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Molecular characteristics of high-grade gastroenteropancreatic neuroendocrine neoplasms

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Background

High-grade (HG) gastroenteropancreatic (GEP) neuroendocrine neoplasms (NEN) are rare and have poor outcome. Molecular data for HG GEP-NEN is limited and the WHO classification based on morphology and proliferation, while treatment strategies are extrapolated from small-cell lung cancer (SCLC). We aimed to characterize molecular features and relate these to classification, primary site and potential new treatments.

Methods

After pathological re-evaluation, we analysed 360 cancer genes in tumours and matched blood from 172 HG GEP-NEN patients; 147 neuroendocrine carcinomas (NEC) and 25 neuroendocrine tumours (NET G3).

Results

For NEC, frequently mutated genes were *TP53* (65%), *APC* (28%), *KRAS* (22%) and *BRAF* (20%). *RB1* was only mutated in 14%, but CNAs affecting *RB1* were seen in 48%. Other frequent losses were *ARID1A* (48%), *ESR1* (41%) and *ATM* (45%). Frequent amplifications were found in *MYC* (50%) and *KDM5A* (46%). While these molecular features had limited similarities with SCLC, we found potentially targetable mutations in 72% of the NEC samples. Mutations and CNA varied according to primary tumour site with *BRAF* mutations mainly seen in colon (49%), and *FBXW7* mutations mainly seen in rectal cancers (25%). 9/147 (6%) NEC were MSI. Alterations affecting *TP53* and *RB1* signalling were associated with improved prognosis. NET G3 had frequent mutations in *ATRX* (16%), *MEN1*, *MYO5B*, *SF3B1*, *SMAD2* and *TP53* (each 12%).

Conclusions

We performed a comprehensive assessment of the molecular tumour alterations in a large series of gastroenteropancreatic high-grade neuroendocrine neoplasms. We found few RB1 mutations and a marked difference in the molecular profile compared to prior results in SCLC and LCLC, challenging the use of SCLC as a paradigm for GEP-NEC. We found a quite similar profile comparing large-cell and small-cell GEP-NEC, but a profile variation according to primary tumour site and suggest a possible molecular strategy to separate NEC from NET G3. Our study shows a very high fraction of GEP-NEC with targetable mutations, pointing to novel important therapeutic strategies.

Legal entity responsible for the study

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