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HGG-23. DECIPHERING THE RELATIONSHIP OF MICROSATellite-INSTABILITY AND MUTATIONAL BURDEN IN HIGH-GRADE GLIOMA PATIENTS WITH CONSTITUTIONALLY IMPAIRED DNA DAMAGE RESPONSE
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Multiple large-scale genomic studies across pediatric tumors have reported an overall frequency of ~6-10% of patients with constitutional pathogenic variants, but associations of cancer predisposition with distinct tumor types vary between zero and 100%. We analyzed sequencing and DNA methylation data from 363 patients to explore the landscape of
cancer predisposition in pediatric high-grade gliomas (pedHGG). Almost all pedHGG with constitutional alterations resulting in DNA mismatch repair deficiency (MMRD) were classified to IDH-mutant or pedRTK1a DNA methylation classes. Conversely, 70% of pedRTK1a and nearly 60% of IDH-mutant pedHGG (<18 years) arose in patients with either Lynch or cMMRD syndromes. Biallelic MMR inactivation (cMMRD) was found almost exclusively to affect the exchangeable part of the mismatch repair machinery complex (MSH6/PMS2; 75%), while heterozygous loss affected non-exchangeable core members MLH1 or MSH2 (93%). IDH-mutant MMRD tumors showed substantially lower overall tumor mutational burden (TMB < 40), less microsatellite instability, and frequent MSH6 mutation (60%), while pedRTK1a-MMRD tumors often harbored additional alterations in POLE, leading to an ultra-mutator phenotype (TMB < 100), had higher microsatellite instability burden, and more often linked to PMS2 or MSH2 loss. Both IDH-mutant- and pedRTK1-MMRD tumors were associated with poor outcome, with MMRD-associated IDH-mutant pedHGG resulting in significantly shorter survival compared with sporadic IDH-mutant tumors (p=0.0015). We observed a nonlinear correlation between increasing numbers of point mutations, InDels and microsatellite instability. Exemplary, patients with pathogenic constitutional variants in MSH6 showed a significantly lower number of InDels compared with overall TMB, which might be due to repair ability of the replacement protein MSH3. As newer studies point towards an important role of InDels in antigen presentation and therefore as a potential biomarker for immune checkpoint inhibition, further exploration of these detailed molecular associations in conjunction with clinical outcome and response data is warranted.