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Impact of tenofovir antiviral treatment on survival of chronic hepatitis B related hepatocellular carcinoma after hepatectomy in Chinese individuals from Qingdao municipality

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Abstract

The impact of different antiviral regimen on prognosis of chronic hepatitis B (CHB) related hepatocellular carcinoma (HCC) remains to be explored.

A total of 479 CHB-related HCC patients after curative liver resection were enrolled receiving tenofovir (TDF, TDF group) or lamivudine, telbivudine, and entecavir (non-TDF group). Both the overall survival and diseases-free survival were analyzed and compared.

A total of 242 patients received TDF treatment and 237 patients received other antiviral regimen. Child-Pugh score, serum α-fetoprotein (AFP) level, total bilirubin level, status of hepatitis B e antigen (HBeAg), and cirrhosis were compared between groups. Kaplan–Meier analysis revealed that patients with TDF treatment had significantly longer overall survival than those of patients with other regimen ($P = .015$). Similarly, compared with patients with non-TDF treatment, disease-free survival time was longer ($P = .042$) in those with TDF treatment. Multivariate analysis showed that TDF treatment ($P = .04$), AFP level ($P = .03$) were significant independent factors associated with overall survival of CHB-related HCC patients. While TDF treatment ($P = .04$) and serum AFP level ($P = .03$) were independent factors associated with disease-free survival.

Anti-virus treatment with TDF benefits for both overall survival and disease-free survival of CHB-related patients than other Nucleos (t)ide analogues.

Abbreviations: AFP = α-fetoprotein, CHB = chronic hepatits B, DFS = disease-free survival, ETV = entecavir, HBeAg = hepatitis B e antigen, HBsAg = hepatits B surface antigen, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, LAM = lamivudine, LdT = telbivudine, NAs = Nucleus(t)ide analogues, OS = overall survival, SD = standard deviation, TDF = tenofovir.

Keywords: chronic hepatitis B, hepatocellular carcinoma, nucleus(t)ide analogues, survival, tenofovir

1. Introduction

Hepatocellular carcinoma (HCC) is among the most common malignancies of high morbidity and mortality, especially in China.[1–3,21] Among which chronic hepatitis B virus (HBV) infection is highly related to HCC development.[4–7] Serum HBV-DNA level is associated with progressive hepatic impairment and it has been proved to be correlated to cirrhosis progression.[8] The contribution of persistent HBV replication to liver cirrhosis and HCC in chronic hepatitis B (CHB) patients has been determined in several studies.[9–11] Thus, sustained suppression of HBV

Editor: Jianxun Ding.

ZG and JM have contributed equally and co-first author to this work.

Ethics approval and consent to participate: This study was conducted under compliance with the Declaration of Helsinki and was approved by both the Human Ethics Committee of Qingdao 6th People's Hospital and the Human Ethics Committee of Qingdao Municipal Hospital. Written consents were obtained from all patients enrolled.

Consent for publication: Not applicable.

The authors declare that they have no competing interests.

Funding: Not applicable.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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How to cite this article: Ge Z, Ma J, Qiao B, Wang Y, Zhang H, Gou W. Impact of Tenofovir antiviral treatment on survival of chronic hepatitis B related hepatocellular carcinoma after hepatectomy in Chinese individuals from Qingdao municipality. Medicine 2020;99:32(e21454).

Received: 6 March 2019 / Received in final form: 11 May 2020 / Accepted: 25 June 2020

http://dx.doi.org/10.1097/MD.0000000000021454

replication is critical to reduce liver cirrhosis or HCC progression.[12] Nucleos(t)ide analogues (NAs) have been approved due to the high effectiveness for suppressing HBV replication, as well as regression of cirrhosis and reduction of HCC incidence.[12–14]

Surgical resection is regarded as the main curative therapy for HCC.[15–18] Previous studies have revealed that sustained HBV replication is strongly associated with HCC recurrence in CHB-related HCC patients after surgery.[19] Recent studies have confirmed that NAs can decrease the recurrence rate in CHB-related HCC patients receiving hepatic resection.[19–21] However, although many NAs have been proved to be effective in CHB-related HCC patients,[20,21] it remains to be explored that whether there is any differences in the prolonged survival time in CHB-related HCC. Tenofovir (TDF) is recommended as first-line Nucleos(t)ide analouges for CHB in clinical practice guidelines because of its high antiviral efficacy and low rate of resistance.[22] Recent study found that higher serum interferon-λ3 levels were induced in patients treated with TDF, but not in other NAs.[23] Interferon-λ3 has shown potent antitumor activity in murine models of cancer, including HCC.[24,25] However, whether TDF can improve the prognosis of HCC better than other NAs has not been reported.

