ISSN: 2469-584X

Lu et al. J Clin Gastroenterol Treat 2019, 5:067
DOI: 10.23937/2469-584X/1510067
Volume 5 | Issue 1
Open Access

Journal of
Clinical Gastroenterology and Treatment

RESEARCH ARTICLE

Lamivudine in the Prevention of Hepatitis B Virus Reactivation after Chemotherapy in Cancer Patients

Yanda Lu[1,2], Donghua Xie[3], Wei Huang[4], Heyi Gong[4], Qiuhe Song[5] and Jinming Yu[4]*

[1]*Third People's Hospital of Jiujiang City, Jiujiang, China*

[2]*Department of Oncology, The First Affiliated Hospital of Hainan Medical College, Hainan Province, China*

[3]*Dade County Urologist LLC, Florida, USA*

[4]*Cancer Prevention and Treatment Research Institute in Shandong Province, Jinan, China*

[5]*The Affiliated Hospital of Jiujiang Medical College, Jiujiang, Jiangxi Province 332000, China*

***Corresponding author:** *Jinming Yu, Cancer Prevention and Treatment Research Institute, Jinan, Shandong 250117, China, Tel: (011-86)-0531-87984777, Fax: (011-86)-0531-87984079*

Abstract

Background and aim: To investigate the role of lamivudine in preventing hepatitis B virus (HBV) reactivation after chemotherapy in patients with tumors.

Methods: 43 cases of HBV carriers were divided into control group (n = 22) and prevention group (n = 21) accordingly to disease type. The two groups received chemotherapy at standard dose intensity. For the prevention group lamivudine 100 mg/d was added. Liver function, HBV markers, and HBV-DNA level were tested for every patient before and after chemotherapy.

Result: Control group of 22 patients completed three to six (average 3.85) cycles of chemotherapy, of which dose adjustment 2, delayed chemotherapy 5, suspension of chemotherapy 3, totaling 12 cases (54.6%); prevention group of 21 patients completed chemotherapy 5 to 6 (average 5.63) cycles, of which dose adjustment 2, delayed chemotherapy 2, totaling 4 cases (19.1%). There was an increase of HBV-DNA positive rate in the control group in the course of chemotherapy; it was 81.8%, 86.4%, 86.4%, and 90.9% at 4, 8, 16, 24 weeks, respectively; in the prevention group HBV-DNA conversion rate was 40.0%, 53.3%, 66.7%, and 80.0% at 4, 8, 16, 24 weeks, respectively. Reactivation rate in the control group was 45.5% while in the prevention group was 9.5%. There was a significant difference between the two groups in completion of chemotherapy, dynamic change of HBV-DNA level, and HBV reactivation ($P < 0.01$, $P < 0.01$, and $P < 0.05$, respectively).

Conclusion: Use of lamivudine can prevent HBV reactivation to a certain extent and then ensure the smooth progress of chemotherapy.

Keywords

Lamivudine, Hepatitis B virus, Reactivation, Cancer, Chemotherapy

Introduction

China is a high prevalence area for hepatitis B virus (HBV) infection, and cancer patients with HBV infection are common. After cytotoxic drugs or immunosuppressive drugs treatment in HBV carriers, reactivation phenomenon occurs; resulting in enhanced HBV replication; causing liver injury. With chemotherapy in cancer therapy widely used, HBV reactivation is becoming a common clinical problem and arouses people's attention. Application of preventive antiviral drugs can avoid or reduce HBV re-activation; so as to ensure the smooth progress of chemotherapy; however, there are not enough related reports in the literature. This study was designed to observe the preventive role of lamivudine in HBV reactivation in patients after cancer chemotherapy.

Patients and Methods

General data

The 43 cases were cancer patients in the Oncology Center of Third People's Hospital of Jiujiang City from June 2005 to June 2010. They were confirmed of cancer

Citation: Lu Y, Xie D, Huang W, Gong H, Song Q, et al. (2019) Lamivudine in the Prevention of Hepatitis B Virus Reactivation after Chemotherapy in Cancer Patients. J Clin Gastroenterol Treat 5:067. doi.org/10.23937/2469-584X/1510067

Accepted: June 19, 2019: **Published:** June 21, 2019

Table 1: Clinical data comparison for 2 groups of patients.

