

Reactivation of Hepatitis B with Chemotherapy

Because of conflicting studies in reference to whether the antibody to hepatitis B surface antigen (anti-HBs), protects against reactivation in patients with resolved hepatitis B infection receiving chemotherapy for hematological malignancies, a meta-analysis was conducted to determine if anti-HBs reduces HBV reactivation risk. English language studies were carried out through 3/1/2016 in MEDLINE and other sources that examined reactivation in patients with resolved HBV infection receiving chemotherapy for hematologic malignancies. The absolute risks and odds ratio (OR) of reactivation with vs. without anti-HBs were estimated at random effects model meta-analyses.

In 20 studies involving 1672 patients not receiving antiviral prophylaxis, the reactivation risk was 14%. In 388 patients who had antibodies to hepatitis B core antigen only vs. 5% in 1284 patients who also had anti-HBs, anti-HBs reduced reactivation risk with a pooled OR of 0.21 vs. patients with hepatitis B core antigen only.

Similar results were found when limiting the analysis to rituximab chemotherapy (OR = 0.19), and lymphoma (OR = 0.18).

It was concluded that in patients with resolving HBV receiving chemotherapy for hematologic malignancies without antiviral prophylaxis, anti-HBs positivity is associated with a decreased risk of activation; HBV screening in this population should include the routine use of anti-HBs.

Paul, S., Dickstein, A., Saxena, A., et al. "Role of Surface Antibody and Hepatitis B Reactivation in Patients with Resolved Infection and Hematologic Malignancy: A Meta-Analysis." *Hepatology* 2017; Vol. 66, 379-388.

Low-Level HBV Viremia and Risk of Hepatocellular Carcinoma

To determine whether the development of low-level viremia (LLV – less than 2 iu/mL) during entecavir monotherapy requires a change in therapy, a retrospective cohort of 875 treatment-naïve, chronic HBV monoinfected patients who received Entecavir monotherapy were analyzed for development of hepatocellular carcinoma (HCC). The HCC risk was compared between patients who maintained virologic

response (MVR), defined by persistently undetectable HBV DNA (less than 12 iu/mL) in patients who experienced LLV, defined by either persistent or intermittent episodes of less than 2000 iu/mL detectable HBV DNA.

During a median 4.5 years of follow-up, HCC was diagnosed in 85 patients (9.7%). HCC developed more frequently in patients who experienced LLV than MVR (14.3% vs. 7.5% at 5 years). The Hazzard ratio comparing those with LLV to MVR was 1.98. Among patients with cirrhosis, those with LLV exhibited a significantly higher HCC risk than those with MVR (23.4% vs. 10.3%, adjusted HR = 2.20). However, for patients without cirrhosis, there was no significant difference in the HCC risk between LLV and MVR.

It was concluded that LLV observed during Entecavir monotherapy was associated with a higher risk of HCC, especially for those with cirrhosis, indicating that LLV during potent antiviral therapy is consequential.

Kim, J., Sinn, D., Kang, W., et al. "Low-Level Viremia and the Increased Risk of Hepatocellular Carcinoma in Patients Receiving Entecavir Treatment." *Hepatology* 2017; Vol. 66, pp. 335-343.

Fundic Gland Polyps with Dysplasia

While fundic gland polyps (FGPs) rarely exhibit dysplasia of the surface epithelium, that circumstance is felt to be a strong marker for familial adenomatous polyposis (FAP), although sporadic, non-syndromic FGPDs also occur. While FGPD may prompt clinical evaluation for FAP, to evaluate the positive predictive value of incidental FGPDs for FAP, incidental FGPDs were identified from 2004 to 2005 in patients without FAP at biopsy. All clinical follow-up data was reviewed and germline analysis for APC and MUTYH mutations were performed in consenting patients.

