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Risk factors for damaged liver function after chemotherapy in hepatitis B virus carriers with non-Hodgkin lymphoma

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ABSTRACT. The goal of this study was to investigate damaged liver function after chemotherapy in hepatitis B virus (HBV) carriers with non-Hodgkin lymphoma (NHL) and to evaluate risk factors associated with a high risk of damaged liver function. Clinical histories of 134 HBV carriers with NHL who were treated with chemotherapy were obtained and analyzed for the occurrence of damaged liver function and other related high-risk factors. Analysis showed that 76 patients (56.7%) had damaged liver function after chemotherapy: 6 patients (7.9%) had I degree, 17 patients (22.4%) had II degree, 20 patients (26.3%) had III degree, and 33 patients (43.4%) had IV degree damage. After treatment, 18 patients (23.7%) continued to receive chemotherapy according to their original schedule, 39 patients (51.3%) delayed chemotherapy, 16 patients (21.1%) stopped chemotherapy, and 3 patients (3.9%) died. Analysis of a binary multivariate logistic regression model showed

that administration of steroids was a high-risk factor for damaged liver function after chemotherapy in NHL patients. The incidence of damaged liver function after chemotherapy is high among HBV carriers with NHL; therefore, administration of steroid chemotherapy is a high-risk factor.

Key words: Chemotherapy; High-risk factors; Non-Hodgkin lymphoma

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is mainly treated with combination chemotherapy. The rate of hepatitis B virus (HBV) infection in China is 8 to 20% (Yeo et al., 2000; Yu and Yuan, 2004; Zhou et al., 2009). Chemotherapy can damage liver function in HBV-infected NHL patients, and can even endanger their lives (Sugauchi et al., 2011). Therefore, establishing prevention and control liver damage before and after chemotherapy is particularly important. This study retrospectively analyzed the occurrence of chemotherapy-induced damaged liver function in 134 HBV carriers with NHL who were treated at Xinjiang Medical University Cancer Hospital between January 2005 and December 2012. Clinical consequences of treatment were also analyzed to discern high-risk factors related to chemotherapy-induced damaged liver function in HBV-positive NHL patients. The goal of this study was to obtain information that can help prevent or reduce chemotherapy-induced liver damage in the future and ensure patient safety.

MATERIAL AND METHODS

Cases

A total of 134 HBV carriers with NHL treated at the Affiliated Tumor Hospital at Xinjiang Medical University between January 2005 and December 2012 were selected as subjects in this study. Patients had to meet certain criteria to be included in this study. First, patients had to have basically normal liver function before chemotherapy: alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin levels not exceeding 1.25 times the upper limit of normal; alkaline phosphatase and glutamyl transpeptidase levels not exceeding 2.5 times the regular upper limit; and albumin levels ≥30 g/L. Secondly, patients included in the study underwent serological examination to ensure that there was no indication of combined infection with hepatitis A and C before chemotherapy. Thirdly, imaging and clinical features of patients included did not suggest any tumor invasion into the liver before chemotherapy. Fourthly, patients in the study who did not experience damaged liver function from chemotherapy underwent at least 4 more courses of chemotherapy. Finally, patients in the study did not receive any antiviral therapeutics, such as lamivudine or interferon. This study was conducted in accordance with the Declaration of Helsinki. The Ethics Committee of the Affiliated Tumor Hospital at Xinjiang Medical University approved this study. Written informed consent was obtained from all participants.

General data

There were 134 NHL patients who met the inclusion criteria. The group included 74

males and 60 females with ages ranging from 12 to 75 years (median, 41 years). A total of 88 patients were positive for HBV surface antigen (HBsAg), HBV e antibody (HBeAb), and HBV core antibody (HBcAb), while 46 patients were positive for HBsAg, HBeAg, and HBcAb. There were 103 patients receiving their first chemotherapy treatment and 31 patients undergoing retreatment. Notably, 101 patients received anthracycline-containing drugs for chemotherapy, whereas 116 patients received hormone-containing drugs for chemotherapy (Table 1).

Table 1. Analysis of factors related to liver damage in 134 hepatitis B virus carriers with non-Hodgkin lymphoma after chemotherapy (logistic single factor analysis).

