A META-ANALYSIS ON THE EFFECTS OF ANTIVIRAL THERAPY PRIOR TO HEPATECTOMY ON VIRAL REACTIVATION, OVERALL SURVIVAL AND DISEASE-FREE SURVIVAL AMONG PATIENTS WITH CHRONIC HEPATITIS B-RELATED HEPATOCELLULAR CARCINOMA

LML Canseco, HM Babaran, CR Cuano, JC Sunglao, AD Salvana

Section of Gastroenterology, Department of Medicine, Philippine General Hospital

ABSTRACT

Significance

Liver cancer is the 2nd most common cause of cancer death. EASL 2018 recommends surgical resection for non-cirrhotic HCC patients. This study will investigate the long-term benefit of early Antiviral treatment, in terms of overall survival, disease-free survival and viral reactivation, prior to hepatectomy.

Methodology

Systematic literature search using electronic database with inclusion criteria: 1)Chronic Hepatitis B-related Hepatocellular Carcinoma patients >/= 18 yrs old, 2) Curative resection, 3) Antiviral prior to hepatectomy for the experimental arm compared to no antiviral control, 4) With data on viral recurrence or survival on follow-up. Exclusion criteria 1)co-infection with other viral hepatitis or HIV, 2) Main form of therapy for HCC other than hepatectomy. Relevant data were compared and analyzed using Review Manager 5.3 software

Results

Four studies having a total of 833 for study population, 417 belongs to the antiviral arm and 416 under the control group.
Patients given nucleoside analogues prior to liver resection had a significantly reduced risk of viral reactivation by 88% (RR 0.12, 95% CI 0.04 – 0.36) compared to the control.
For the 1, 3 and 5-year disease-free survival, treating with nucleoside analogues prior to surgery, showed a trend towards increased survival rate with an RR of 1.23, 1.18 and 1.13 respectively. There was a significant increased overall survival among patients given nucleoside analogues prior to hepatectomy with risk ratios at 1.11, 1.26 and 1.17 respectively.

Conclusion

For Chronic Hepatitis B-related HCC patients, giving nucleoside analogues prior to liver resection significantly decreases viral reactivation and improves disease-free and overall survival.

Keywords: Chronic Hepatitis B, Hepatocellular Carcinoma, Metaanalysis, Liver resection, Nucleoside analogues

INTRODUCTION

In the study done by Akinyemiju et al, there was a 75% increase in the incidence of liver cancer between 1990 and 2015 (2017). Currently, liver cancer is the 2nd most common cause of cancer death, majority of which is of the hepatocellular carcinoma type and is seen predominantly in East Asia followed by the Asia Pacific region. Among the top contributory factors include Hepatitis B and C virus.

The annual incidence of HCC from Chronic Hepatitis B is at 1% for non-cirrhotics and 2-3% for cirrhotics based on the APASL Update 2015. Several scoring systems and risk calculators such as REACH-B had been developed to estimate HCC risk for Chronic Hepatitis B patients. Those with high risk to develop HCC should be appropriately managed.

The latest European Association for the Study of the Liver (EASL) 2018 Guidelines still strongly recommend surgical resection as the treatment of choice for non-cirrhotic HCC patients. Five year survival rate was estimated at 60-80% for well-selected candidates who will undergo surgical management.

A Meta-analysis by Sun et al in 2014 showed that after curative treatment either through resection, radiofrequency ablation, percutaneous ethanol injection (PCEI) or cryoablation plus RFA, nucleoside analogues led to an increase in recurrence-free survival and overall survival among patients with Hepatitis B-related Hepatocellular Carcinoma. This is likewise found in the meta-analysis of Zhou et al which emphasized that elevated HBV DNA is associated with a high risk for developing Hepatocellular carcinoma thus, nucleoside analogues which inhibit HBV replication was found to decrease the recurrence of HCC among patients who underwent liver resection (2014).

