Antiviral drug resistance increases hepatocellular carcinoma: A prospective decompensated cirrhosis cohort study

Lei Li, Wei Liu, Yu-Han Chen, Chun-Lei Fan, Pei-Ling Dong, Fei-Li Wei, Bing Li, De-Xi Chen, Hui-Guo Ding

Lei Li, Yu-Han Chen, Chun-Lei Fan, Pei-Ling Dong, Bing Li, Hui-Guo Ding, Department of Gastroenterology and Hepatology, Beijing You’an Hospital Affiliated with Capital Medical University, Beijing 100069, China
Wei Liu, Department of Internal Medicine, Beijing Ji Shui Tan Hospital Affiliated with Peking University, Beijing 100035, China
Fei-Li Wei, De-Xi Chen, Viral Laboratory of Liver Diseases Research Institute, Capital Medical University, Beijing 100069, China

Author contributions: Li L, Liu W and Chen YH equally contributed to the data collection and follow-up of patients in this study; Li L and Ding HG analysed the manuscript; Wei FL and Chen DX supervised the drug resistance mutation detection; Ding HG was responsible for this project and the final manuscript; the other authors contributed to the data acquisition and patient care.

Supported by: The Major Projects on Infectious Disease, No. 2012ZX10002-008-005; the Beijing Science and Technology Commission Research Projects, No. H010210110129, Z111107058811067; and the High-level Talent Academic Leader Training Program, No.2011-2-19

Correspondence to: Hui-Guo Ding, MD, PhD, Director, Department of Gastroenterology and Hepatology, Beijing You’an Hospital Affiliated with Capital Medical University, Fengtai district, Beijing 100069, China. dinghuiguo@medmail.com.cn
Telephone: +86-10-83997155 Fax: +86-10-63295525
Received: July 24, 2013 Revised: September 22, 2013
Accepted: September 29, 2013
Published online: December 7, 2013

Abstract

AIM: To study the clinical outcome of antiviral therapy in hepatitis B-related decompensated cirrhotic patients.

METHODS: Three hundred and twelve patients with decompensated hepatitis B cirrhosis were evaluated in a prospective cohort. With two years of follow-up, 198 patients in the group receiving antiviral therapy with nucleos(t)ide analogues and 39 patients in the control group without antiviral treatment were analysed.

RESULTS: Among the antiviral treatment patients, 162 had a complete virological response (CVR), and 36 were drug-resistant (DR). The two-year cumulative incidence of hepatocellular carcinoma (HCC) in the DR patients (30.6%) was significantly higher than that in both the CVR patients (4.3%) and the control group (10.3%) (P < 0.001). Among the DR patients in particular, the incidence of HCC was 55.6% (5/9) in those who failed rescue therapy, which was extremely high. The rtA181T mutation was closely associated with rescue therapy failure (P = 0.006). The Child-Pugh scores of the CVR group were significantly decreased compared with the baseline (8.9 ± 2.3 vs 6.0 ± 1.3, P = 0.043).

CONCLUSION: This study showed that antiviral drug resistance increased the risk of HCC in decompensated hepatitis B-related cirrhotic patients, especially in those who failed rescue therapy.

© 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Hepatitis B; Decompensated cirrhosis; Nucleos(t)ide analogues; Hepatocellular carcinoma; Drug resistance

Core tip: This study was performed to analyse the clinical data of 312 patients with decompensated hepatitis B cirrhosis in a prospective cohort. These data showed that complete virological response could improve the clinical outcome in decompensated hepatitis B cirrhotic patients. However, clinicians should be aware of the high risk of hepatocellular carcinoma and liver failure in antiviral drug-resistant patients.

BRIEF ARTICLE

Online Submissions: http://www.wjgnet.com/esps/ bpgoffice@wjgnet.com doi:10.3748/wjg.v19.i45.8373

World J Gastroenterol. 2013 December 7; 19(45): 8373-8381
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
© 2013 Baishideng Publishing Group Co., Limited. All rights reserved.
September 7, 2013

Antiviral drug resistance increases hepatocellular carcinoma: A prospective decompensated cirrhosis cohort study.