Thus, we designed a retrospective cohort study to explore the potential difference among CHB-related HCC patients with different NAs regimens.

2. Materials and methods

2.1. Patients and study design

In this study, we continuously enrolled patients with HBV-related HCC who received NAs after resection. The flow chart was shown in Fig. 1. All patients enrolled in our study were diagnosed with HCC and underwent curative liver resection in Qingdao municipal hospital (Shandong, China) from May 2011 to November 2013. All patients received anti-HBV treatment and were followed in Qingdao 6th People hospital (Shandong, China). Inclusion criteria were: histologically confirmed HCC; serum hepatitis B surface antigen (HBsAg) positive >6 months; Child-Pugh scoring ≤9 prior to surgery. The exclusion criteria were: HCV and/or HDV coinfection; alcoholic hepatic diseases; schistosomiasis; invalid clinical characteristics and laboratory outcomes. Lack of medical records since loss of follow-up. Liver cirrhosis were also confirmed by the tissues obtained from liver resection with pathological evidences.

This study was conducted under compliance with the Declaration of Helsinki and was approved by both the Human Ethics Committee of Qingdao 6th People's hospital and the Human Ethics Committee of Qingdao municipal hospital.

2.2. Laboratory detection

Quantification of serum HBV DNA was measured by real-time quantitative PCR assay with Roche LightCycler (Roche Diagnostics, Basel, Switzerland) and suitable reagents (PG Biotech, Shenzhen, China), of which the lower limit of quantification is 1000 copies/mL. Contrast-enhanced CT, ultrasonography, or liver biopsy were conducted to screen HCC recurrence during follow-up. Child-Pugh scoring was applied for consideration of surgical treatment and prognosis as previously reported (26).

2.3. Anti-HBV treatment

All patients received NAs treatment for at least 6 months prior to surgery. A total of 242 patients were received TDF anti-HBV treatment. The other patients received LAM (n = 143), ETV (n = 62), or telbivudine (LdT) (n = 32) anti-HBV treatment, respectively. The dosage of NAs in all patients were 300 mg per day for TDF, 100 mg per day for LAM, 0.5 mg per day for ETV, and 600 mg per day for LdT.

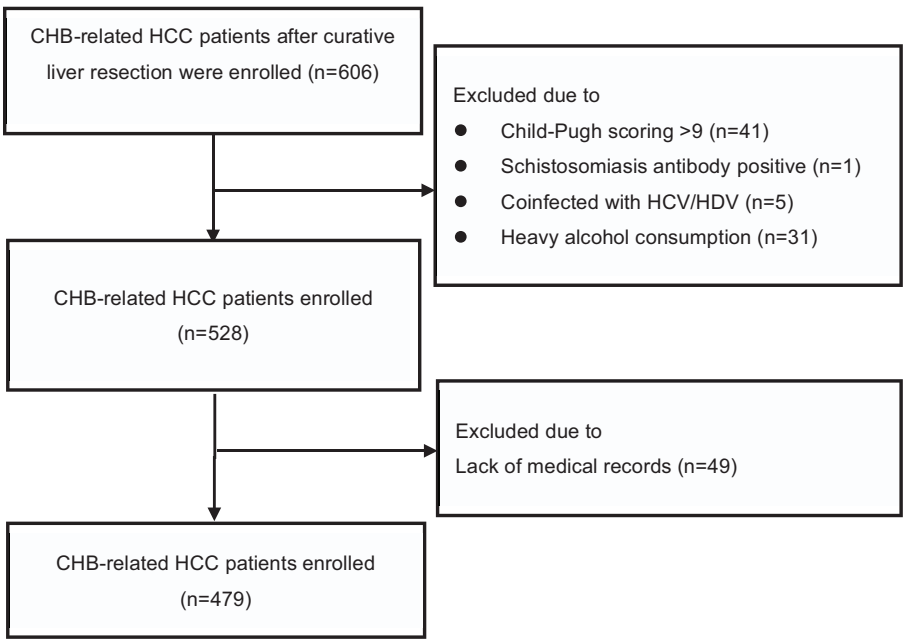

Figure 1. Flow chart of the study.

