Left-side and right-side colon cancers

MOLECULAR VARIANCE

Elena Tsvetkova, MD, FRCPC, Medical Oncologist, Juravinski Cancer Centre, Hamilton

TRIAL SUMMARY: Differentiating left-sided cancers

Marshall J, Lenz HJ, Xiu J, et al. Molecular variances between rectal and left-sided colon cancers. *J Clin Oncol* 35, 2017 (suppl 4S; abstract 522).

Recent analysis of the CALGB 80405 study showed that left-sided colon tumours (LT) respond differently to biologics compared with right-sided tumours, likely due to molecular differences. This study explores molecular variations between LT and rectal tumours seen in the tissue samples collected in CALGB 80405. A total of 1,457 left-sided primary tumours were profiled using immunohistochemistry, microsatellite instability by polymerase chain reaction (PCR), in situ hybridization techniques, and next-generation sequencing, including tumours with origins clearly defined as splenic flexure to descending colon (SFT), tumours of the sigmoid colon (SgT), and tumours of the rectum (RT). Tumour mutational load (TML) was calculated using only somatic non-synonymous missense mutations. Chi-square tests were used for comparative analyses.

Results: In total, 1,457 primary tumours (SFT 125; SgT 460, and RT 872) were examined. When compared with SFT, RT had a higher frequency of TP53 and APC mutations; a lower frequency of PIK3CA, BRAF, GNAS, HNF1A, and CTNNB1 mutations, and a higher expression of TOPO1, ERCC1, and MGMT mutations. When compared with SgT, RT had higher expression of TLE3, TOPO1, TUBB3, and MGMT.

There were no differences between SFT, SgT, and RT in the frequency of PD-L1 expression on tumour cells, PD-1 expression on tumour-infiltrating lymphocytes, or HER2 expression and amplification.

Microsatellite instability was seen in 7% of SFT, 4% of SgT, and 0.7% of RT (total LT vs RT, p=0.01). The percentage of tumours carrying 17 or more mutations per megabase, defined as the tumour mutation load (TML), was higher among descending colon tumours (9%) as compared with sigmoid (1.6%) and rectal (4%) tumours. In all 3 cohorts, a TML >17 mutations per megabase was highly concordant with microsatellite instability. There was a correlation between PD-1 and TML in RT (p = 0.04) but not in SFT or SgT. There were no correlations between PD-L1 and TML.

Tumours arising in the rectum may carry genetic alterations that are distinct from left-sided colon tumours and appear along a continuum of molecular alterations. A better understanding of disease biology may help to identify therapeutic targets and advance precision medicine.

IN BRIEF

Already known
- Left-sided colon tumours appear to respond differently to biologics compared with right-sided tumours.

What this study showed
- Tumours arising in the rectum may carry genetic alterations that are distinct from left sided colon tumours and appear along a continuum of molecular alterations.

Next steps
- Pursue understanding of these differences to identify precision therapeutic targets.

COMMENTARY: The incidence, molecular pathway, pathogenesis and outcome of colorectal cancers (CRC) differ according to the tumour location: right-sided or left-sided.[4] Treatment approaches for colon and rectal cancer also are different. However, there is little information available on dissimilarities in the biology of left-sided colon and left-sided rectal cancers. This study investigated molecular variances of left-sided colon and rectal cancers that may potentially influence treatment decisions and disease prognosis.

Patients with rectal cancer constituted more than half of the study population, which may not reflect the relative prevalence of this group in real-world colorectal cancer cohorts. Microsatellite instability was reported in 7% of SFT, 4% of SgT, and 0.7% of RT. This observation supports findings that microsatellite instability rates decrease with tumour left-sidedness.[5] Distal colon cancer is usually associated with specific chromosomal instability. Multiple mutations were identified, such as PIK3CA, BRAF, GNAS, HNF1A, CTNNB1, TOPO1, ERCC1, MGMT, etc. The role of some of these mutations in cancer development and metastatic process, as well as their prognostic importance, has been identified; the function of other mutations still requires clarification. Tumour mutational load of more than 17 mutations per megabase was highly concordant with microsatellite instability. Interestingly, a correlation between PD-1 and TML was observed in rectal cancer but not in sigmoid or left colon cancers. This study contributes to the current precision medicine approach in oncology.