World J Gastroenterol 2013; 19(45): 8373-8381 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i45/8373.htm
DOI: http://dx.doi.org/10.3748/wjg.v19.i45.8373

INTRODUCTION

Chronic hepatitis B virus (HBV) infection, the main aetiology of liver cirrhosis and hepatocellular carcinoma (HCC), remains a major public health problem worldwide, especially in China[1-3]. Among these patients, the annual incidence of HCC is 2%-5%[3,4]. The most effective method to prevent HCC is to control HBV infection through vaccination[5-7]. In patients already infected with HBV, antiviral therapy remains the best strategy to prevent liver cirrhosis and HCC[8-9]. Major progress in the treatment of chronic hepatitis B has recently been made during the last decade with the development of antiviral drugs, especially nucleos(t)ide analogues (NUCs)[10-12]. Some data supporting the benefit of antiviral therapy on the prevention of HCC in chronic hepatitis B patients have been reported in several randomised controlled trials[12-13]. Nonetheless, antiviral drug resistance is important in determining the success of long-term therapy for chronic hepatitis B patients[14,15]. Based on recent clinical data, the development of resistance to NUCs is associated with an exacerbation of liver disease, including the development of cirrhosis and HCC[16]. In addition, the risk of HCC remains high in HBV-related cirrhosis patients who are treatment-naïve for NUCs[17]. Decompensated cirrhosis is the end stage of the disease and is characterised by high mortality and an extremely high risk of HCC. In HBV-related decompensated cirrhotic patients (DCPs), antiviral therapy using NUCs is recommended according to the 2005 global guideline[18-20]. However, clinical data regarding the incidence of HCC in HBV-related DCPs with NUC antiviral therapies are limited. Therefore, the aim of the current study was to evaluate the two year outcomes in HBV-related decompensated cirrhotic, treatment-naïve patients using NUCs in a real life practical prospective cohort.

MATERIALS AND METHODS

Patients
The patients were enrolled due to HBV-related decompensated cirrhosis in a clinical practice between January 2008 and July 2012 at the Beijing Youan Hospital Affiliated Capital Medical University. Four hundred and seventy-two patients who fulfilled the inclusion criteria and were prospectively enrolled in this study. The study protocol was approved by the Ethical Committee at Beijing Youan Hospital of Capital Medical University. All the patients provided written informed consent before being included in the study. Clinical parameters (gender, age, family history of hepatitis B, alcohol abuse, Child-Pugh scores, HBeAg positive, HBV DNA load, renal function, and presence of ascites, encephalopathy, or variceal bleeding) were recorded. A diagnostic work-up for decompensated liver cirrhosis was performed, including clinical manifestations, physical examination, and laboratory tests, according to the criteria suggested by the Chinese Medical Association in 2005 for liver diseases[18]. The inclusion criteria were as follows: (1) chronic hepatitis B history and/or signs; (2) abnormal liver function accompanied by portal hypertension, such as ascites, encephalopathy, and esophageal or gastric variceal bleeding; (3) B-ultrasound scanning (LOGIQ9; GE Company, Fairfield, United States) and computerised tomography (CT; GE HISPEED DXI; GE Company) results consistent with the signs of liver cirrhosis without images of liver cancer; and (4) no NUC medications taken prior to entry. The exclusion criteria were as follows: (1) co-infection with HAV, HCV, HDV, HEV, and HIV as determined by an electrochemical luminescence method for the detection of the HAV and HCV antibodies and by an enzyme-linked immunosorbent assay for the HDV, HCV, and HIV antibodies; CMV and EBV IgM-positive patients as determined by an enzyme-linked immunosorbent assay for the detection of CMV and EBV IgM; (2) use of hepatotoxic drugs, including long-term analgesics and antipyretics, antibiotics, anti-lipidemic drugs, hypoglycaemic drugs, and herbal medicines; (3) HCC or metastatic liver cancer; (4) poor compliance and uncontrolled serious cardiovascular, respiratory, digestive, and nervous system diseases; (5) pregnant or lactating; and (6) Child-Pugh score ≥12. Alcohol abuse was defined in this study as follows: (1) alcohol abuse >5 years, (2) drinking the ethanol equivalent of >40 g/d for men or 20 g/d for women, or (3) heavy drinking in the most recent 2wk equivalent to ethanol >80 g/d.

In addition, 10 mL of venous blood was collected and centrifuged at 4°C. All serum samples were stored at -80°C in the Medical Bioinformation Research Center Biobank (Beijing, China).