Several studies have shown favorable outcomes for Hepatitis B-related Hepatocellular carcinoma patients given nucleoside analogues post- surgery. This study will investigate the benefits of early Antiviral treatment, in terms of overall survival, disease-free survival and viral reactivation, prior to hepatectomy.

MATERIALS AND METHODOLOGY

Literature Search

A systematic literature search was done using electronic databases (PubMed, Cochrane, Medline and EMBASE without language restrictions. MESH terms used were “Nucleoside analogues”, “Chronic Hepatitis B”, “Hepatocellular Carcinoma”, “Entecavir”, “Tenofovir”, “Adefovir”, “Lamivudine”, “Telbivudine”, “Liver resection”, “Hepatectomy”, “Viral reactivation”, “Overall survival”, “Disease-free survival”. Only human studies were included. Reference lists of associated papers were manually checked for additional articles.

Inclusion and Exclusion criteria

Inclusion criteria are as follows: 1)Chronic Hepatitis B-related Hepatocellular Carcinoma patients 18 yrs old and above regardless of gender, 2) Management is Curative resection for HCC, 3) Nucleoside analogues given prior to hepatectomy for the experimental arm compared to no antiviral control group, 4) With data on viral recurrence or survival on follow-up

Exclusion criteria consists of 1)co-infection with other viral hepatitis or HIV, 2) Main form of therapy for HCC other than hepatectomy

Data extraction

Two authors independently screened the studies in accordance to the set inclusion and exclusion criteria. All studies were evaluated for methodological quality. Disagreements were resolved through a third author by consensus.

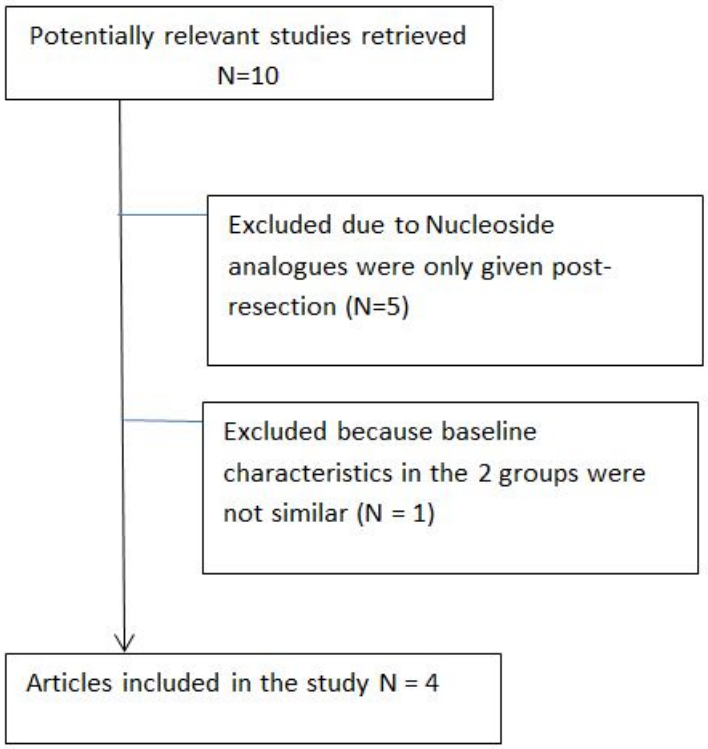

Figure 1. Data Extraction

Statistical analysis and synthesis

Relevant data were compared and analyzed using Review Manager 5.3 software. Dichotomous outcomes were combined using risk ratios (RR). Heterogeneity was assessed using the I-squared statistic. Less than 25% was assessed as minimal heterogeneity, 25-50% was moderate and >50% was substantial heterogeneity. Chi ^{2} test was also used to test for significant heterogeneity (P > 0.10).

