Molecular profiling of bile duct and gallbladder cancer reveals different therapeutic options

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Abstract

Background: Biliary tree carcinomas arising in different anatomic locations (intrahepatic IHBC; extrahepatic, EHBC) and gallbladder (GBC) are rare tumors with a poor prognosis. An unmet medical need exists in identifying biomarkers of drug response. We interrogated biomarkers from a large cohort of patient samples with a multiplatform approach and considered associated therapeutic options.

Methods: 643 cases (291 IHBC, 115 EHBC, 237 GBC) were evaluated using a commercial multiplatform profiling service (Caris Life Sciences, Phoenix, AZ). Specific testing performed included a combination of gene sequencing (Sanger, NGS), protein expression (IHC) and gene amplification (CISH or FISH).

Results: Overall IHC showed high TOP2A (51%), TOPO1 (43%), SPARC (39%) and low RRM1 (76%), ERCC1 (72%) and TS (70%), indicating potential benefit from anthracycline, irinotecan, nab-paclitaxel, gemcitabine, platinum and fluoropyrimidine, respectively. 16 of 45 genes had mutations, with the highest rates seen in TP53 (29%), KRAS (19%), SMAD4 (9%) and IDH1 (9%). When comparing IHBC, EHBC and GBC, a number of statistically significant differences were observed (p values ranged from <0.0001 to 0.03). IHBC was characterized by the presence of IDH1 mutation (18% vs. 0% vs. 0%), low TP53 mutation (15% vs. 40% vs. 46%), and low HER2 amplification (2% vs.17% vs. 16%); IDH1 and TP53 mutations were mutually exclusive, and IDH1 was associated with high Pgp IHC (89% vs. 47%). EHBC had the highest KRAS mutation rate (EHBC 32% vs. IHBC 18% vs. GBC 13%). GBC had higher TOP2A IHC than IHBC and EHBC (71% vs. 36% vs. 46%) and higher RRM1 IHC (34% vs. 17% vs. 15%). Further, SMAD4 mutation was found in 20% (6/30) of metastatic tumors and 2.3% (1/44) of primary tumors (p=0.02).

Conclusions: Multiplatform cancer profiling reveals different biomarker characteristics of biliary tree carcinomas arising in different locations, suggesting a different biology and the need for different therapeutic approaches. Biomarker differences detected by IHC and ISH prompt considerations of HER2-targeted therapies in EHBC and GBC, and anthracyclines in GBC, highlighting the need for individualizing patient treatment based on tumor profiling in biliary tree carcinomas.

Background

- Biliary tree cancers diagnosed in ~ 12,000 patients in the US in 2013.
- Poor prognosis and very limited treatment options.
- IHBC, EHBC and GBC subtypes of biliary tree cancers treated similarly.

Hypotheses

- Through biomarker analysis from a large cohort of patients, we could differentiate potential treatment options for biliary tree cancers.
- IHBC, EHBC and GBC subtypes of biliary tree cancers would have different molecular expression patterns.

Methods

All biliary tract cancer cases referred to Caris Life Sciences between 2009 thru 2013 from 50 states and 59 countries were evaluated; diagnoses were collected from referring physicians and classified at intake based on pathology and clinical history. Specific testing was performed per physician request and included a combination of sequencing (Sanger NGS), protein expression (immunohistochemistry), gene amplification (CISH or FISH), promoter methylation (pyrosequencing) and/or RNA fragment analysis. Biomarker associations were calculated by two-tailed Fisher Exact tests.

Results

Table1: Number of cases included in the study

Biliary tract cancer types	Total	With NGS data
Intrahepatic bile duct cancer (IHBC)	291	39
Extrahepatic bile duct cancer(EHBC)	115	10
Gallbladder cancer (GBC)	237	28
Total	**643**	**77**

Figure 1: 4 ISH (CISH or FISH) and 16 IHC biomarkers and associated therapies in biliary tract cancers. Stand-of-care therapies as well as uncommon therapies that can potentially benefit biliary tract patients were identified based on the biomarker features.

