Concordance Analysis Between Microsatellite Instability Status and Tumor Mutational Burden in Colorectal Cancer Patients: A Nested Case-Control Study.

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BACKGROUND

Mismatch repair (MMR) deficiency and microsatellite instability (MSI) are approved predictive biomarkers of PD1/PD-L1 therapy in colorectal cancer (CRC) patients. Tumor Mutational Burden (TMB) quantifies the number of somatic mutations in tumoral DNA and is reported as number of mutations per DNA Megabase (mut/Mb). TMB is being investigated as a novel predictive biomarker for immune checkpoint inhibitors. In this study we explore the feasibility and potential utility of calculating TMB with a next-generation sequencing (NGS) based panel and its correlation with MMR and MSI.

DESIGN

We designed a nested case-control study in our cohort of 442 CRC patients with complete morpho-molecular characterization from 2009 till July 2019. All patients had previous MSI assessment with a 5 microsatellites panel kit (MSI Analysis System, Promega) and immunohistochemical analysis of MMR proteins (MLH1, MSH2, MSH6 and PMS2) (Figure 1). Cases were defined as CRC patients with high-MSI. Controls (MSS, 1:1) were selected among CRC patients without high-MSI. Genomic DNA was extracted from paired FFPE normal and malignant tissue sections (RecoverAll Kit for FFPE, ThermoFisher). TMB was assessed with a targeted NGS assay detecting somatic mutations and Indels from 409 genes, spanning 1.7 Mb of genomic space (Oncomine TMB. ThermoFisher). High-TMB was defined as ≥ 10 mut/Mb. Analysis was performed using SSPS v20.

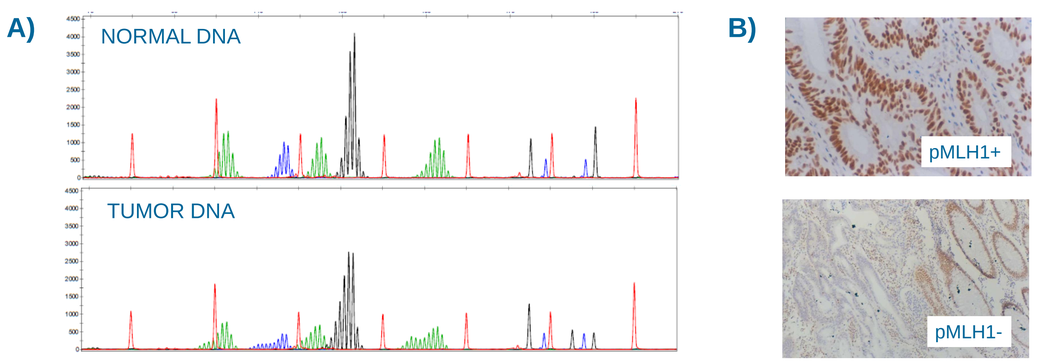

Figure 1. A) MSI assesment. **B)** MLH1 immunohistochemical analysis.

RESULTS

The 9.7% of CRC patients from the total series showed high-MSI. The concordance rate between MSI status and MMR IHC was 100% and 87.5% in MSS and high-MSI patients, respectively. Sixty CRC patients were included: 30 high-MSI and 30 MSS without differences regarding age or gender (68% females, median age 68 years). The concordance rate between MSI status and MMR expression was 97.7%. All but one TMB studies were informative. Median TMB was higher in the high-MSI group compared to the MSS group [28.1 (15.2-50.2) vs 5.3 (1.7-18.5) Mut/Mb respectively, p=0.000]. A TMB threshold ≥ 10 mut/Mb was associated with a high-MSI status in 98.3%. One (3.4%) MSS tumor with no MMR deficiency showed an unexpected high-TMB (18.48mut/Mb) (Figure 2).

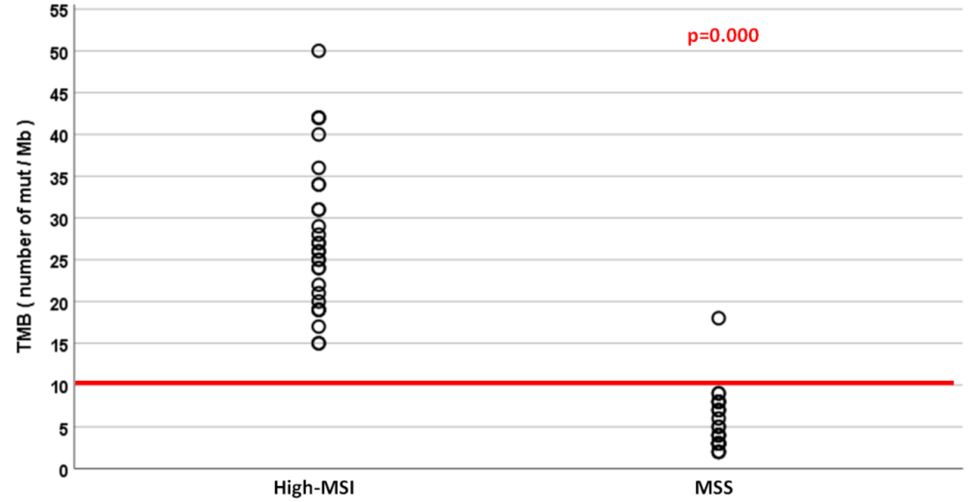

Figure 2. TMB (Number of mutations/Mb) according to MSI status in the CRC series.

CONCLUSIONS

- **The concordance rate between MSI status and TMB in CRC is excellent.**
- **A TMB threshold ≥ 10mut/Mb accurately identifies CRC patients with high-MSI.**
- **TMB is able to identify a small proportion of MSS patients suitable to respond to immunotherapy not previously detected by MSI or MMR studies.**

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