	Prevention Group	Control Group
Case Number	21	22
Male	8	9
Female	13	13
Age (year)	45.9	47.3
Tumor Type		
Non-Hodgkin's lymphoma	6	6
Breast Cancer	4	4
Non-small cell lung cancer	4	5
Small cell lung cancer	2	1
Colorectal cancer	2	3
Stomach cancer	2	2
Ovarian cancer	1	1
Tumor Stage		
II	8	8
III	7	8
IV	6	6
Before chemotherapy		
HBeAg (+)	12	14
HBeAg (-)	9	8
ALT (U/L)	30.49 ± 8.62	31.25 ± 9.14
TSB (μmol/L)	16.51 ± 4.68	15.03 ± 5.17
HBV-DNA (+)	71.4% (15/21)	72.7% (16/22)
Serum HBV-DNA levels (after a Log conversion)	3.47 ± 1.82	3.39 ± 1.73

diseases by histopathology and were admitted to the hospital for chemotherapy. Included were non-Hodgkin's lymphoma, 12 cases; breast cancer, 8 cases; non-small cell lung cancer (NSCLC), 9 cases; small cell lung cancer, 3 cases; colorectal cancer, 5 cases; gastric cancer, 4 cases; ovarian cancer, 2 cases. There was no liver metastasis. Chemotherapy regimens are CHOP (cytoxan, doxordbicin, vincristine, prednisone); FAC (5-fluorouracil, doxordbicin, cytoxan), NP (navelbine, cisplatin), TP (taxol, cisplatin), GP (gemcitabine, cisplatin), EP (etoposide, cisplatin), FOLFOX (5-fluorouracil, leucovorin, oxaliplatin), and so on. All 43 cases are HBV carriers who meet with the standard of people living with chronic HBV infection according to "Guidance for chronic hepatitis B prevention and treatment" [1]. These cases are divided into disease control or prevention group. There was no significant difference between 2 groups in gender, age, chemotherapy regimen, liver function and serum HBV-DNA (Table 1).

Treatment

Both groups were treated with chemotherapy by using the dose of standard intensity. The control group was treated with conventional regimen such as glutathione to protect liver. For the prevention group lamivudine 100 m/d was added in addition to the medications in the control group, from seven days before the start of chemotherapy to a month after the end of the chemotherapy. To observe the dynamic change of HBV-DNA level and the incidence of HBV reactivation, liver function, HBV markers, and HBV-DNA quantitative level were tested for every patient every time before and after chemotherapy. Chemotherapy dose adjustment or withdrawal was needed when serum total bilirubin (TSB) ≥ 2~4 constant high limit (ULN), alanine aminotransferase (ALT) ≥ 2~5 ULN, HBV DNA determination.

All specimens were studied by a single person under the same conditions. Liver function tests were done by using Olympus AU640 automatic biochemical analyzer. HBV markers were detected by Enzyme-Linked ImmunoSorbent Assay (ELISA) in accordance with the manual. The kits were provided by the Beijing the Fourth Ring Biotechnology Plant. Serum HBV DNA levels were detected by a fully automated ABI-fluorescence quantitative PCR analysis. The value threshold is < 103 copies/ml.

Definition of HBV reactivation

According to the diagnostic criteria made by Yeo [2], hepatitis occurs during or immediately after a cytotoxic chemotherapy accompanied by HBV-DNA level not less than 10-fold increase, or if absolute value is up to 1 × 109 copies/m1 or higher, can be diagnosed as HBV reactivation after ruling out other infections.

Statistical analysis

Statistical analysis was performed by using SPSS12.0 data analysis software, count data were compared by using x^2 test, measurement data were compared by using t test, serum HBV-DNA level was compared as measurement data by using t-test after a logarithm (Log) conversion.

Results

Completion of chemotherapy

22 cases in the control group completed 3 to 6 cycles of chemotherapy, an average of 3.85 cycles, of which dose adjustment, 4 cases; delayed chemotherapy, 5 cases; suspension of chemotherapy, 3 cases; totaling 12 cases (54.6%). Among the 12 cases, non-Hodgkin's lymphoma 5/6 cases (83.3%), breast cancer 2/4 cases (50.0%), stomach 1/2 cases (50.0%), NSCLC 2/5 cases (40.0%), colorectal cancer 1/3 cases (33.3%), ovarian cancer 1/1 case (100.0%), respectively. Of prevention group, all 21 cases completed 5 to 6 cycles of chemotherapy, an average of 5.63 cycles, of which dose adjustment, 2 cases; delayed chemotherapy, 2 cases; suspension of chemotherapy, 0 cases; the total 4 cases (19.1%). Among the 4 cases, non-Hodgkin's lymphoma 1/6 cases (16.7%), breast cancer 1/4 cases (25.0%), colorectal cancer 1/3 cases (33.3%), non-small cell lung cancer 1/5 cases

Table 2: The dynamic change HBV-DNA level of the two groups in the course of chemotherapy (after a Log conversion).

	Before Chemotherapy	4 weeks	8 weeks	16 weeks	24 weeks
Control Group	3.39 ± 1.73 (n = 16)	4.13 ± 1.81 (n = 18)	4.27 ± 1.54 (n = 19)	5.02 ± 2.16 (n = 19)	5.19 ± 1.77 (n = 20)
Prevention Group	3.47 ± 1.82 (n = 15)	3.53 ± 1.69 (n = 9)	3.59 ± 1.41 (n = 7)	3.64 ± 1.19 (n = 5)	3.75 ± 1.20 (n = 3)

(20.0%), respectively. There was a very significant difference ($P < 0.01$) between the two groups.

