Temozolomide Induced Hypermutation in Pancreatic Neuroendocrine Tumors: A Case Series

Osama M. Mosalem [1], Jason S. Starr [1], Mohamad Bassam Sonbol [2], Timothy Hobday [3], Steven Alberts [3], Rachel Eiring [3], Patrick McGarrah [3], Thorvardur R. Halfdanarson [3]

[1] Division of Hematology & Oncology Mayo Clinic Florida, [2] Division of Hematology & Oncology Mayo Clinic Arizona, [3] Department of Medical Oncology Mayo Clinic Rochester

ABSTRACT

- Immune checkpoint inhibitors (ICIs) are typically ineffective against well-differentiated neuroendocrine tumors (NETs), but transforming "cold" tumors into "hot" tumors remains a promising area of research.
- Temozolomide (TMZ) induces DNA methylation, potentially leading to hypermutation and high tumor mutational burden (TMB-H). This phenomenon is well-documented in gliomas, where TMZ-induced hypermutation arises from acquired MMR defects during treatment.[1]
- Although rare, similar hypermutations have been observed in NETs following TMZ treatment, raising the question of whether these patients might respond to ICI therapy.2,3

METHODS

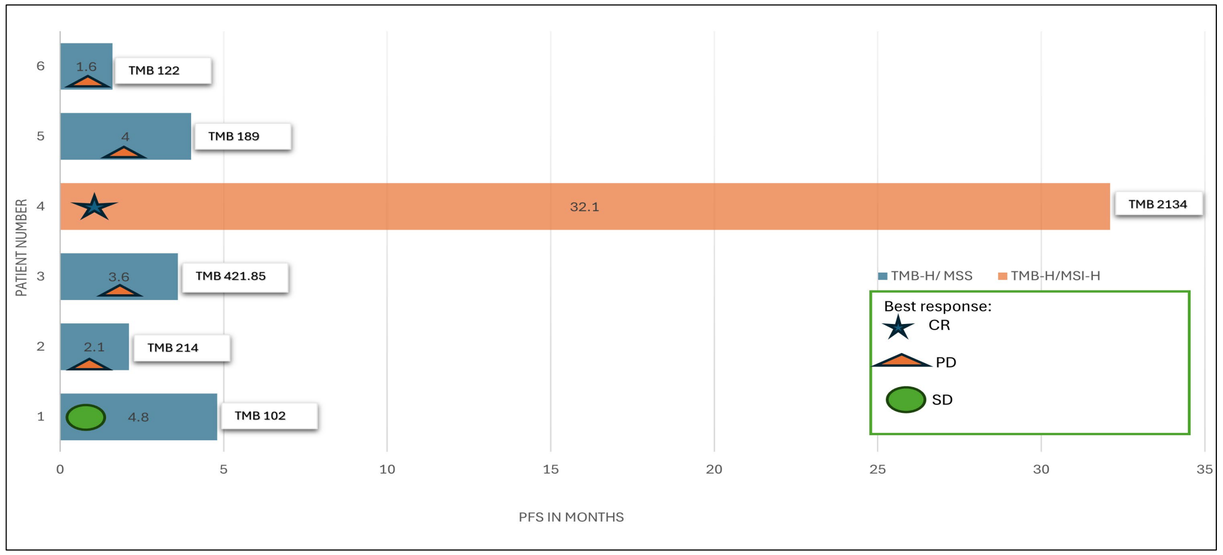
- Retrospective study across Mayo clinic.
- Included patients with advanced well-differentiated NETs treated with Capecitabine and Temozolomide (CAPTEM) who had TMB-H and/or microsatellite instability-high (MSI-H) through standard molecular testing.
- Seven patients were identified with ultra-hypermutated TMB (>100 mut/Mb) following TMZ exposure.

mosalem.osama@mayo.edu

OsamaMosalemMD

RESULTS

Out of the Six patients treated with ICIs following TMZ exposure and had an ultra-hypermutated TMB, five did not respond to ICIs (all being MSS). The only exception was a patient with MSI-H status and a TMB of 2134 mutations/Mb, who did respond to dual ICIs.



Patient (n=7)	Age at diagnosis; years	PFS on CAPTEM; months	Ki-67 at time of progression; %	TMB (mut/Mb)	MSI-Status	Immunotherapy treatment	Best Response; PFS
1	44	5.6	63	102	MSS	Pembrolizumab	SD; PFS=4.8 m
2	47	18.6	69	214	MSS	Pembrolizumab	PD; PFS=2.1 m
3	63	8	37	421.85	MSS	Nivolumab/Ipilimumab	PD; PFS= 3.6 m
4	68	21	67.2	2134	MSI-H	Pembrolizumab then Nivolumab/Ipilimumab	CR; Ongoing > 2 y
5	56	17	60	189	MSS	Atezolizumab (In combination with carboplatin/ etoposide)	PD; PFS= 4 m
6	57	17.6	60	122	MSS	Pembrolizumab	PD; PFS 1.6 m
7	63	11	83	131.6	MSS	No exposure to ICIs	-----

DISCUSSION

- In our study, identification of subsequent ultra-hypermutated TMB after TMZ exposure has led to subsequent treatment with ICIs. Despite this, Five of the Six have been already been treated with ICIs
- Despite the ultra hypermutated TMB, most patients did not respond to ICI therapy (all MSS). The only patient who responded to ICI and achieved a durable response in our cohort was MSI-H.
- Previous trials have attempted to manipulate the tumor microenvironment as an approach to overcome resistance to ICIs via the induction of hypermutation by a temozolomide priming treatment. 4,5
- In NETs, this hypothesis has been elucidated in a few case reports in the literature.

CONCLUSIONS

- This case series highlights that, even though the incidence of TMZ induced hypermutations remains unknown, most patients did not respond to ICI therapy. The only patient in our cohort who showed a response was MSI-H/dMMR and received dual ICI treatment.
- 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.
- Even though that the incidence of TMZ induced hypermutations remains unknown, clinicians should check NGS, and mismatch repair testing in pancreatic NETs especially after prior exposure to TMZ.

REFERENCES

1- Yu Y. Et al. Neuro Oncol. 2021.
2- Klempner, Et al. JCO PO. 2020.
3- Sun Et al. JCO PO. 2022.
4- Owen Et al. Clin Cancer Res 2023.
5- Morano Et al. JCO 2022.