RESULTS

Eligible studies

There were four studies who met the inclusion and exclusion criteria, having a total of 833 for study population, 417 of which belongs to the antiviral arm who received nucleoside analogues and 416 are under the control group. Two studies investigated the overall survival and disease-free survival of patients given nucleoside analogues prior to hepatic resection. Different nucleoside analogues were used in the studies as shown in table 1. Another 2 studies assessed the benefit of antivirals in terms of viral reactivation. For Chong and Sakamoto's studies, the antiviral group included a pre and post-resection treatment arm with nucleoside analogues. All the studies used liver resection as a curative treatment however Dan's article also utilized RFA. Risk of bias for all included studies were at low risk.

TABLE 1. Studies included in the Meta-Analysis

	Dan 2013	Chong 2015	Sakamoto 2015	Gong 2017
N	93	404	162	174
P	HBV related HCC	HBV related HCC Antiviral: 254 (pre-resection 97, post-resection 157) No antiviral: 150	HBV related HCC Antiviral: 62 (pre-resection 24, post-resection 38) No antiviral 100	HBV related HCC
I	Lamivudine Adefovir Entecavir	Entecavir 61% Lamivudine 30.3% Adefovir 5.5% Tenofovir, Telbivudine and a combination of Adefovir and Lamivudine (3.2%)	Lamivudine (21) Lamivudine plus Adefovir (6) Lamivudine switched to Entecavir (5) Entecavir (31)	Entecavir 0.5mg/day starting 3 days before hepatectomy
C	No Antiviral	No Antiviral	No Antiviral	No Antiviral
O	HBV Reactivation	1, 3, 5- year disease free survival 1, 3, 5- year overall survival	1, 3, 5- year disease free survival 1, 3, 5- year overall survival	HBV reactivation
M	Retrospective August 2006 to August 2011	Prospective (Feb 2010 - June 2012)-retrospective (Jan 1999 - Feb 2010)	Prospective Cohort January 2001 to March 2012	Prospective July 2012 to June 2016

Viral Reactivation

The results were summarized in Figure 2. Patients who were given nucleoside analogues prior to liver resection had a significantly reduced risk of viral reactivation by 88% (RR 0.12, 95% CI 0.04 – 0.36) compared to the control group. Heterogeneity is absent in the two studies (I^2= 0%).

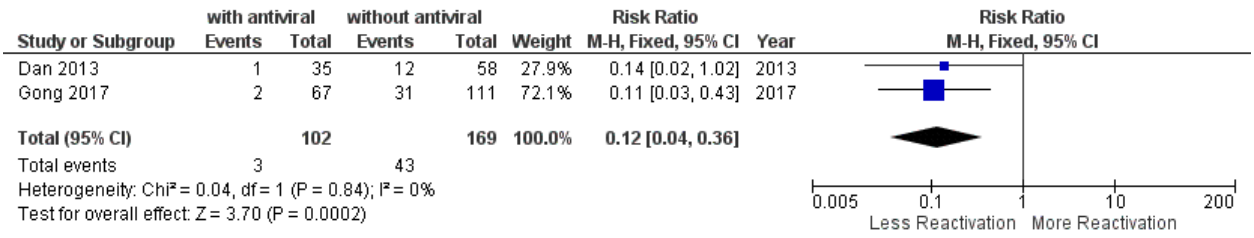

Figure 2. Viral Reactivation

Disease-free Survival

Studies by Sakamoto and Chong presented 1, 3 and 5-year disease-free survival as shown in figures 3, 4 and 5. Treating with nucleoside analogues prior to surgery, showed a trend towards increased disease-free survival rate with an RR of 1.23, 1.18 and 1.13 respectively. Studies were homogeneous as well (I^2= 0%).

