Mutations in Pancreatic Cancers Are Unique from Other Hepatobiliary Cancers

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Introduction

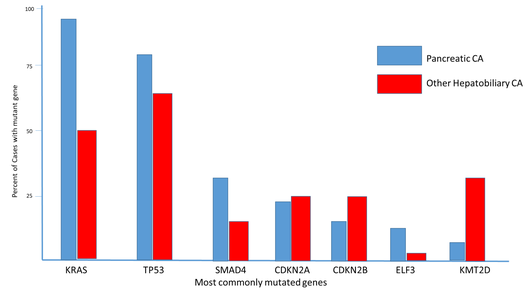
- Next-generation sequencing (NGS), has facilitated the identification of potential actionable targets for personalized therapies in pancreatic and other cancers.
- Targeted therapies against specific genetic alterations, such as KRAS inhibitors and DNA damage repair inhibitors, hold promise in improving treatment outcomes for pancreatic cancer patients.
- This study attempted to ascertain and define the unique NGS profile for pancreatic cancer in our patients when compared with other hepatobiliary tumors.

Methods

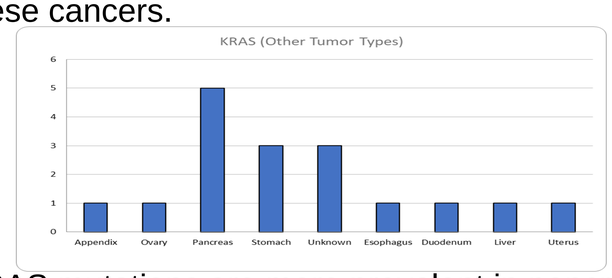
- In collaboration with the genetic testing company Tempus, we have an ongoing analysis of our cancer patient population in which their tumor DNA is screened for genetic changes, to determine the most common mutations associated with particular tumor types, and how those mutations relate to outcomes within a given treatment regimen.
- Utilizing the Tempus xT assay (NGS of 648 genes with known implications for cancer), we analyzed retrospective samples from 30 patients with metastatic pancreatic cancer.
- We analyzed the spectrum of mutations in pancreatic CA and compared them to hepatocellular and cholangiocarcinoma malignancies (n=33).

Results

- In pancreatic cancers, the most common somatic mutations were KRAS (92%) and TP53 (77%).
- In addition, other common pancreatic mutations were SMAD4 (31%), CDKN2A (23%), CDKN2B (15%), ELF3 (13%), and KMT2D (7%).
- In contrast, the most common hepatobiliary CA mutations were TP53 (63%), KRAS (50%), SMAD4 (13%), CDKN2A (25%), CDKN2B (25%) and KMT2D (38%).



- This figure shows the comparison of commonly mutated genes in pancreatic CA to other hepatobiliary cancers in our cohort
- Differences between SMAD, ELF3 and KMT2D mutations may permit a unique genetic profile for these cancers.



- KRAS mutations are more prevalent in pancreatic cancer than in other types.

Discussion

- The hepatobiliary tumors appear to demonstrate a unique mutational burden.
- NGS of pancreatic cancer shows KRAS and TP53 mutations appear to occur at higher levels than in hepatobiliary tumors (92% vs 50%, and 77% vs 63%, respectively).
- SMAD4 mutations were increased in pancreatic tumors over hepatobiliary tumors as well (34% vs 13%).
- Most interestingly, KMT2D mutations occurred in 7% of pancreatic tumors, compared to 38% of hepatobiliary tumors, perhaps signifying a unique genetic profile for hepatobiliary tumors.
- Similarly, ELF3 mutations were more prevalent in pancreatic cancer than in other HPB cancers (13% vs 3%)

Conclusion

- Our study has demonstrated a high degree of somatic mutational burden in HPB cancers.
- We have identified differences between the pancreatic and hepatobiliary tumors, specifically within the KMT2D gene, which appears enriched in hepatobiliary tumors as compared to pancreatic tumors.
- This study was limited by a small sample size. Larger studies are necessary to validate these preliminary findings.
- In the future, these differences may help to inform prognosis and guide treatment response.

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