A total of 25 incidental FGPDs in patients not known to have FAP (11.6% of FGPs, 1% of all FGPs), were identified. Four patients had a family history of gastric polyps or gastrointestinal cancers. Clinical management included completion polypectomy and gastric endoscopic surveillance (44%), endoscopic surveillance alone (32%), no follow-up (24%), colonoscopy referral (12%) and genetic counseling (4%.

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Colonoscopies on record revealed 0 to 7 cumulative adenomas. Follow-up average was 4.4 years. No clinical evidence of FAP, gastric cancer, death or surgery occurred. None of the 11 patients consenting to germline APC and MUTYH testing had genomic alterations.

It was concluded that incidental FGPDs in the series were all found to be sporadic (25/25) by endoscopic, clinical and molecular findings, and thus, FGPDs were not harbingers of FAP. As isolated findings, this does not appear to warrant follow-up genetic counseling or testing.

Lloyd, I., Kohlmann, W., Gigorich, K., et al. "A Clinico-Pathologic Evaluation of Incidental Fundic Gland Polyps With Dysplasia: Implication for Clinical Management." *American Journal of Gastroenterology*, 2017; Vol. 112, pp. 1094-1102.

Adenoma Detection Rate and Risk of CRC and Death

To investigate whether increasing adenoma detection rate (ADR) from individual endoscopists is associated with reduced risk of interval colorectal cancer and subsequent death, a prospective cohort study of individuals who underwent a screening colonoscopy within the National Colorectal Cancer Screening Program in Poland, from 1/1/2014 through 12/31/2008 was carried out. Data was collected from 146,860 colonoscopies performed by 294 endoscopists, with each endoscopist having participated at least twice in annual editions of primary colonoscopy screening.

Annual feedback and quality benchmark indicators were used to improve colonoscopy performance. ADR quintiles in the whole data set were used to categorize the annual ADRs for each endoscopist. An increased ADR was defined as an increase by at least one quintile category or the maintenance of the highest category in subsequent screening years. Multivariate frailty models were used to evaluate the effects of increased ADR on the risk of interval colorectal cancer in depth.

Throughout the enrollment period, 219 endoscopists (74.5%) increased their annual ADR category during 895,916 person/years of follow-up evaluation through the National Cancer Registry, 168 interval colorectal cancers were identified and 44 interval cancer deaths. An increased ADR was associated with an adjusted Hazard ratio for interval colorectal cancer of 0.63, and

for cancer death of 0.50, compared with no increase in ADR, reaching or maintaining the highest quintile ADR category, decreased the adjusted Hazard ratios for interval colorectal cancers to 0.27 and 0.18, respectively.

It was concluded that in a prospective study of individuals who underwent screening colonoscopy within a national colorectal screening program, increased ADR was associated with a reduced risk of interval colorectal cancer and death.

Kaminski, M., Wieszczy, D., Rupinski, M., et al. "Increased Rate of Adenoma Detection Associates With Reduced Risk of Colorectal Cancer and Death." *Gastroenterology* 2017; Vol. 153, pp. 98-105.

Annual Risk of Esophageal Adenocarcinoma in Barrett's Esophagus

To investigate the risk of esophageal adenocarcinoma (EAC) in Barrett's esophagus (BE) patients in relationship to number of success of endoscopies, years of follow-up and calendar year, a retrospective cohort study of male veterans with newly diagnosed BE during 2004 to 2009 with follow-up until 9/30/2011 was carried out. EAC was verified using detailed structural electronic medical records review.

Poisson regression was used to determine incidence, rate ratios (RR), and corresponding 95% confidence intervals (CI) for EAC, according to number of successive endoscopies, years of follow-up independent of numbers of follow-up endoscopies and calendar year of BE diagnosis.

Among 28,561 male patients with BE, a total of 406 developed EAC during 140,999 person/years of follow-up. EAC incidence rates increased with each additional endoscopy following a previous negative endoscopy, (RR for additional endoscopy 1.43).