Antiviral therapy
In the HBV-related DCPs in this cohort, the antiviral therapy included lamivudine (LAM; 100 mg/d; n = 39), adefovir (ADV; 10 mg/d; n = 73), telbivudine (LDT; 600 mg/d; n = 36), and entecavir (ETV; 0.5 mg/d; n = 54) monotherapies or combinations of LAM (100 mg/d) and ADV (10 mg/d; LAM + ADV; n = 39) or of LDT (600 mg/d) and ADV (10 mg/d; LDT + ADV; n = 25) according to clinical real-life practices. The control group consisted of patients who declined antiviral therapy (n = 46). All patients were followed every 3mo, and their virologic, biochemical, and clinical parameters were obtained. Among these patients, 75 were excluded because they had follow-up <24mo or were lost to follow-up; thus, 198 patients in the antiviral therapy group and 39 in the control group were included in the analysis. The antiviral therapy patients were subdivided into a drug-resistant...
Patients with decompensated cirrhosis ($n = 476$) → Enrolled patients ($n = 312$) → Antiviral group ($n = 266$) → Control group ($n = 46$)

Exclusion criteria:
- Co-infection with HCV
- Long-term use of hepatotoxic drugs
- Poor compliance
- Child Pugh scores ≥ 12
- NUCs medicine taken prior to entry

Follow-up

$39$ were included in the analysis

$198$ were included in the analysis

**Figure 1 Flow chart of enrolled patients.** NUCs: Nucleos(t)ide analogues; HCC: Hepatocellular carcinoma; DR: Drug-resistant; CVR: Complete virologic response; LAM: Lamivudine; ADV: Adefovir; LDT: Telbivudine; ETV: Entecavir; HCV: Hepatitis C virus.

**Detection of HBV**

Serum hepatitis B markers were detected by an electrochemiluminescence immunoassay using a Roche E170 modular immunoassay analyser (Roche Diagnostics, Mannheim, Germany) following the manufacturer’s protocol. The serum HBV-DNA was quantified using a real-time polymerase chain reaction (PCR, FQ-PCR Kit; DaAn Gene Co., ShenZhen, China) and a GeneAmp 5700 Sequence Detection System (PE. Applied Biosystems, Boston, United States). The lower limit of HBV DNA detection was 500 copies/mL. CVR was defined as HBV-DNA being undetectable and persistently negative during the antiviral therapy for two years. Successful rescue therapy was defined as undetectable HBV-DNA 12 wk after changing antiviral drugs.

**DR mutation detection by HBV polymerase**

DR was defined as the conversion of HBV DNA to positive (virologic rebound) or the detection by sequence analysis of mutations known to be related to drug resistance during the NUC treatment. Serum HBV DNA was extracted according to the instructions of a commercial kit (Qiagen Blood Kit, Dusseldorf, Germany), using Platinum Taq DNA polymerase high fidelity (Invitrogen, CA, United States) for nested PCR amplification.
### Table 1  Rescue therapy strategies in drug resistance patients

| DR patients | Rescue therapy prescriptions | HBN DNA after rescue therapy 12 w < 500 copies/mL | > 500 copies/mL |
|-------------|------------------------------|---------------------------------------------|-----------------|
| LAM (n = 11) | + ADV (n = 6) | 4 | 2 |
| | ---ETV + ADV (n = 5) | 3 | 2 |
| ADV (n = 12) | + ETV (n = 5) | 4 | 1 |
| | + LAM (n = 7) | 6 | 1 |
| LDT (n = 8) | + ADV (n = 6) | 4 | 2 |
| | ---ETV + ADV (n = 2) | 2 | 0 |
| ETV (n = 2) | + ADV (n = 2) | 2 | 0 |
| LAM+ADV (n = 2) | ---ETV + ADV (n = 2) | 1 | 1 |
| LDT+ADV (n = 1) | ---ETV + ADV (n = 1) | 1 | 0 |

*: Add-on; →: Altered drug. DR: Drug resistance; LAM: Lamivudine; ADV: Adefovir; LDT: Telbivudine; ETV: Entecavir; HBV: Hepatitis B virus.

### Table 2  Clinical characterizations of the enrolled patients at baseline n (%)

| DR | CVR (n = 162) | Control (n = 39) |
|----|---------------|-----------------|
| Gender n (male/female) | 25/13 | 109/53 | 24/15 |
| Age, mean ± SD (yr) | 56.9 ± 14.6 | 58.4 ± 11.2 | 52.2 ± 10.8 |
| Family history of HCC | 6 (16.7) | 21 (12.9) | 7 (17.9) |
| Alcohol abuse | 4 (11.1) | 22 (13.5) | 10 (26.2) |
| HBeAg positive | 20 (53.6) | 95 (58.6) | 22 (56.4) |
| Child-Pugh Score, mean ± SD | 9.0 ± 2.8 | 8.6 ± 2.3 | 7.9 ± 2.1 |
| qHBV DNA (log), mean ± SD | 5.4 ± 3.3 | 4.9 ± 4.7 | 4.9 ± 1.7 |
| PTINR, mean ± SD | 1.98 ± 0.87 | 2.24 ± 1.29 | 2.03 ± 1.16 |
| BUN, mean ± SD (mmol/L) | 8.3 ± 3.7 | 9.1 ± 4.2 | 8.0 ± 2.5 |
| Cr, mean ± SD (μmol/L) | 87.6 ± 39.3 | 77.4 ± 45.8 | 74.8 ± 20.4 |
| Ascites | 21 (58.3) | 90 (55.6) | 20 (51.3) |
| Encephalopathy | 0 (0) | 2 (1.2) | 1 (2.6) |
| Variceal bleeding | 17 (47.2) | 85 (52.4) | 18 (46.1) |

