■ S-605 ■

Oncogenic deregulation of the methyltransferase EZH2 in hepatocellular carcinoma

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Background: Epigenetic mechanisms underlying nuclear chromatin remodeling are increasingly being recognized as crucial factors in hepatocellular carcinoma (HCC). Polycomb group member Ezh2 is a key epigenetic regulator of embryonic stem cell identity; however, its role in HCC is poorly understood. **Methods:** To investigate the roles of EZH2 and H3K27me3 in HCC, we conducted a review of patients who received surgical resection for HCC from 2009 to 2013. We analyzed EZH2 expression and H3K27me3 methylation status in 67 human HCC samples, and the global RNA expression by RNA-sequencing (RNA-seq) based on different EZH2 expression. Additionally, we used the EZH2, H3K4me3, and H3K27me3 chromatin immunoprecipitation-sequencing (ChIP-seq) data in ENCODE HepG2 for interpreting our RNA-seq results. **Results:** In contrast to our previous results of combined Ezh1 and Ezh2 loss in mouse experimental data, H3K27me3 expression was significantly related with EZH2 expression in 67 human HCC samples ($p = 0.01$). High EZH2 expression was related with short overall survival ($p = 0.05$), but H3K27me3 expression was not related with prognosis. Transcriptome analysis of HCC samples with high EZH2 expression by RNA-seq showed up-regulation of genes related to the cell cycle and DNA replication and down-regulation of estrogen response related genes. ChIP-seq for EZH2, H3K4me3, and H3K27me3 showed that estrogen receptor 1 (ESR1) and early growth response gene-1 (EGR-1) were regulated by EZH2 through methyltransferase function. **Conclusions:** This study shows that high EZH2 expression is related with poor prognosis in HCC. The EZH2 gene functions as a tumor oncogene by suppressing ESR1 and EGR-1 through methyltransferase function in human HCC. **Key words:** EZH2; Histone methylation; Hepatocellular carcinoma

■ S-606 ■

Prognostic Impact of HBV Infection in Advanced Intrahepatic Cholangiocarcinoma Treated with GEMCIS

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Background: Hepatitic B virus(HBV) infection is a well-known risk factor of Intrahepatic cholangiocarcinoma(iCCA). However, its prognostic impact has rarely been investigated in patients (pts) with advanced iCCA who received chemotherapy. **Methods:** Between April 2010 and May 2015, a total of 296 pts with histologically documented advanced iCCA received first-line GEMCIS(Gemcitabine plus cisplatin) in Asan Medical Center, Seoul, Korea, and were included in this retrospective analysis. Primary endpoint was overall survival(OS). In the multivariate analysis, variables that showed potential association with survival($p < 0.15$) in the univariate analysis were included. **Results:** Median age was 59 years(range, 27-78), and 62(20.9%) pts with hepatitis B surface antigen positive formed the HBV group. Initially metastatic disease was the most common disease status at the time of GEMCIS(n = 184, 62.2%) followed by recurrence after curative surgery(n = 69, 23.3%) and locally advanced unresectable disease(n = 43, 14.5%). In comparison with the non-HBV group, HBV group were related with young age(mean age 56.4 vs 60.0), male predominance(74.2% vs 57.3%), lower rates of elevated CA 19-9(42.0% vs 68.5%) and alkaline phosphatase(42.6% vs 60.5%) ($p < 0.05$ for all). In univariate analysis, HBV infection showed marginal relationship with poor OS (vs non-HBV infection; median 8.3 vs 10.0 months; HR = 1.27, $p = 0.13$). In multivariate analysis including potential prognostic factors, however, HBV group was significantly associated with poorer OS (HR = 1.52, $p = 0.02$). In addition, initially metastatic disease (vs locally advanced/recurrent disease; HR = 1.49), number of metastatic sites ≥2 (vs 0-1; HR = 1.50), poor ECOG performance status (2 vs 0-1; HR = 1.94), elevated total bilirubin (vs normal; HR = 1.83), and albumin < 3.5 g/dL (vs ≥3.5 g/dL; HR = 1.53) were significantly associated with poorer OS ($p < 0.05$ for all). **Conclusion:** Our results suggest that HBV infection might be an independent poor prognostic factor in pts with advanced iCCA treated with first-line GEMCIS. Further translational research is needed to define the differences in the molecular phenotypes between HBV- and non-HBV-associated iCCA.