Compared to the EAC incidence rate of the first follow-up EGD, the EAC incidence rate at the fifth follow-up EGD was 9-fold higher (adjusted RR 8.82). EAC incidence was highest at the first year of follow-up (5.34 per 1000 person/years); however, EAC rates started from the second follow-up year increased during successive years of follow-up.

Compared to the EAC incidence rate in the second year of follow-up, the EAC incidence rate was 1.5-fold higher in EGDs conducted greater than 5 years after the index BE date (adjusted RR 1.49). In contrast, there was no significant change in EAC incidence rates by

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calendar year.

It was concluded that persistence of non-neoplastic BE on multiple consecutive endoscopies was not associated with lower EAC risk. These findings argue against discontinuance of endoscopic surveillance in patients with persistent nondysplastic BE after multiple negative endoscopies.

Nguyen, T., Thrift, A., Yu, X., et al. "The Annual Risk of Esophageal Adenocarcinoma Does Not Decrease Over Time in Patients With Barrett's Esophagus." *American Journal of Gastroenterology* 2017; Vol. 112, pp. 1049-1055.

POEM in Treatment of Achalasia

The safety of per oral endoscopic myotomy (POEM) was evaluated for safety considerations, studying the prevalence of adverse events (AEs), and factors associated with occurrence of AEs in patients undergoing that procedure at 12 tertiary care centers between 2009 and 2015.

Control patients were selected for each AE case, matched for age, gender and disease classification (achalasia type I and II versus type III spastic esophageal disorder). A total of 1826 patients underwent POEM and 156 AEs occurred in 137 patients (7.5%). A total of 51 (2.8%) had inadvertent mucosotomies. Mild, moderate and severe AEs had a frequency of 116 (6.4%), 31 (1.7%) and 9 (0.5%), respectively.

Multivariate analysis demonstrated a sigmoid-type esophagus (OR 2.28), endoscopic experience of less than 20 cases (OR 1.98), use of a triangular tip knife (OR 3.22), and use of an electro-surgical current different than spray coagulation (OR 3.09). These were significantly associated with the occurrence of AEs.

It was concluded in this study that POEM is a relatively safe procedure when performed by experts at tertiary centers with an overall 7.5% prevalence of AEs and with rare severe AEs. Predisposing factors to AE occurrence were as reported above.

Haito-Chavez, Y., Inoue, H., Beard, K., et al. "Comprehensive Analysis of Adverse Events Associated with Per Oral Endoscopic Myotomy in 1826 Patients: An International, Multi-Center Study." *American Journal of Gastroenterology* 2017; Vol. 112, pp. 1267-1276.

HCC in HCV Patients Treated with Direct-Acting Antiviral Agents

To examine the risk and determinants of HCC in patients cured with direct-acting antivirals (DAA), a retrospective cohort study was conducted of HCV patients who were treated with DAA in any of the 129 Veterans Health Administration hospitals between 1/1/2015 and 12/31/2015.

The annual incidence rates of HCC by SVR was calculated. Cox regression models were used to compare the risk of HCC in patients with SVR versus those without SVR, and to identify factors associated with incident HCC among patients with SVR. A sample of HCC patients for tumor size and stage were reviewed at diagnosis.

Among 22,500 patients treated with DAA (9518 with SVR; 2982 without SVR), the mean age was 61.6 years and 39% had cirrhosis. There were 271 new cases of HCC, including 183 in patients with SVR.

Compared with patients without SVR, those with SVR had a significantly reduced risk of HCC (0.90 vs. 3.45 HCC/100 person-years). Patients with cirrhosis had the highest annual incidence of HCC after SVR (1.82 vs. 0.34/100 person-years; in patients without cirrhosis, adjusted hazard ratio 4.73). Most HCC (greater than 44.8%), were classified as stage I. Maximum size of the largest lesion was 5 cm in over 75% of cases.