SD: Standard deviation; HCC: Hepatocellular carcinoma; DR: Drug-resistant; CVR: Complete virologic response; BUN: Blood urea nitrogen; Cr: Creatinine; HBV: Hepatitis B virus; HBeAg: Hepatitis B e antigen.

The first-round primer sequences were as follows: P54, 5'-TYCTGCTGGTTGGCT CCAGTTCC-3' (nt54-75) and P1287, 5'-CATACTGGGAACTCTAGCG-3' (nt1267-1287). The second-round primer sequences were as follows: P253, 5'-CTCGTGTTGGACTTCTCTCT-3' (nt253-271) and P1000, 5'-GCAANCCCM AAA GRC-CCAC-3' (nt1000-1019). The primers were synthesised by the Yingjun Biotechnology Company (Shanghai, China). The PCR products were sequenced with an ABI 3730XL sequencer using the bi-directional method. The sequencing results were spliced and corrected by Contig Express and Bioedit software. The spliced and corrected sequencing results were submitted to the Stanford University webpage for antiviral resistance and genotypic resistance location analysis (http://www.hiv-grade.de/hbvgrade/deployed/).

### Assessment of liver and renal functions

The parameters of the liver and renal biochemical profiles, such as alanine aminotransferase, aspartate aminotransferase, total bilirubin, albumin, blood urea nitrogen, and creatinine (Cr) levels, were tested with an Olympus automatic biochemical analyser (Olympus AU640, Tokyo, Japan). The prothrombin time (PT) was measured using a blood coagulation analyser (Ael Top; Beckman Coulter, CA, United States). The Child-Pugh scores were calculated according to the parameters.

### HCC screening

The incidence of HCC was monitored by serum alpha fetoprotein (AFP) and liver ultrasonography every 3 mo in the HBV-related DCPs. HCC was diagnosed according to the criteria suggested by the Chinese Anticancer Association in 2001[25]. In brief, the diagnostic criteria for HCC were as follows: (1) AFP > 400 ng/mL and positive-B-ultrasound and CT findings or (2) serum AFP < 400 ng/mL, positive-B-ultrasound and CT findings, and pathological findings for HCC in a liver biopsy specimen. The serum AFP levels were tested by electrochemiluminescence (Abbott Ltd, IL, United States).

### Study endpoints

The study endpoints were considered to be patient death, liver transplantation, or diagnosis with HCC.

### Statistical analysis

Parametric data were expressed as the mean with SD when a normal distribution was assumed. The statistical analysis was conducted using SPSS (version 16.0; SPSS, Inc., Chicago, IL, United States). Logistic regression analysis was performed to evaluate the association of variables with liver failure, death, and HCC. The Kaplan-Meier method was used to estimate the cumulative incidence of HCC, liver failure, and cumulative survival and compared with the log-rank test. Categorical variables were analysed using the Fisher test. Differences between paired and unpaired samples were determined with the non-parametric Wilcoxon paired sample test, the Mann-Whitney U test, or the Kruskal-Wallis test. All tests were two-sided, and a P value < 0.05 was considered statistically significant.

### RESULTS

#### Clinical characteristics

No differences in the gender, age, family history of hepatitis B or HCC, alcohol abuse, Child-Pugh score, HBeAg positivity, HBV DNA load, renal function, or the presence of ascites, encephalopathy, or variceal bleeding existed among each group at baseline (P > 0.05; Table 2). The Child-Pugh score of the CVR group was significantly decreased at 2 years, compared with the baseline (8.9 ± 2.3 vs 6.0 ± 1.3, P = 0.043). In the control group and
DR patients, however, the Child-Pugh score showed an increasing trend at 2 years without significance \((P > 0.05)\). Compared with the DR and control groups, the serum HBV DNA level during the course of antiviral therapy over 2 years in the CVR group declined sharply and was maintained at an undetectable level (Figure 2).

