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Cabozantinib therapy in patients with previously treated well differentiated grade 3 neuroendocrine tumors (G3 NETs)

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BACKGROUND

G3 NETs are a recently recognized entity among well differentiated neuroendocrine tumors but little is known about the optimal therapy sequencing, especially in later lines. Small studies have suggested benefit of multikinase inhibitors in G3 NETs. Recently, PRRT was shown to be an effective therapy for G3 NETs in a prospective trial and other trials are ongoing. The efficacy of later line therapy is unclear. In this study, we report on an expanded cohort of heavily pretreated patients with G3 NETs treated with cabozantinib.

METHODS

Cases of patients with G3 NETs treated with cabozantinib were identified using the search tools of the Mayo Clinic electronic medical record. Information on baseline patient and tumor characteristics, tolerability and efficacy were extracted.

RESULTS

Eleven patients (4 women, 7 men), median age 61 years (range 40 – 79) met inclusion criteria. Seven had pancreatic primary tumor; one each had duodenal, small bowel, rectal and a NET of unknown primary. The median Ki-67 was 15.5 (range 0.89 – 55) on the initial biopsy and 51.4 (range 23.4 – 97) on a repeat biopsy prior to starting cabozantinib. Nine patients had genomic studies completed and 2 had TMB > 200 m/Mb, presumably temozolomide-induced hypermutated state. Nine patients had prior somatostatin analogs, six had prior PRRT and all patients had prior CAPTEM before starting cabozantinib. Nine patients had other chemotherapy prior to cabozantinib (all had irinotecan or oxaliplatin regimens). Four patients had everolimus and 1 patient (with high TMB) had immunotherapy without a response. Five patients had an objective response, but one has not had follow up imaging. Nine patients progressed but 2 patients died shortly after starting therapy. The median mPFS was 2.8 months (range 2.2 – 14) and the median OS from start date of cabozantinib was 24.5. Two patients had to discontinue cabozantinib for toxicity and 3 needed a dose reduction.

CONCLUSIONS

Cabozantinib appears to have antitumor activity in this small cohort of extensively pretreated mostly pancreatic G3 NET patients. Although the overall mPFS is modest, some patients had both a profound imaging response and encouragingly long PFS despite very high nuclear grade. Cabozantinib may be a viable option for patients with advanced and heavily pretreated G3 NETs and further studies are warranted.

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