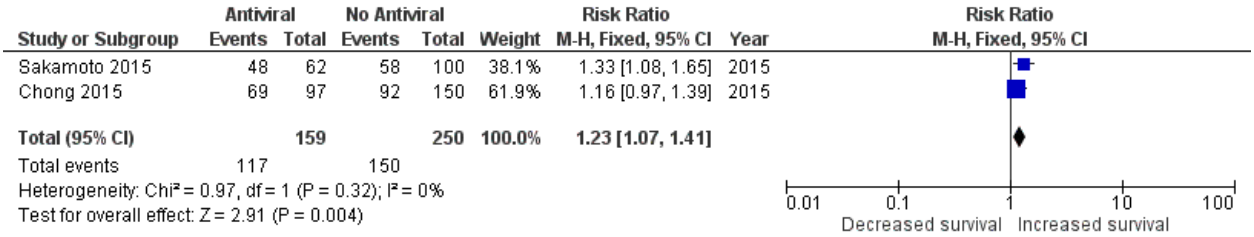

Figure 3. 1 year Disease-free survival

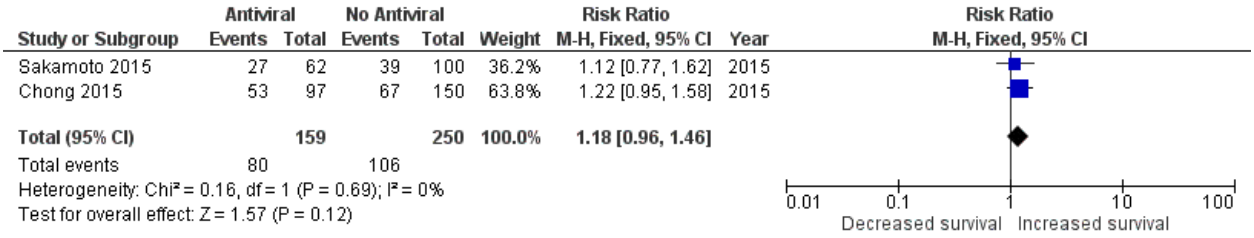

Figure 4. 3 year Disease-free survival

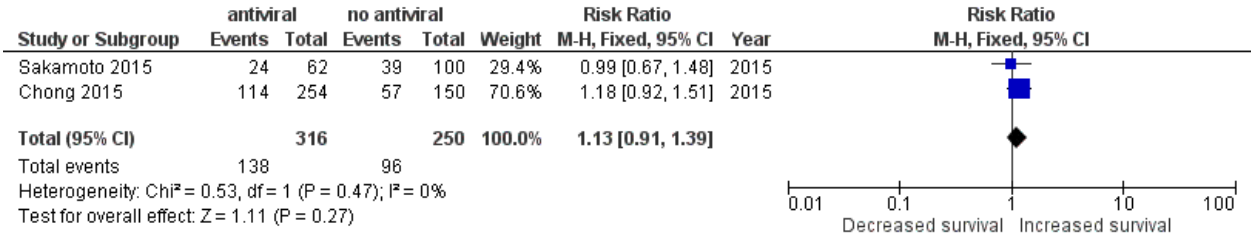

Figure 5. 5 year Disease-free survival

Overall Survival

Figures 6-8 presented significant increased overall survival at 1, 3, and 5 years, among patients given nucleoside analogues prior to hepatectomy with risk ratios at 1.11, 1.26 and 1.17 respectively. Studies did not show heterogeneity at 5 years (I^2= 0%) but were noted to be moderate and substantial at 1 (I^2= 23%).and 3 years (I^2= 68%) respectively.