Incidence of HCC
The two-year cumulative incidence of HCC in the DR patients (30.6%) was significantly higher than that in both the CVR patients (4.3%) and control group (10.3%) \((P < 0.001)\). Among these DR patients, the incidence of HCC was 55.6% \((5/9)\) in those who failed rescue therapy, which was extremely high. The Kaplan-Meier curves representing the incidence of HCC in the DR, CVR, and control groups are shown in Figure 3A and B. The 2-year cumulative incidence of HCC in the DR group was higher than in the CVR \((RR = 7.1; 95\% CI: 2.2-16.1; P < 0.001)\) and control groups \((RR = 3.0; 95\% CI: 1.3-9.5; P = 0.042)\). However, there was no difference in the two-year cumulative HCC incidence between the patients who received antiviral therapy and the controls \((P = 0.805)\). The mutations associated with HBV polymerase-related antiviral drug resistance are shown in Table 3. The rtA181T mutation was closely associated with rescue therapy failure \((P = 0.006)\). The mutation combination rate in the subgroup of failed rescue therapy was markedly higher than that in the subgroup of successful rescue therapy \((66.7\% \text{ vs } 11.1\%, P = 0.004)\).

Prognosis
The cumulative survival rates in the DR, CVR and control groups were 88.9% \((32/36)\), 96.9% \((157/162)\), and 84.6% \((33/39)\), respectively. No significant difference was observed in the two-year cumulative survival between the DR and CVR groups \((P = 0.059)\) (Figure 3C). There was no significant difference between the subgroups of failed rescue therapy and successful rescue therapy \((77.8\% \text{ vs } 92.6\%, P = 0.221)\) (Figure 3D). The cumulative incidence of liver failure in the DR, CVR and control groups was 5.6% \((2/36)\), 0.6% \((1/162)\), and 28.2% \((11/39)\), respectively. The two-year cumulative incidence of liver failure in the CVR group was significantly lower than those in the DR \((RR = 9.0, 95\% CI: 2.8-34.5, P < 0.001)\) and control \((RR = 45.69, 95\% CI: 13.8-96.4, P < 0.001)\) groups (Figure 3E). However, there was no significant difference between the subgroups of failed rescue therapy and successful rescue therapy \((11.1\% \text{ vs } 3.7\%, P = 0.401)\) (Figure 3F). These results suggested that the CVR patients had a good prognosis.

DISCUSSION
HBV infection remains a global public health problem. The geographic distribution of the rates of chronic HBV infection and HCC are strikingly parallel. The incidence and mortality of HBV-related cirrhosis and HCC, however, have increased significantly\[^{[1,23]}\]. The clinical evidence clearly shows that the differences in clinical outcomes after HBV infection might be related to the HBV DNA level, antiviral treatment response, and immune activation\[^{[22-24]}\]. All guidelines for the prevention and treatment of chronic hepatitis B in China and in other countries state that the main aim of the treatment for chronic hepatitis B is to reduce the incidence and death rate of cirrhosis and liver cancer, to prolong life, and to improve the quality of life\[^{[15,25]}\]. For patients with liver cirrhosis, especially those in the compensation period, the clinical outcomes after antiviral therapy with nucleoside analogues are unclear\[^{[26,27]}\]. NUCs are effective drugs for the suppression of HBV reproduction, and compliance is good amongst most chronic hepatitis B patients, especially those with HBV-related cirrhosis. Failure of the antiviral treatment and drug resistance are serious factors for liver disease progression and for increases in the incidence of liver cancer\[^{[28]}\]. Bae et al\[^{[24]}\] reported that 58.2% of patients showed complete antiviral responses using LAM in decompensated HBV-related cirrhosis, which can improve the clinical prognosis. A single randomised double-blind controlled trial of LAM in patients with HBeAg and/or high serum HBV DNA levels showed that antiviral therapy prevented disease progression and reduced the incidence of HCC\[^{[29]}\]. Several studies have shown that the failure of the antiviral treatment of chronic hepatitis B or drug resistance increases the risk of liver cirrhosis and liver cancer and also causes the progression of...
Recently, a beneficial effect of antiviral therapy on the risk of HCC was also shown in cohort studies and meta-analyses, particularly among responders. A greater effect was observed in patients who achieved a sustained virologic response, whereas the benefit in non-responders was unclear\cite{12,17,22}. In this study, we found that antiviral therapy patients with a CVR response may show significantly improved liver function. The Child-Pugh score in the CVR group was significantly decreased over 2 years. In the drug-resistance group, however, the
Table 3 Comparison of drug-resistant mutations between successful and failed rescue therapy $n$ (%)