2.4. Statistics

Continuous variables were expressed as mean ± SD with normal distribution and median (range) without normal distribution. The comparison of continuous variables with or without normal distribution was analyzed with Student *t* test and Wilcoxon rank test, respectively. Chi-square and Fisher test were applicated for analysis of categorical variables. $P < .05$ was regarded as statistically significant. The univariate analysis of factors associated with overall survival of patients was conducted through Kaplan–Meier statistics and Log-rank test. To identify different factors for outcomes of CHB-related HCC patients, we have conducted both univariate and multivariate Cox Regression analysis in Forward: Conditional way. Variables with $P < .05$ were employed into the Cox regression model. $P < .05$ was considered as statistically significant. Statistics analysis was conducted with SPSS (version 16.0, SPSS Inc., Chicago, IL) software package.

3. Results

3.1. The baseline characteristics

A total of 479 CHB-related HCC patients underwent curative liver resection and were divided into TDF group (n = 242) and non-TDF group (n = 237). Male patients were predominant in both groups. The percentage of patients with cirrhosis was 80% (n = 193) in TDF group and 78% (n = 186) in non-TDF group. As shown in Table 1.

At baseline, mean HBV DNA viral load in the TDF group was 2.21 ± 2.53 $\log_{10}$ copies/mL, compared with 2.54 ± 2.75 $\log_{10}$ in the non-TDF group ($P = .17$). We continued to compare the HBV DNA load after 1 year of surgery. The mean HBV DNA viral load in the TDF group was 0.91 ± 1.07 $\log_{10}$ copies/mL, compared with 1.07 ± 1.22 $\log_{10}$ copies/mL in the non-TDF group ($P = .12$).

3.2. Survival in CHB-related HCC patients

To determine the effect of TDF antiviral treatment on DFS and OS of patients with HCC, we conducted a Kaplan–Meier survival analysis. Kaplan–Meier analysis revealed that patients with TDF treatment had significantly better outcomes in terms of overall survival ($P = .015$, Fig. 2). Similarly, compared with patients with non-TDF treatment, disease-free survival time was longer ($P = .042$, Fig. 3) in those with TDF treatment.

Table 1

Baseline characteristics of CHB-related HCC.

	TDF-treatment (n = 242)	Non-TDF treatment (n = 237)	*P*-value
Age, (mean ± SD)	50 ± 11	50 ± 12	.75
Gender			.35
Male	212 (87.6%)	214 (90.3%)	
Female	30 (12.4%)	23 (9.7%)	
Cirrhosis			.49
Yes	193 (80%)	186 (78%)	
No	49 (20%)	51 (22%)	
HBeAg			.73
Positive	176 (72%)	169 (71%)	
Negative	66 (28%)	68 (29%)	
Child-Pugh score			.49
A	232 (96%)	224 (94%)	
B	10 (4%)	13 (6%)	
AFP, ng/mL, median (range)	94.5 (1.2–1210)	77.2 (1.5–1210)	.70
Total bilirubin, μmol/L, median (range)	15.1 (5.5–65.0)	13.7 (5.3–36.4)	.14

AFP = α-fetoprotein, HBeAg = hepatitis B e antigen, SD = standard deviation.

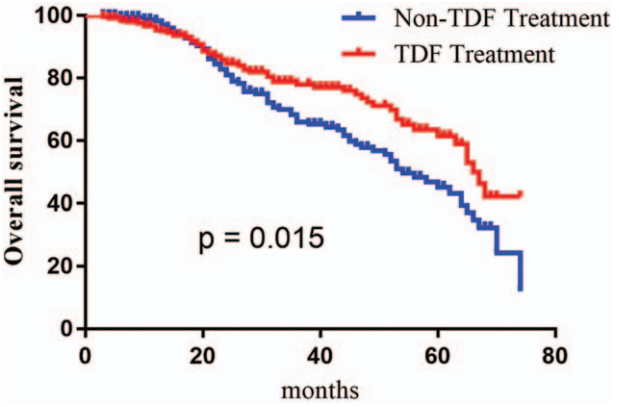

Figure 2. Comparison of overall survival between TDF group and non-TDF group. Kaplan–Meier analysis revealed that patients with TDF treatment had significantly better outcomes in terms of overall survival ($P = .015$). TDF = tenofovir.

