vs. 71%, lung in 40% vs. 34%, peritoneal in 14% vs. 18%, and distant lymph node in 26% vs. 22% of G12C compared with other KRASmt. Systemic therapy was given to 90% vs. 86% of G12C vs. other KRASmt cases, with no differences for number of lines of therapy, drug exposures, responses, and median overall survival (mOS). Metastasectomy and/or local ablations were performed in 38% vs. 28% for G12C vs. other KRASmt cases, and best supportive care in 9% vs. 13%, affecting mOS non-significantly (31.5 vs. 22.8 months; HR 0.83; CI95% 0.64-1.08), but not mOS within each separate treatment group (metastasectomy, systemic therapy and best supportive care alone). Differences to RAS & BRAF wildtype tumours (n=456) showed the same associations for G12C as for other KRAS or NRAS (n=54) mutations. BRAFmt cases had poorer survival.

Conclusions: In this real-life/population-based cohort, there were no significant differences in patient characteristics, treatments provided, and outcomes between the 91 KRAS-G12Cmt cases compared to those with other KRAS or NRAS mutations. This contrasts to the results of previous studies claiming differences in several aspects, however, not consistently. To show differences between rare tumour properties, large and non-selected patient series are required. When specific drugs are developed, as for this mutation, differences in outcome will hopefully emerge.

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