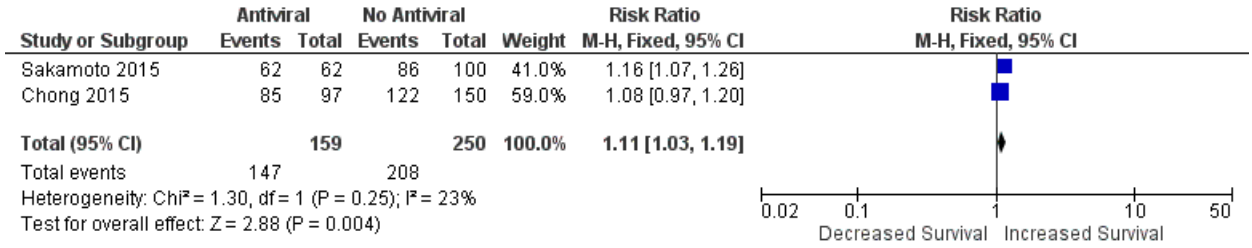

Figure 6. 1 year Overall survival

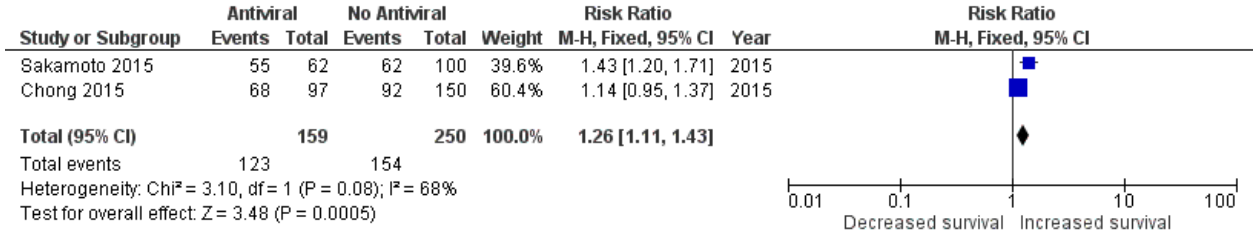

Figure 7. 3 year Overall survival

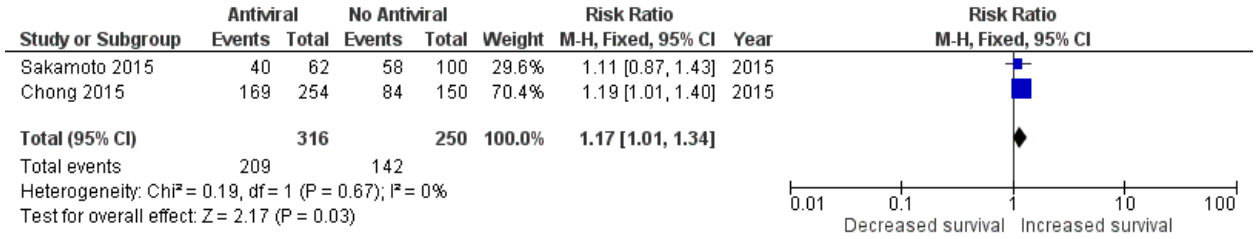

Figure 8. 5 year Overall survival

DISCUSSION

Chronic Hepatitis B can progress to hepatocellular carcinoma directly by modifying the expression of oncogenes and tumor suppressor genes through the incorporation of HBV DNA into the genome and indirectly by persistent hepatic injury leading to apoptosis and necroinflammation (Fung, 2017). Thus, targeting viral suppression can lead to HCC prevention. The importance of which is due to the fact that at present, HCC is the fifth most common cancer worldwide according to the World Health Organization.

The American Association for the Study of Liver Diseases 2018 recommends prophylactic antiviral therapy, particularly Entecavir and Tenofovir, prior to anticancer treatment and immunosuppressive therapy for Chronic Hepatitis B regardless of HBV DNA level as this leads to mortality and reactivation reduction (AASLD CHB, 2018). However, recommendations for antivirals prior to liver resection for Chronic Hepatitis B-related Hepatocellular Carcinoma have not yet been included in the recent guidelines.

Hepatic resection is favored over radiofrequency ablation for HCC patients with Child Pugh A cirrhosis or T1 or T2 status (AASLD HCC, 2018). Hepatectomy could lead to HBV reactivation believed to be due to the physiological decline in immune status brought about by the stress of surgery. Late recurrences are associated with the remnant liver's viral load, cirrhotic status and inflammation. Thus antivirals such as nucleoside analogues could prevent tumor recurrence (Fung, 2017).

