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IMMUNOTHERAPY

Exploiting mismatch repair in GBM

Recurrent glioblastoma multiforme (GBM) is a deadly cancer, with most patients surviving less than 6 months. In childhood malignancies, germline biallelic mismatch repair deficiency (bMMRD) is a syndrome often characterized by a high mutational burden. This fact prompted the international bMMRD consortium to study the molecular events underlying bMMRD cancers, in order to establish a surveillance protocol to improve patient survival. The researchers showed that bMMRD GBM had significantly higher mutational loads and more neoantigens than sporadic adult and childhood gliomas. In fact, Uri Tabori and his team "uncovered that bMMRD cancers have the highest mutational load of all human cancers". As immune-checkpoint inhibitors are efficacious for tumours with a high mutational load, this finding provided the impetus to test the anti-PD-1 nivolumab in children harbouring hypermutant recurrent GBM.

Two siblings with bMMRD and recurrent GBM were treated with nivolumab. Both patients initially experienced seizures following treatment, but with a short course of steroids, this resolved, and follow-up data accrued over several months showed sustained tumour shrinkage and complete disappearance of imaging abnormalities, resulting in both children resuming normal daily activities. Multiple foci disappeared with nivolumab, which illustrates that the immune response is not constrained by the blood–brain barrier. This study is the first report of durable responses of recurrent GBM to immune-checkpoint inhibition, showing that a targeted treatment approach based on genetic predisposition can improve survival. Tabori highlights the importance of "sequencing tumours before embarking on a blinded therapeutic approach".

As the therapeutic significance of bMMRD in several common adult cancers (leukaemia, gastrointestinal or genitourinary cancers) is currently unclear, this study highlights the utility of germline predisposition in guiding immunotherapy to transform treatment in patients with other cancers. Tabori emphasizes the broader implications of this research: "similar data could expand our understanding of the replication repair machinery to find the Achilles' heel of hypermutant cancers, and to help prevent tumours in patients with other cancer predisposition syndromes".

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ORIGINAL ARTICLE Bouffet, E. *et al.* Immune checkpoint inhibition for hypermutant glioblastoma multiforme resulting from germline biallelic mismatch repair deficiency. *J. Clin. Oncol.* http:dx.doi.org/10.1200/JCO.2016.66.6552 (2016)