3.3. Univariate and multivariate analyses of prognostic variables in HCC

In order to identify potential factors for overall survival of CHB-related HCC patients, both univariate and multivariate analysis were conducted. Univariant analysis indicated that TDF treatment ($P = .02$), AFP level ($P = .02$), and HBeAg positive ($P = .03$) were significantly associated with overall survival of CHB-related HCC patients. Multivariate analysis showed that TDF treatment ($P = .04$), AFP level ($p = 0.03$) were independent factors associated with survival of CHB-related HCC patients. As shown in Table 2.

The independent factors associated with disease-free survival (Table 3) were further explored. Univariate analysis showed that TDF treatment and serum AFP level were factors associated with disease-free survival. Multivariate analysis showed that TDF

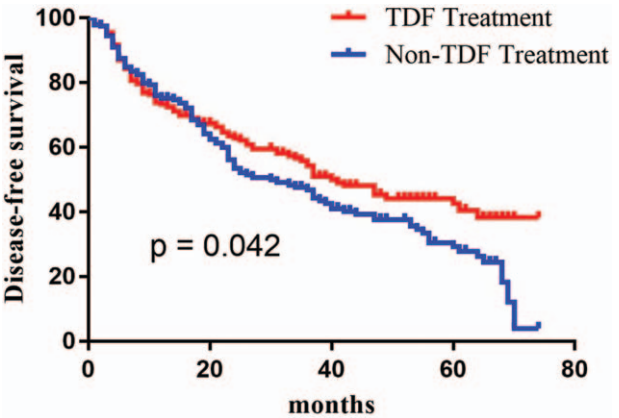

Figure 3. Comparison of disease-free survival between TDF group and non-TDF group. Compared with patients with non-TDF treatment, disease-free survival time was longer ($P = .042$) in TDF treatment group. TD = tenofovir.

Table 2

Univariate and multivariate analysis for overall survival.

	Univariant analysis	*P*-value	Multivariant analysis	
	HR (95% CI)		HR (95% CI)	*P*-value
Age	1.00 (0.99–1.01)	.89		
Gender	0.98 (0.57–1.69)	.78		
Child-Pugh score	0.48 (0.21–1.10)	.15		
TDF-treatment	0.66 (0.48–0.92)	.02	0.67 (0.48–0.93)	.04
AFP level	0.69 (0.49–0.98)	.02	0.72 (0.51–0.99)	.03
Total bilirubin	1.15 (0.69–1.91)	.19		
HBeAg status	1.53 (1.05–2.24)	.03		

AFP = α-fetoprotein, HBeAg = hepatitis B e antigen.

treatment ($P = .04$) and serum AFP level ($P = .03$) were independent factors associated with disease-free survival.

3.4. Impact of HBeAg status on survival in CHB-related HCC patients

In order to investigate the impact of HBeAg status in HCC patients, we also compared the overall survival and disease-free survival between HBeAg positive and HBeAg negative HCC patients receiving TDF treatment. In the HBeAg positive group, the proportion of males was 86%. In the HBeAg-negative group, the proportion of men was 91% ($P = 0.039$) as shown in supplementary Table 1, http://links.lww.com/MD/E604. Interestingly, we found that 98% of patients in HBeAg positive group were confirmed with cirrhosis (n = 173) and 20% in HBeAg negative group (n = 20), which was significantly different between both sub-groups ($P < .001$). We found that baseline HBV DNA viral loads were 1.93 ± 2.07 $\log_{10}$ copies/mL in the HBeAg-positive group, compared with 2.42 ± 2.89 $\log_{10}$ in the HBeAg-negative group ($P = .14$). After 1 year of treatment, the mean HBV DNA viral load in the HBeAg-positive group was 0.72 ± 1.02 $\log_{10}$ copies/mL, compared with 1.03 ± 1.84 $\log_{10}$ copies/mL in the HBeAg-negative group ($P = .09$).