Hepatitis B reactivation is defined as a significant increase in HBV replication (2 log increase compared to baseline) or detection of up to 100IU/ml for those with undetectable or stable levels prior or HBV DNA of 20,000 IU/ml for those without baseline values (APASL, 2015). An elevated viral load is also associated with poorer overall survival and tumor-related death.

Two meta-analyses on nucleoside analogues after curative treatment for Chronic Hepatitis B- related Hepatocellular Cancer showed a significant decrease in recurrence and mortality, the effects of which were attributed to a the suppression of viral replication that lead to carcinogenesis (Sun 2014, Zhou 2014).

In this study, we have shown a significant viral reactivation risk reduction by 88% as well as significant 1, 3, and 5 year overall survival for Chronic Hepatitis B-related HCC patients given nucleoside analogues prior to liver resection. Though there was a favorable trend in terms of disease-free survival, it was not shown to be significant at 1, 3 and 5 years. These findings are attributed to the nucleoside analogues' effect in improvement in liver function.

CONCLUSION

For Chronic Hepatitis B-related HCC patients, giving nucleoside analogues prior to liver resection significantly decreases viral reactivation and improves disease-free and overall survival. Thus this should be given to such patients before hepatectomy. Furthermore, this should likewise be included in the next guidelines for managing HCC patients.

REFERENCES

1) Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, Allen C, et al. The burden of primary liver cancer and underlying etiologies from 1990 to 2015 at the global, regional, and national level. *JAMA Oncol* 2017;3:1683–1691.

2) EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. *Journal of Hepatology* 2018 vol. 69 j 182–236.

3) Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. Hepatol Int (2016) 10:1–98.

4) Sun P, Dong X, Cheng X, Hu Q, Zheng Q (2014) Nucleot(s)ide Analogues for Hepatitis B Virus-Related Hepatocellular Carcinoma after Curative Treatment: A Systematic Review and Meta-Analysis. PLoS ONE 9(7): e102761. doi:10.1371/journal.pone.0102761

5) Zhou Yanming et al. Antiviral Therapy Decreases Recurrence of Hepatitis B Virus-related Hepatocellular Carcinoma after Curative Resection: A Meta-analysis. World J Surg. May 2014. DOI 10.1007/s00268-014-2586-z.

6) AASLD Guidelines for the Treatment of Hepatocellular Carcinoma. HEPATOLOGY, VOL. 67, NO. 1, 2018

7) Update on Prevention, Diagnosis, and Treatment of Chronic Hepatitis B: AASLD 2018 Hepatitis B Guidance. HEPATOLOGY, VOL. 67, NO. 4, 2018

8) Fung, James and Kenneth S.H. Chok. The role of oral antiviral therapy in hepatitis B-related hepatocellular carcinoma. *Hepatoma Res* 2017;3:284-93

9) Gong et al. Effects of antiviral therapy on post-hepatectomy HBV reactivation and liver function in HBV DNA-negative patients with HBV-related hepatocellular carcinoma. Oncotarget, 2017, Vol. 8, (No. 9), pp: 15047-15056.

10) Chong et al. Antiviral therapy improves post-hepatectomy survival in patients with hepatitis B virus-related hepatocellular carcinoma: a prospective-retrospective study. Aliment Pharmacol Ther 2015; 41: 199–208

11) Sakamoto et al. Antiviral Therapy and Long-term Outcome for Hepatitis B Virus-related Hepatocellular Carcinoma after Curative Liver Resection in a Japanese Cohort. ANTICANCER RESEARCH *35*: 1647-1656 (2015)

12) Dan et al. Hepatitis B virus reactivation after radiofrequency ablation or hepatic resection for HBV-related small hepatocellular carcinoma: A retrospective study. EJSO 39 (2013) 865e872.