| Mutations                  | Successful rescue therapy ($n = 27$) | Failed rescue therapy ($n = 9$) | $P$ value |
|----------------------------|--------------------------------------|---------------------------------|-----------|
| rtM204V                    | +                                    | 1 (3.7)                         | 26 (96.3) | 8 (88.9) | 0.443   |
|                           | -                                    | 26 (96.3)                       |           |          |         |
| rtM204I                    | +                                    | 4 (14.8)                        | 23 (85.2) | 6 (66.7) | 0.333   |
|                           | -                                    | 25 (92.6)                       |           |          |         |
| rtA181T                    | +                                    | 2 (7.4)                         | 25 (92.6) | 4 (44.4) | 0.255   |
|                           | -                                    | 25 (92.6)                       |           |          |         |
| rtL180M                    | +                                    | 2 (7.4)                         | 25 (92.6) | 4 (44.4) | 0.255   |
|                           | -                                    | 25 (92.6)                       |           |          |         |
| rtL80I                     | +                                    | 0 (0)                           | 27 (100)  | 2 (22.2) | 0.057   |
|                           | -                                    | 27 (100)                        |           |          |         |
| rtN236T                    | +                                    | 0 (0)                           | 27 (100)  | 0 (0)    | 0.057   |
|                           | -                                    | 27 (100)                        |           |          |         |
| rtT184I                    | +                                    | 0 (0)                           | 27 (100)  | 1 (11.1) | 0.250   |
|                           | -                                    | 27 (100)                        |           |          |         |
| rtS202G                    | +                                    | 1 (3.7)                         | 26 (96.3) | 0 (0)    | 1.000   |
|                           | -                                    | 26 (96.3)                       |           |          |         |
| rtA181T + rtM204I          | +                                    | 1 (3.7)                         | 26 (96.3) | 1 (11.1) | 0.443   |
|                           | -                                    | 26 (96.3)                       |           |          |         |
| rtA181T + rtL180M          | +                                    | 1 (3.7)                         | 26 (96.3) | 0 (0)    | 1.000   |
|                           | -                                    | 26 (96.3)                       |           |          |         |
| rtM204V + rtL180M          | +                                    | 1 (3.7)                         | 26 (96.3) | 0 (0)    | 1.000   |
|                           | -                                    | 26 (96.3)                       |           |          |         |
| rtA181T + rtN236T          | +                                    | 0 (0)                           | 27 (100)  | 2 (22.2) | 0.057   |
|                           | -                                    | 27 (100)                        |           |          |         |
| rtA181T + rtL80I           | +                                    | 0 (0)                           | 27 (100)  | 1 (11.1) | 0.250   |
|                           | -                                    | 27 (100)                        |           |          |         |
| rtA181T + rtM204I + rtT184I| +                                    | 0 (0)                           | 27 (100)  | 1 (11.1) | 0.250   |
|                           | -                                    | 27 (100)                        |           |          |         |
| rtM204I + rtL180M + rtL80I | +                                    | 0 (0)                           | 27 (100)  | 1 (11.1) | 0.250   |
|                           | -                                    | 27 (100)                        |           |          |         |

+: DR mutations positive; -: DR mutations negative; DR: Drug resistance.

Successful rescue therapy could be a better prescription for NUC-resistant HBV patients in this cohort study. In this study, the rtA181T mutation was found to be closely associated with rescue therapy failure, which may be related to the high incidence of HCC in patients with antiviral drug-resistance. Yeh et al. reported that the emergence of the rtA181T/sW172 mutation in the LAM-resistant patients increased the risk of HCC development during the subsequent courses of antiviral therapy. In this cohort study, we also found that the 2-year cumulative incidence of HCC was 22.2% in the successful rescue therapy group and 55.6% in the failed rescue therapy group among the DR patients. Therefore, we conclude that effective antiviral therapies might have benefits and a good prognosis for decompensated HBV-related cirrhosis. However, we observed an increased incidence of HCC in the patients with antiviral drug-resistance. The aetiology for carcinogenesis is still being studied.

Therefore, the maintenance of virologically persistent remission is important for the reduction of HCC risk in DCPs. More effective and more affordable antiviral therapies are needed for patients with HBV-related decompensated cirrhosis to ensure that more patients could benefit from the treatment and more HCCs could be prevented, which might have a major impact on the global incidence of HCC.

In conclusion, a complete virological response should reduce the incidence of HCC and improve the clinical outcomes in decompensated cirrhosis cohort patients. However, clinicians should be aware of the extremely high risk of HCC and liver failure in antiviral drug-resistant patients or in those not treated with antiviral therapy.

COMMENTS

**Background**

The decompensated cirrhosis is the end stage of the disease and is characterised by high mortality and an extremely high risk of hepatocellular carcinoma (HCC). In HBV-related decompensated cirrhotic patients (DCPs), antiviral therapy using nucleos(t)ide analogues (NUCs) is recommended according to the 2005 global guidelines. The antiviral therapy remains the best strategy to prevent liver cirrhosis and HCC in chronic hepatitis B patients. However, clinical data regarding the incidence of HCC in HBV-related DCPs with NUCs antiviral therapies are limited.