Dynamic change of HBV-DNA level in the course of chemotherapy

There was no one case of conversion in the course of chemotherapy for patients who were HBV-DNA positive in the control group, on the contrary positive rate was increased after chemotherapy. It was 81.8% (18/22), 86.4% (19/22), 86.4% (19/22), 90.9% (20/22) at 4, 8, 16, 24 weeks after initiating chemotherapy, respectively. After 4 weeks of chemotherapy HBV-DNA level was gradually increased, compared with the level before chemotherapy and there was a significant difference ($P < 0.05$). In prevention group HBV-DNA conversion rate was 40.0% (6/15), 53.3% (8/15), 66.7% (10/15), 80.0% (12/15) at 4 weeks, 8 weeks, 16 weeks, and 24 weeks after initiating chemotherapy, respectively. There was no significant increase in its level for patients who were HBV-DNA positive. There was a very significant difference between the two groups ($P < 0.01$) (Table 2).

Incidence of HBV reactivation in two groups in the course of chemotherapy

Preventive application of lamivudine significantly reduced the rate of HBV re-activation. The rate of HBV re-activation in the prevention group was 9.5% (2/21), non-Hodgkin's lymphoma, breast cancer one case each, respectively. The rate of reactivation in the control group was 45.5% (10/22) in which non-Hodgkin's lymphoma 4/6 cases (66.7%), breast cancer 2/4 cases (50.0%), NSCLC 2/5 cases (40.0%), colorectal cancer 1/3 cases (33.3%), ovarian cancer 1/1 case (100.0%). There was a significant difference between the two groups ($P < 0.05$). There were 3 cases severe hepatitis occurred in the control group with two cases of non-Hodgkin's lymphoma patients receiving CHOP chemotherapy, and one case of breast cancer patient receiving chemotherapy on FAC regimen. No occurrence in the treatment group. There was no occurrence of severe hepatitis in patients with gastrointestinal cancer in either group.

Side effect of lamivudine

All 21 patients in the prevention group had long-term tolerance to this drug, no toxic reaction was noted.

Discussion

Hepatitis B virus re-activation is HBV replication during the treatment for patients with chronic HBV infection which can lead to liver cell continuous necrosis and gradual decline of liver function and ultimately produce varying degrees of damage to the liver. For patients with mild symptoms, they present as hepatitis symptoms; for patients with serious symptoms, they present as fulminant hepatic failure. HBV reactivation may occur in the course of chemotherapy or after the end of the chemotherapy course. As reported in the literature [3] in the past 10 years, the HBV re-activation rate was rising in patients with solid tumors, the re-activation rate was 60 percent in patients with hepatocellular carcinoma, HBV reactivation rate was 25% to 40% in patients with other cancers patients. The re-activation rate over 50 percent in patients received hematopoietic stem cell transplantation. Although HBV re-activation can be resolved after treatment in some patients, but abnormal liver function and increased level of HBV DNA often make anti-cancer therapy delayed or even suspended, and possibly jeopardize the prognosis of patients. The studies show that patients with breast cancer, in HBV reactivation and the need for chemotherapy or interruption of treatment for affected patients over 70 percent, not a re-activation of HBV patients, only 30 percent need to interrupt or affect chemotherapy treatment programme [4].

The mechanism HBV re-activation in cancer patients after chemotherapy is not yet entirely clear probably due to: (1) Chemotherapy drugs are mostly cytotoxic drugs and immunosuppressants, can lead to a certain degree of liver damage, which may become the initiating factor, breaking down the immune tolerance status inside the liver cells. For example, *in vitro* experiments show that anthracycline antibiotics can stimulate the 2.2.15 cell (source from HepG2 cell) to secrete HBV DNA in a dose-dependent model [5]. Also as reported, HBV DNA contains a glucocorticoid reflecting component. This component can promote HBV replication. Thus glucocorticoid and anthracycline antibiotics are the most common HBV reactivation -related drugs [6]. Study confirmed that cytotoxic chemotherapy regimen including glucocorticoid in patients with positive HBsAg results in significantly higher HBV reactivation than the patients without glucocorticoid treatment. (2) Chemotherapy drug can induce extreme, long-lasting B and T cell depletion, although dissolution of the liver cells infected with HBV is mediated by the CD8 + cytotoxic T-cells. B-cell can also be used as antigen presenting cells which initiate the cytotoxic T-lymphocytes specific response in HBV infection [7], leading to inflammatory necrosis of liver cells. (3) Tumor necrosis after chemotherapy leads

to the release of more tumor necrosis factor which is one of the major media of liver cell injury aggravation including liver necrosis.

