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Temozolomide Induced Hypermutation in Pancreatic Neuroendocrine Tumors: A Case Series

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BACKGROUND

Based on the current data, well-differentiated NETs generally do not respond to immune checkpoint inhibitors (ICIs). However, ongoing research is exploring strategies to transform these immunologically "cold" tumors into "hot" tumors (i.e. NETs). Temozolomide (TMZ) is an alkylating agent that induces DNA methylation at the O6 position of guanine, leading to mismatched base pairing, DNA replication errors, and cell death. Prolonged exposure to TMZ can cause defects in DNA polymerase and mismatch repair (MMR) genes, resulting in a hypermutated phenotype, characterized by a high tumor mutational burden (TMB-H). This phenomenon is well-documented in gliomas, where TMZ-induced hypermutation arises from acquired MMR defects during treatment. Although rare, similar hypermutations have been observed in NETs following TMZ treatment, raising the question of whether these patients might respond to ICI therapy. In this study, we present a series of NETs that developed an ultra-hypermutated phenotype after TMZ exposure.

METHODS

We conducted a retrospective chart review across all three Mayo Clinic sites, focusing on patients with advanced well-differentiated NETs treated with CAPTEM who were found to be TMB-H and/or microsatellite instability-high (MSI-H) through standard molecular testing. Clinical characteristics and outcomes were extracted from electronic medical records.

RESULTS

Seven patients were identified with ultra-hypermutated TMB (>100 mut/Mb) following TMZ exposure. The median age at diagnosis was 57 years (range 44-63), with the majority being males (n=5). All patients had metastatic pancreatic NETs (G2, n=4; G3, n=3). CAPTEM was administered either as first (n=3) or second-line (n=4) therapy. The median number of CAPTEM cycles was 12 (range 5-15), with a median cumulative dose of TMZ of 2250 mg/m2. Next-generation sequencing (NGS) was performed post-progression on CAPTEM using either tissue-based assays (n=6) or blood samples (n=2).
The median TMB in this cohort was 189 mut/Mb (102-2134 mut/Mb). The majority of patients were microsatellite stable (MSS, n=6), with one patient being MSI-H. Six patients initiated immunotherapy: one patient remains disease-free (TMB=2134 mut/Mb, MSI-H) after 2 years on Nivolumab/Ipilimumab, one patient achieved stable disease as their best response but progressed after 6 months, and three patients experienced disease progression after 4 cycles of ICIs.

CONCLUSIONS

This case series illustrates that despite TMZ-induced hypermutation and elevated TMB, the majority of patients do not respond to ICI therapy. Further research is needed to understand the molecular changes occurring within neuroendocrine tumor cells in this context, which may help identify strategies to generate immunogenicity in these historically “cold” tumors. This research also suggests that NGS and mismatch repair testing are warranted in pancreatic NETs.

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