**Research frontiers**

Some cohort studies and meta-analyses have shown a beneficial effect of antiviral therapy on the risk of HCC, particularly among responders. A greater effect was observed in patients who achieved a sustained virologic response, whereas the benefit in non-responders is unclear, especially in those DCPs.

**Innovations and breakthroughs**

This study revealed that, in decompensated cirrhotic patients, a complete virologic response (CVR) should reduce the incidence of hepatocellular carcinoma and improve the clinical outcomes in decompensated hepatitis B cirrhotic patients. However, in those with antiviral drug resistance the risk of HCC increased, especially in those who failed rescue therapy.

**Applications**

From this study, it is suggested that the maintenance of virologically persistent remission is important for the reduction of HCC risk in DCPs. The clinicians should be aware of the extremely high risk of HCC and liver failure in antiviral drug-resistant patients. Therefore, more effective and more affordable antiviral therapies are needed for patients with HBV-related decompensated cirrhosis to ensure that more patients could benefit from the treatment and more HCC could be prevented.
Terminology
A CVR was defined as HBV-DNA being undetectable and persistently negative during the antiviral therapy for two years.

Peer review
This is a large single centre prospective cohort study based on real life clinical practice aimed to evaluate the relationship between drug-resistance and the outcome of liver disease.

REFERENCES
1. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009; 50: 661-662 [PMID: 19714720 DOI: 10.1002/hep.23190]
2. Liaw YF, Leung N, Kao JH. Prevention of hepatocellular carcinoma in patients with chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol 2010; 53: 348-356 [PMID: 20483498 DOI: 10.1016/j.jhep.2010.02.035]
3. European Association for The Study of The Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol 2009; 50: 227-242 [PMID: 19054588 DOI: 10.1016/j.jhep.2008.10.001]
4. Committee of Liver Cancer, Chinese Anti-cancer Association. The clinical diagnosis and staging criteria of primary liver cancers. Chin J Hepatol 2001; 9: 324-328
5. Ohishi W, Chayama K. Treatment of chronic hepatitis B with nucleos(t)ide analogues. Hepatol Res 2012; 42: 219-225 [PMID: 22176139 DOI: 10.1111/j.1872-034X.2011.00992.x]
6. Di Marco V, Di Stefano R, Ferraro D, Almasio PL, Bonura C, Giglio M, Parisi P, Cappello M, Alaimo G, Craxi A. HBV-DNA suppression and disease course in HBV cirrhosis patients on long-term lamivudine therapy. Antivir Ther 2005; 10: 431-439 [PMID: 15918354]
7. Bae SH, Yoon SK, Choi JY, Jang JW, Cho SH, Yang JM, Han NI, Ahn BM, Chung KW, Sun HS. Timing of lamivudine administration according to Child class in patients with decompensated cirrhosis. J Gastroenterol Hepatol 2005; 20: 1527-1532 [PMID: 16174069]
8. European Society for the Study of the Liver. EASL clinical practice guidelines: management of chronic hepatitis B. J Hepatol 2012; 57: 167-185 [PMID: 22436845 DOI: 10.1016/j.jhep.2012.02.010]
9. Das K, Das K, Datta S, Pal S, Hembram JR, Dhali GK, Santra A, Chowdhury A. Course of disease and survival after onset of decompensation in hepatitis B virus-related cirrhosis. Liver Int 2010; 30: 1033-1042 [PMID: 20492502 DOI: 10.1111/j.1478-3231.2010.02255.x]
10. Manolakopoulos S, Triantos C, Theodoropoulos J, Vlachogiannakos J, Kougiontuzan A, Papatheodoridis G, Tzourmakiotis D, Karamanolis D, Burroughs AK, Archimandritis A, Raptis S, Avgerinos A. Antiviral therapy reduces portal pressure in patients with cirrhosis due to HBsAg-negative chronic hepatitis B and significant portal hypertension. J Hepatol 2009; 51: 468-474 [PMID: 19616339 DOI: 10.1016/j.jhep.2009.05.031]
11. Zoulim F. Hepatitis B virus resistance to antiviral drugs: where are we going? Liver Int 2011; 31 Suppl 1: 111-116 [PMID: 21205148 DOI: 10.1111/j.1478-3231.2010.02388.x]
12. Zhang QQ, An X, Liu YH, Li SY, Zhong Q, Wang J, Hu HD, Zhang DZ, Ren H, Hu P. Long-term nucleos(t)ide analogues therapy for adults with chronic hepatitis B reduces the risk of long-term complications: a meta-analysis. Virology 2011; 8: 72 [PMID: 21324130 DOI: 10.1186/1743-422X-8-72]
13. Jin YJ, Shihm JH, Lee HC, Yoo DJ, Kim KM, Lim YS, Suh DJ. Suppressive effects of entecavir on hepatitis B virus and hepatocellular carcinoma. J Gastroenterol Hepatol 2011; 26: 1380-1388 [PMID: 21884247 DOI: 10.1111/j.1440-4446.2011.06776.x]
14. Lim SG, Aung MO, Mak B, Sutesda J, Lee YM, Lee GH, Fernandez M, Low HC, Lai V, Dan YY. Clinical outcomes of lamivudine-adefovir therapy in chronic hepatitis B cirrhosis. J Clin Gastroenterol 2011; 45: 818-823 [PMID: 21921845 DOI: 10.1097/MCG.0b013e318214ab5d]
15. Tufios SR, Lee WM. New advances in chronic hepatitis B. Curr Opin Gastroenterol 2012; 28: 193-197 [PMID: 22450894 DOI: 10.1097/MOG.0b013e3283572e7c]
16. Yeh CT, Chen T, Hsu CW, Chen YC, Lai MW, Liang KH, Chen TC. Emergence of the rtA181T/sW172* mutant increased the risk of hepatoma occurrence in patients with lamivudine-resistant chronic hepatitis B. BMC Cancer 2011; 11: 398 [PMID: 21933446 DOI: 10.1186/1471-2407-11-398]
17. Papatheodoridis GV, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. J Hepatol 2010; 53: 114-121 [PMID: 20483498 DOI: 10.1016/j.jhep.2010.02.035]
18. Chinese Medical Association. The guidelines of prevention and treatment for chronic hepatitis B. Zhonghua Ganzangbing Za Zhi 2005; 13: 881-891 [PMID: 16491521]
19. Jhaiveri R, Murray N. An omission in the AASLD Practice Guidelines on Chronic Hepatitis B. Hepatology 2007; 46: 280; author reply 280 [PMID: 17596892]
20. European Association For The Study of The Liver. EASL Clinical Practice Guidelines: management of chronic hepatitis B. J Hepatol 2009; 50: 227-242 [PMID: 19054588 DOI: 10.1016/j.jhep.2008.10.001]
chronic hepatitis B resistant to lamivudine and adefovir. *J Hepatol* 2010; 53: 449-454 [PMID: 20646776 DOI: 10.1016/j.jhep.2010.03.020]

