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c-MET Expression in MEN1-associated Neuroendocrine Tumors

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BACKGROUND

Multiple studies have shown that approximately 50-70% of patients with MEN1 die of causes directly related to MEN1 particularly gastroenteropancreatic (GEP) neuroendocrine tumors (NETs). While non-functional GEP-NETs are the most common in the general population, gastrinomas (40%) are the most common functional GEP-NETs in patients with MEN1. *c-Met* is a proto-oncogene that encodes for c-MET, a tyrosine kinase receptor which promotes tumor cell motility, proliferation, survival, invasion, and metastasis. Studies in patients with sporadic gastrinomas and pancreatic NETs (PNETs) have shown that c-MET expression correlates with decreased survival.

While c-met inhibitors are currently in various stages of investigation for treatment of carcinoids and sporadic PNETs, data regarding their efficacy in patients with MEN1-related GEP NETs is lacking. Majority of trials in patients with GEP-NETs exclude or do not report the number of patients with MEN1. Importantly, somatic *MEN1* mutations are observed in 20-40% of sporadic NETs (gastrinomas, PNETs, lung NETs, etc.) but correlation of cMET expression with the presence of somatic or germline *MEN1* mutations has not been reported. We sought to investigate the expression of c-MET in tumor tissue from germline MEN1 patients with metastatic GEP-NETs.

METHODS

We identified subjects with a germline positive MEN1 mutation and pathologically confirmed distant metastasis who had a follow-up visit between 2018-2020. Of these, we selected subjects with available tissue specimens (including either multiple organ sources or different tumor types). Where available, we identified specimens from multiple source or tumor types. Immunohistochemistry (IHC) to detect c-MET was performed with anti-MET (Cell Signaling) using the DAKO IHC kit (Agilent). IHC slides were imaged and observed to score the level of c-MET staining (-, 1+ to 5+). A score of 3+ or higher was considered consistent with overexpression. We investigated if age at initial GEP-NET presentation, tumor type, tissue source, tumor grade, total number of surgeries for GEP-NET, number of sites of distant metastasis and disease status from overall GEP-NET burden over the preceding 12 months (stable/progressive) predicted c-MET expression.

RESULTS

Eight subjects with available tissue specimens were identified, of which six had tissue from multiple organs while five had tissue from multiple tumor types. Six subjects (75%) showed increased expression of c-MET in one or more tumor specimen(s). The frequency of c-MET overexpression varied with tumor types – carcinoids (n=2/2; 100%), gastrinomas (n=3/5; 60%) and non-functional tumors (n=3/6; 50%). c-MET expression also varied among different tumors in the same patient. Tumor tissue from liver (n=2/2), duodenum (n=3/4), stomach (n=1/1), ovary (n=1/1), pancreas (n= 1/5), and lymph nodes (n=1/3), all showed over-expression of c-MET. No clear predictors of c-MET overexpression emerged.

CONCLUSIONS

Our finding suggests a role for c-MET expression in personalizing therapy for patients with MEN1-related GEP-NETs with distant metastases.

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