Twenty two cases in the control group were cancer patients carrying HBV, 10 cases with HBV reactivation after chemotherapy, HBV reactivation rate was 45.5 percent, of which six cases of non-Hodgkin's lymphoma patients HBV re-activation in four cases, four cases of breast cancer patients appear to have HBV re-activation in two cases, HBV reactivation rates were 66.7 percent, 50.0 percent, respectively, significantly higher than other cancer patients, which may be related to chemotherapy regimens containing anthracycline drugs or glucocorticoid. This study indicated that non-Hodgkin's lymphoma and breast cancer are risk factors for activation of HBV which is similar to report in literature [8].

As the incidence of HBV reactivation inevitably interferes with the anti-tumor treatment and delay or even termination of chemotherapy. Therefore, prevention may be more meaningful than treatment for HBV carriers who need chemotherapy. Nucleoside analogue lamivudine is recognized currently as one of the effective anti-HBV drugs which suppresses hepatitis B virus replication through one of the following two mechanisms: (1) Through the integration to a new synthesis of HBV DNA and leads to the termination of its replication. (2) Competitive inhibition of DNA polymerase coding by HBV. Virus replication appears before hepatitis symptoms after chemotherapy in cancer patients with HBV infection, and provides a basis for preventive application of lamivudine. In a prospective study Lau and others reported [9] that 30 lymphoma patients receiving chemotherapy were randomly divided into 2 groups; one group was given a preventive application of lamivudine; the other group was given lamivudine when there was evidence of serum HBV reactivation. The former approach can significantly reduce the incidence of HBV reactivation (0% and 53%), and can significantly improve the survival rate of virus reactivation-free hepatitis. However, long-term use of lamivudine can lead to danger of drug resistance.

In this study 21 of 43 patients received lamivudine preventive anti-viral treatment in the course of chemotherapy; two cases of HBV reactivation phenomenon were observed and reactivation rate was 9.5 percent. These 21 patients completed 5 to 6 cycles of unsuspended chemotherapy. There was dosage adjustment in two cases, delayed chemotherapy in two cases for a total of four cases (19.1%). With 22 patients in the control group with a rate of reactivation of 45.5% (10/22) and completion 3 to 6 cycles of chemotherapy, there was dosage adjustment in four cases, delayed chemotherapy in five cases, suspension of chemotherapy in three cases, totaling 12 cases (54.6%), There are significant differences between the two groups which confirmed that lamivudine can, to a certain extent, prevent HBV reactivation to ensure the smooth progress of chemotherapy. However, when to start using lamivudine, the duration of application, and the treatment after drug resistance and other issues remain to be further explored.

References

1. Chinese Society of Hepatology, Chinese Medical Association: Chinese Society of Infectious Diseases, Chinese Medical Association (2005) The guideline of prevention and treatment for chronic hepatitis B. Zhonghua Gan Zang Bing Za Zhi 13: 881-891.
2. Yeo W, Chan PK, Zhong S, Ho WM, Steinberg JL, et al. (2000) Frequency of hepatitis B virus reactivation in cancer patients undergoing cytotoxic chemotherapy: A prospective study of 626 patients with identification of risk factors. J Med Virol 62: 299-307.
3. Yeo W, Johnson PJ (2006) Diagnosis, prevention and management of hepatitis B virus reactivation during anticancer therapy. Hepatology 43: 209-220.
4. Yeo W, Chan PK, Hui P, Ho WM, Lam KC, et al. (2003) Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: a prospective study. J Med Virol 70: 553-561.
5. Hsu CH, Hsu HC, Chen HL, Gao M, Yeh PY, et al. (2004) Doxorubicin activates hepatitis B virus (HBV) replication in HBV harboring hepatoblastoma cells. A possible novel mechanism of HBV reactivation in HBV carriers receiving systemic chemotherapy. Anticancer Res 24: 3035-3040.
6. Cheng AL (1996) Steroid free chemotherapy decreases the risk of hepatitis flare up in hepatitis B virus carriers with non-Hodgkin's lymphoma. Blood 87: 1202.
7. Lazdina U, Alheim M, Nystrom J, Hultgren C, Borisova G, et al. (2003) Priming of cytotoxic T cell responses to exogenous hepatitis B virus core antigen is B cell dependent. J Gen Virol 84: 139-146.
8. Yeo W, Zee B, Zhong S, Hultgren C, Borisova G, et al. (2004) Comprehensive analysis of risk factors associating with hepatitis B virus (HBV) reactivation in cancer patients undergoing cytotoxic chemotherapy. Br J Cancer 90: 1306-1311.
9. Lau GK, Yiu HH, Fong DY, Hultgren C, Borisova G, et al. (2003) Early is superior to deferred preemptive lamivudine therapy for hepatitis B patients undergoing chemotherapy. Gastroenterology 125: 1742-1749.