31 Shim JH, Lee HC, Kim KM, Lim YS, Chung YH, Lee YS, Suh DJ. Efficacy of entecavir in treatment-naïve patients with hepatitis B virus-related decompensated cirrhosis. *J Hepatol* 2010; 52: 176-182 [PMID: 20006394 DOI: 10.1016/j.jhep.2009.11.007]

32 Singal AK, Fontana RJ. Meta-analysis: oral anti-viral agents in adults with decompensated hepatitis B virus cirrhosis. *Aliment Pharmacol Ther* 2012; 35: 674-689 [PMID: 22257108 DOI: 10.1111/j.1365-2036.2011.04990.x]

33 Papatheodoridis GV, Manolakopoulos S, Touloumi G, Vourli G, Raptopoulou-Gigi M, Vafiadis-Zoumbouli I, Vasiliadis T, Mimidis K, Gogos C, Ketikoglou I, Manesis EK. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEIPNET Greece cohort study. *Gut* 2011; 60: 1109-1116 [PMID: 21270118 DOI: 10.1136/gut.2010.221846]

34 Kim HJ, Park JH, Park DJ, Cho YK, Sohn CI, Jeon WK, Kim BI. Rescue therapy for lamivudine-resistant chronic hepatitis B: comparison between entecavir 1.0 mg monotherapy, adefovir monotherapy and adefovir add-on lamivudine combination therapy. *J Gastroenterol Hepatol* 2010; 25: 1374-1380 [PMID: 20659226 DOI: 10.1111/j.1440-1746.2010.06381.x]

35 Ha M, Zhang G, Dao S, Lin M, Wu J, Sun L, She H, Shen L, Huang C, Shen W, Huang Z. Rescue therapy for lamivudine-resistant chronic hepatitis B: adefovir monotherapy, adefovir plus lamivudine or entecavir combination therapy. *Intern Med* 2012; 51: 1509-1515 [PMID: 22728482]

P- Reviewers: Kodama EN, Lai Q, Romero MR
S- Editor: Cui XM L- Editor: O’Neill M E- Editor: Wang CH
