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

Abstract

Background: Biliary tree carcinomas arising in different anatomical locations (intrahepatic HBc, extrahepatic, EHBC, and gallbladder [GBC]) are rare tumors with poor prognosis and limited treatment options. Identification of biomarkers for drug response is critical. We interrogated biomarkers from a large cohort of patients with a multiparameter approach and considered associated therapeutic options.

Methods: 643 cases (291 IHBC, 115 EHBC, 237 GBC) were evaluated using a commercial multiparameter profiling service (Caris Life Sciences, Phoenix, AZ). Specific testing performed included a combination of gene 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: Among the 643 biliary tract cancer cases referred to Caris Life Sciences between 2009 thru 2013 from 50 states and 59 countries, significant differences were observed (p values ranged from <0.0001 to 0.03). IHBC was characterized by the presence of a higher KRAS mutation rate (18% vs. 0% vs. 6%), low TP53 mutation (15% vs. 40% vs. 46%), and low HER2 amplification (2% vs. 17% vs. 2%). IHBC was associated with high Pgp IHC (89% vs. 47%). EHBC had the highest KRAS mutation rate (32% vs. 18% vs. 1%), low IHC expression of MGMT (25% vs. 40% vs. 46) and high RRM1 IHC (34% vs. 17% vs. 15%). Further, SMAD4 mutation was found in 26% (260/993) of metastatic tumors (p=0.02). Conclusions: Multiparameter cancer profiling reveals biomarker characteristics of biliary tree carcinomas arising in different locations, suggesting a different biology and the need for different therapeutic approaches.

Background

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

Methods

• 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.

Results

• Significant differences were observed (p values ranged from <0.0001 to 0.03). IHBC was characterized by the presence of a higher KRAS mutation rate (18% vs. 0% vs. 6%), low TP53 mutation (15% vs. 40% vs. 46%), and low HER2 amplification (2% vs. 17% vs. 2%). IHBC was associated with high Pgp IHC (89% vs. 47%). EHBC had the highest KRAS mutation rate (32% vs. 18% vs. 1%), low IHC expression of MGMT (25% vs. 40% vs. 46) and high RRM1 IHC (34% vs. 17% vs. 15%). Further, SMAD4 mutation was found in 26% (260/993) of metastatic tumors (p=0.02).

Conclusions

• Retroreproductive biomarker analysis in a large cohort of biliary tract cancer patients using a multiparameter approach identifies a significant proportion of patients who can potentially benefit from chemotherapeutically targeted agents that are part of standard of care as well as 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. The associated therapeutic approaches are potentially more likely to benefit GBC and anthracyclines are potentially more likely to benefit IHBC.
• Three genes show significantly different mutation rates in the three cancer types. A higher KRAS mutation rate in IHBC suggests cetuximab and panitumumab are more likely to benefit IHBC and GBC. The associated therapeutic approach could be trastuzumab, which is potentially more likely to benefit EHBC and anthracyclines.
• IDH1 mutation is found exclusively in IHBC and is mutually exclusive of TP53 mutations.

References

1. Noel, M.S., et al. (2013) Oncor Targets and Therapy. 6: 1545-1552