However, analysis of overall survival and disease-free survival between HBeAg positive and negative group didn't show any significant difference, although both survival analysis showed slightly better results of HBeAg positive group than that of HBeAg negative group (Supplementary Fig. 1, http://links.lww.com/MD/E603).

4. Discussion

Our study demonstrated that anti-HBV treatment with TDF is related to better survival of CHB-related HCC patients. Both overall survival and disease-free survival in TDF group were significantly longer than those of non-TDF group. Although there was no significant difference in survival between HBeAg positive and negative subgroups within patients receiving TDF treatment, further studies with large sample size may confirm the potential effect of HBeAg status in TDF treated HCC patients.

The effect of NAs to induce expression of interferon-λ3 could be one potential mechanism in our study,[23] since interferon-λ3 has been demonstrated to be involved in modulation of immunity during virus infection or autoimune diseases.[26] Inflammation is determined to have a strong association with carcinogenesis and recurrence of HCC.[27] Thus, we supposed that TDF might regulate the immunity through induction of interferon-λ3 to improve the survival of CHB-related HCC patients in our study. However, in patients with HBC-related HCC, whether TDF benefited patients by stimulating interferon release has not been confirmed. The potential different outcome among LAM group, ETV group, and LdT group is interesting. However, in our study, we found that there is no significant difference in OS and DFS between those 3 groups. This result may be caused by the small sample size of patients received LdT treatment since LdT is no longer the first-line NA for CHB treatment.

Some studies have been reported that NAs can affect the outcome of CHB-related HCC treatment, which is due to the sustained HBV suppression.[19,28] Previous studies in patients with hepatic resection revealed that patients with a high HBV viral load after resection had higher recurrence rate compared with that in patients with a low viral load.[29,30] According clinical guideline by Asian Pacific Association for the Study of the Liver, antiviral therapy after tumor resection is crucial regarding preventing HCC recurrence and improving survival.[31] Another interesting topic is whether TDF could better improves the degree of liver fibrosis than other NAs in CHB-related HCC patients. The comparison of fibrosis-4 index and aspartate transaminase-to-platelet ratio index score in different NAs treated HCC patients is meaningful but need further research.

Recent studies have confirmed the relationship between HBsAg level and HCC progression.[27,32,33] However, the poor access to HBsAg quantification during the period of patients receiving treatment in our study made it difficult to analyze the possible effect of HBsAg level on survival of CHB-related HCC patients. The association between NAs treatment and HBsAg reduction have been proved,[23,34] as well as the relationship between HCC and HBsAg.[35] Thus, a prospective study with HBsAg quantification method would provide a better analysis to the effect of TDF in CHB-related HCC.

There are some limitations in our study. Since it is a retrospective study, limited data restrained our further analysis. Our study lacks data of HBsAg level, so we could not assess the relationship of HBsAg level on survival of CHB-related patients. Also, the sample size of our study is relatively small. It would be better to compare TDF with LAM, ETV, and LdT. However, one-way analysis of variance analysis of the 4 groups will be biased because the sample size is too small. Due to this study conducted in a single center, the data may be biased. In this study, there is no data about the percentage of patients with an acute HBV infection in adulthood or as infants/children born to chronically infected mothers, thus lack providing more correlative insight, for eample, time with HBV leading to HCC to offered treatment/management. Therefore, a multicenter prospective study is needed for further validation of the role of NAs in HCC outcomes.

Table 3

Univariate and multivariate analysis for disease-free survival.

	Univariate analysis	*P*-value	Multivariate analysis	
	HR (95% CI)		HR (95% CI)	*P*-value
Age	0.91 (0.87–1.03)	.72		
Gender	1.01 (0.92–1.19)	.89		
Child-Pugh score	0.82 (0.39–1.93)	.51		
TDF-treatment	0.64 (0.53–0.94)	.03	0.78 (0.41–0.98)	.04
AFP level	0.82 (0.17–0.97)	.02	0.89 (0.29–0.99)	.03
Total bilirubin	1.61 (0.82–1.80)	.12		
HBeAg status	1.47 (0.98–1.97)	.07		

AFP = α-fetoprotein, HBeAg = hepatitis B e antigen.

5. Conclusion

In conclusion, our study proved the benefit of anti-HBV treatment with TDF for the survival of CHB-related HCC patients after hepatic resections.

Acknowledgments

Authors would like to thank help and support from hospital for the study.

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