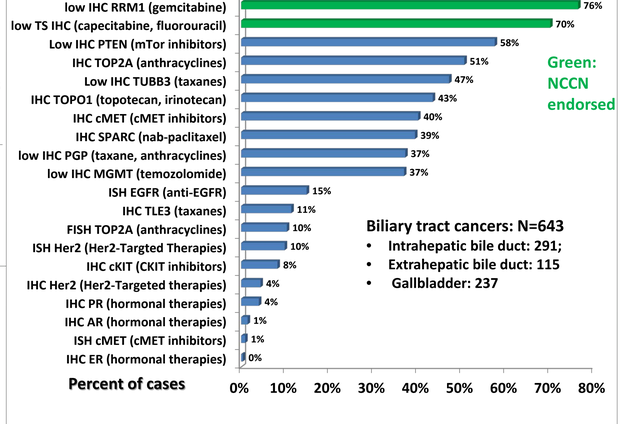


Figure 2: Significant IHC and ISH biomarker differences and therapeutic implications in IHBC, EHBC and GBC. 7 IHC and ISH theranostic biomarkers were found to be significantly differently (all p values <0.01) distributed in the three subtypes of biliary tree cancers. The potential benefit of associated therapies are therefore not uniform across the three cancer types. Based on the biomarker distribution, potential therapies and the corresponding cancer types in which they are more effective in are listed on the right.

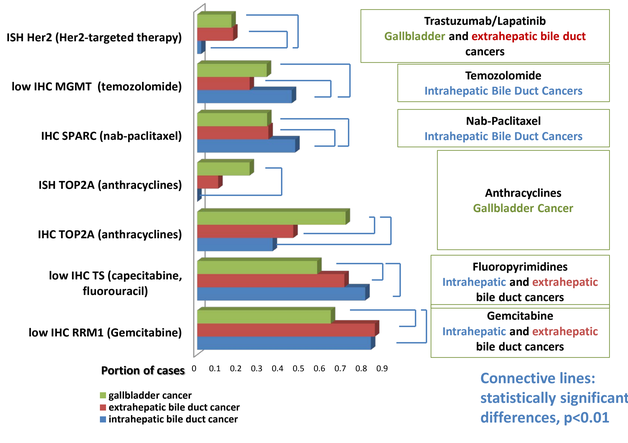
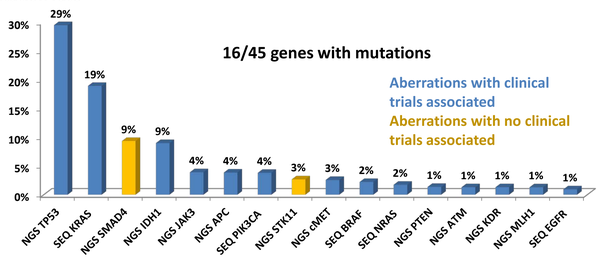


Figure 3: Mutations in biliary tract cancers and associated therapies. Out of the 45 genes tested using a combination of NextGen and Sanger Sequencing, 16 genes were found to be mutated. Aberrations in 13 genes were associated with approved or investigational agents that are being tested in clinical trials.



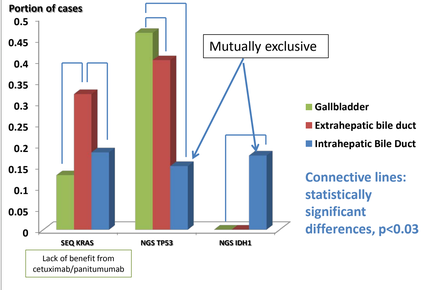


Figure 4. Significant differences in mutation rates in IHBC, EHBC and GBC. Mutation rates of KRAS, TP53 and IDH1 are significantly different in the three cancer types. Cetuximab/panitumumab is potentially less effective in EHBC. Notably, IDH1 mutation is exclusively found in IHBC, and is mutually exclusive of TP53 mutation.

Conclusions

- Retrospective biomarker analysis in a large cohort of biliary tract cancer patients using a multiplatform approach identifies a significant portion of patients who can potentially benefit from chemotherapeutic and targeted agents that are part of standard of care as well as from those that are not typically used for biliary tract cancer treatments.
- Significant differences were observed in 7 predictive IHC and ISH markers when comparing IHBC, EHBC and GBC. When the associated therapies are considered, trastuzumab is potentially more likely to benefit GBC and EHBC and anthracyclines are potentially more likely to benefit GBC.
- Three genes show significantly different mutation rates in the three cancer types. A higher KRAS mutation rate in EHBC suggests cetuximab and panitumumab are more likely to benefit IHBC and GBC than EHBC.
- IDH1 mutation is found exclusively in IHBC and is mutually exclusive of TP53 mutation, suggesting that these two molecular events could potentially drive two types of IHBC.
- Our study shows that using a multiplatform approach for tumor profiling is able to identify biomarker features of biliary tree cancers arising in different locations, suggesting a different biology and the need for different therapeutic approaches. For an individual patient, tailoring therapies based on the predictive biomarkers is important to identify the most effective treatment.

References

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