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Loss of MGMT protein expression by immunohistochemistry is associated with response to capecitabine/temozolomide in neuroendocrine neoplasms (NENs)

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BACKGROUND

A recent prospective phase II study (ECOG-ACRIN E2211) demonstrated that O6-methylguanine-DNA methyltransferase (MGMT) deficiency was associated with a significant response to capecitabine and temozolomide (CAPTEM) in pancreatic neuroendocrine neoplasms (NENs), however, routine MGMT analysis in NENs was not recommended. Our study sought to demonstrate whether loss of MGMT protein expression is associated with improved overall survival (OS) in patients receiving CAPTEM for NENs from various tumor sites.

METHODS

Paraffin-embedded tumor samples were evaluated by immunohistochemistry (IHC) using an MGMT monoclonal antibody. Intact MGMT protein expression (i.e., IHC positivity) was defined as any staining intensity (>1+) in ≥36% of neoplastic cells, according to an internal validation study. IHC and pyrosequencing for MGMT promotor methylation was performed in an independent cohort of 58 NENs. Real-world OS was extrapolated from insurance claims data with Kaplan-Meier estimates from the date of first CAPTEM administration to the last date of contact.

RESULTS

The study cohort included 80 patients (42 men, 38 women) with a median age of 57 years [range: 19-89]). They had various NENs (33 pancreatic, 17 intestinal, 7 pulmonary, 8 other, and 15 of unknown origin) treated with CAPTEM. The median OS for the 48 patients with MGMT negative tumors was 31 months compared to 17.5 months for the 32 patients whose tumors were MGMT positive by IHC (HR: 1.75 [95% CI: 1.066-2.87], p=0.025). IHC results from the independent cohort of 58 NENs showed only 43% concordance with pyrosequencing results.

CONCLUSIONS

MGMT promotor status by IHC may be a clinically useful indicator that predicts improved OS for NENs treated with CAPTEM but does not reliably correlate with the findings of MGMT promoter methylation by pyrosequencing.

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