Molecular Alterations, Tumor Microenvironment and Clinical Correlationsin Thai Cholangiocarcinoma Patients

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Background: The systemic treatment option of unresectable and advanced cholangiocarcinoma (CCA) is limited. The mainstay of treatment is gemcitabine and 5-FU based chemotherapy. Recently, there is the role of promising immunotherapy in MSI-H CCA. This research aims to study molecular alterations and tumor microenvironment in Thai CCA patients in order to explore the novel treatment and the clinical correlations.

Methods: Thirty-six CCA patients in Ramathibodi Hospital between year of 2018 and 2020 with adequate tissue were enrolled. NGS by ThermoFisher (comprehensive panel) for molecular profile and immunohistochemistry (IHC) staining for tumor microenvironment protein expression (CD3,CD4, CD8, CD20, CD138, CD163, FOXP3), and PD-L1 were performed. Clinical data was retrieved from electronic medical record. Survival analysis, univariate and multivariate analysis were performed by Cox-regression analysis. Stata version 16.0 was used for statistical analysis.

Results: Intrahepatic CCA was the most common type of CCA in our population (81%). The top 10 common mutations were TP53 (69%), KMT2D 58%), KMT2B (52%), ARID1A (50%), FAT1 (50%), NOTCH3 (44%), FANCA (42%), SMAD4 (42%), EPHA2 (39%), and ARID1B (39%) (Figure1). We also found the interesting targetable genes in our CCA patients, such as, KRAS (33%), MTOR (33%), HER2 (31%), EGFR (31%), FGFR2 (28%), BRCA2 (25%), PIK3CA (22%), NTRK1 (19%), BRCA1 (17%), NTRK3 (11%), and BRAF (8%). Three patients had ALK fusion gene, 1 patient had NTRK1 fusion and the other one had NTRK3 fusion gene. Twelve out of 36 patients (33%) had MSI-HI and 56% of patients had TMB ≥ 10 mutations/megabase. The clinical factors significantly correlated with poor overall survival (OS) were unresectable disease, stage IV, bilirubin > 1.2, and CEA ≥ 22.5. The NF1, MTOR, HER2 mutations, and FOXP3-negative in stromal cells were significantly associated with longer OS, whereas EGFR, APC, FGFR2 , and BRCA1 mutations might correlate with better OS.

Conclusions: Our study demonstrated the unique molecular profile of Thai CCA patients. We found high prevalence of MSI-HI and high TMB in our population, together with the promising potential of targetable genes for developing targeted therapy in the future. FOXP3 expression was probably one of potential predictive biomarker for immunotherapy. Larger cohort should be explored.