It was concluded that among patients treated with DAA, SVR was associated with a considerable reduction in the risk of HCC. We did not find any evidence to suggest that DAAs promote HCC. In patients with SVR, the absolute risk of HCC remained high in patients with established cirrhosis. These patients should be considered for ongoing HCC surveillance.

Kanwal, F., Kramer, J., Asch, S., et al. "Risk of Hepatocellular Cancer in HCV Patients Treated with Direct-Acting Antiviral Agents." *Gastroenterology* 2017; Vol. 153, pp. 996-1005.

Proton Pump Inhibitor Use and Cognitive Function in Women

Because of reported association between PPI use and dementia, associations between proton pump inhibitor use and performance were examined in tests of cognitive function. Associations for H₂ receptor antagonists (H₂RAs), were added to the study as a secondary aim.

Collected data was used prospectively on medication use and other potential risk factors from 13,864 participants in the Nurses' Health Study II, who had completed a self-administered, computerized neuropsychological test battery. Multivariable linear regression models were used to examine associations between medication use and composite scores of psychomotor speed and attention, learning and working memory, and overall cognition.

A modest association was noted between duration of PPI use and scores for psychomotor speed and attention (mean score difference for PPI use of 9 to 14 years versus nonusers, -0.06, -0.11. After controlling for H2RA use, the magnitude of the score difference was attenuated. Among individuals who did not use PPIs regularly, duration of H2RA use was associated with poorer cognitive scores, with the strongest association apparent for learning and working memory (mean score difference for H2RA users of 9 to 14 years versus never users -0.20, -0.32 to 0.08).

In an analysis of data from the Nurses' Health Study II, it was concluded that a convincing association between PPI use and cognitive function was not observed. This data does not support the suggestion that PPI use increases dementia risk. Findings for H2RAs were recommended to be interpreted with caution.

Lockhead, P., Hagan, K., Joshi, A., et al. "Association Between Proton Pump Inhibitor Use and Cognitive Function in Women." *Gastroenterology* 2017; Vol. 153, pp. 971-979.

Narrow-Band Imaging for Gastric Intestinal Metaplasia

To compare detection of gastric intestinal metaplasia (GIM) with high-definition white-light (HD-WL) endoscopy, NBI and mapping biopsies were carried out in a population with increased gastric cancer risk. Patients underwent upper endoscopy at HD-WL examination by one endoscopist, followed by an NBI examination by a second endoscopist blinded to HD-WL findings. The location of abnormalities detected by HD-WL and NBI were recorded by a research coordinator and targeted biopsies of abnormal areas were performed after NBI.

Subsequently, 5 mapping biopsies were performed per patient. Biopsy specimens were read by a pathologist blinded to mode of acquisition. The primary outcome

was a proportion of patients with GIM.

A total of 112 patients were enrolled; 107 were Hispanic or Asian and 34 had GIM. Higher proportions of patients with GIM were detected by NBI (22/34/65%), and mapping (26/34/76%) versus HD-WL (10/34/29%). GIM was detected by NBI in only 6 patients and only by mapping biopsy in 10 patients; no patient had GIM detected solely by HD-WL. Higher proportion of sites with GIM also were detected with NBI (30/57/53%), and mapping biopsies (38/57/67%), than HD-WL (16/57/28% for both comparisons).

The median number of biopsies per patient with mapping biopsies (5) were significantly higher with NBI (2) or HD-WL (1).

It was concluded that HD-WL endoscopy is insufficient for detection of GIM patients at advanced risk for gastric cancer. NBI-targeted biopsies plus mapping biopsies should be used.

Buxbaum, J., Hormozdi, H., Dinis-Ribeiro, M., et al. "Narrow-Band Imaging Vs White-Light Vs Mapping Biopsy for Gastric Intestinal Metaplasia: A Prospective, Blinded Trial." *Gastrointestinal Endoscopy* 2017; Vol. 86, pp. 857-865.

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