Tumor profiling of biliary tract carcinomas reveals distinct molecular alterations and potential therapeutic targets

Methods: 815 cases (126 EHCC, 434 IHCC, 244 GBCA, 11 NOS) were tested by a commercial multiparameter profiling service (Caris Life Sciences, Phoenix, AZ). Tests included sequencing (Sanger, NGS), gene amplification (CISH/FISH), and protein expression (IHC).

Results: Of 47 tested had mutations, with the highest rates in TP53 (28%), KRAS (18%), IDH1 (9%), and SMAD4 (6%). BRCAl;2 mutations were seen in 3/41 (7.3%) and 5/40 (12.5%) cases. Overall, IHC showed high TOP2A, TOP2A, PO, SPARC and PO-D in 56%, 49, 40%, and 39% of cases and low RRM1, ERCC1 and TS in 83%, 79%, and 76%, respectively, suggesting potential utility of chemotherapeutic and immunomodulatory agents targeting these alterations in selected cases. Mutually exclusive protein loss of chromatin modifiers BAP1 and BRM1 were seen in 17% and 27%. ROS1 break-apart FISH showed negative results in 16 cases tested.

Comparing the three carcinomas (EHCC, IHCC and GBCA, Table), EHCC had the highest KRAS mutation rate; IHCC had the highest IDH1 mutation rate; GBCA and EHCC had significantly higher TP53 mutation rates and HER2 amplification than IHCC. IDH1 and TP53 mutations were mutually exclusive, and IDH1-mutated IHCC had higher P-glycoprotein expression than TP53-mutated IHCC (82% vs. 37%, P<0.01). GBCA had high TOP2A by FISH and IHCC is characterized by IDH1 mutations. The highest SPARC expression and the lowest MGMT expression are seen in IHCC. Low TS expression in IHCC and EHCC compared to IHCC, suggesting Her2-targeted therapy.

Conclusions: Multiplatform cancer profiling reveals distinct biomarker characteristics of biliary tract carcinomas, offering insights into disease biology and suggests potential sensitivity to novel and conventional therapies. Further analyses with clinical correlation are warranted.