Clinical factor	No. of patients	With liver damage after chemotherapy	Without liver damage after chemotherapy	χ^2	P
Nationality				1.628	0.443
Han	75	42	33		
Wei	37	19	18		
Misc.	22	15	7		
Gender				0.000	0.992
Male	74	42	32		
Female	60	34	26		
Age				0.009	0.925
>41	71	40	31		
≤41	63	36	27		
Treatment				0.058	0.810
First treatment	103	59	44		
Re-treatment	31	17	14		
Anthracycline-based drug				14.857	0.000
Yes	101	68	43		
No	34	8	26		
Glucocorticoid				10.078	0.002
Yes	116	72	44		
No	18	4	14		
HBeAg expression				2.062	0.151
Yes	46	30	16		
No	88	46	42		

Evaluating adverse effects on the liver

The definition of damaged liver function after chemotherapy was based on relevant literature (Fermé, 2002). Damaged liver function after chemotherapy was indicated by a post-chemotherapy ALT level that was at least 3.0 times greater than the basic level and 1.25 to 2.5 times greater than the regular upper limit (50 or 100 IU/L). Damaged liver function was also indicated by a total bilirubin level 2.5 times greater than the regular upper limit (50 IU/L). Delayed chemotherapy was defined as chemotherapy that was postponed for more than 8 days due to damaged liver function. We evaluated adverse liver reactions according to the standards set by the World Health Organization. Damaged liver function was classified into the following categories based on ALT, AST, and total bilirubin levels: 0 degree (ALT, AST, or total bilirubin level ≤ 1.25 times the regular upper limit), I degree (ALT, AST, or total bilirubin level that is 1.26 to 2.50 times higher than the regular upper limit), II degree (ALT, AST, or total bilirubin level that is 2.6 to 5.0 times higher than the regular upper limit), III degree (ALT, AST, or total bilirubin level that is 5.1 to 10.0 times higher than the regular upper limit), and IV degree (ALT, AST, or total bilirubin level ≥10.1 times higher than the regular upper limit).

Statistical analysis

Multifactorial analysis was performed using the SPSS software, version 13.0 (SPSS Inc., Chicago, IL, USA), χ^2 tests, Fisher's exact probability tests, and a binary multivariate logistic regression model. $P < 0.05$ was considered to be statistically significant. Factors were screened with $\alpha = 0.05$ using a binary multivariate logistic regression model and the stepwise backward exclusion method of Wald.

RESULTS

Damaged liver function after chemotherapy

Of the 134 HBV carriers with NHL, 76 patients (56.7%) experienced damaged liver function after chemotherapy. This included 6 patients (7.9%) with I degree, 17 patients (22.4%) with II degree, 20 patients (26.3%) with III degree, and 33 patients (43.4%) with IV degree damage. The fourth chemotherapy course was the median time at which damaged liver function occurred (range, 1 to 13 courses until damaged liver function observed). A total of 57 patients (75.0%) experienced damaged liver function after 4 chemotherapy courses or fewer, whereas 19 patients (25.0%) experienced damage after 5 or more courses of chemotherapy.

Clinical outcomes after treatment

A total of 76 HBV carriers with NHL (56.7%) experienced damaged liver function after chemotherapy. After treatment of symptoms, such as liver protection, enzyme reduction, and jaundice removal, 18 patients (23.7%) continued to receive chemotherapy as originally scheduled, 39 patients (51.3%) delayed chemotherapy, 16 patients (21.1%) stopped chemotherapy, and 3 patients (3.9%) died.

High-risk factors for damaged liver function after chemotherapy

χ^2 tests or Fisher's exact tests were used to identify factors that contributed to the occurrence of damaged liver function after chemotherapy. We found that administration of anthracyclines and steroid chemotherapy drugs was related to the occurrence of damaged liver function after chemotherapy ($P < 0.05$) (Table 1). We found that steroid use was the only risk factor for damaged liver function after chemotherapy ($P = 0.006$, odds ratio = 11.050) (Table 2).

Table 2. Binary multivariate logistic analysis of risk factors that affect damaged liver function after chemotherapy in hepatitis B virus carriers with non-Hodgkin lymphoma.

Variable	Partial regression coefficient	Partial regression coefficient standard	Wald statistic	P	Relative risk	95%CI of relative risk
Constant	-0.403	1.334	0.091	0.763	0.669	
Anthracycline-based drug administration	0.312	0.395	0.625	0.429	1.366	0.630-2.963
Glucocorticoid administration	2.402	0.554	9.817	0.006	11.050	3.732-32.717

CI = confidence interval.

DISCUSSION

The rate of HBV infection is high in the general population in China. Also, the incidence of NHL increases every year. As a result, the number of HBV-infected patients with NHL is also increasing (Nath et al., 2010). In recent years, several local and foreign studies have reported that the incidence of damaged liver function after chemotherapy has significantly increased in HBV carriers with tumors, particularly in patients with NHL (Nakamura et al., 1996; Kumagai et al., 1997; Torbenson and Thomas, 2002; Loomba et al., 2008; Liu et al., 2011). Damaged liver function after chemotherapy in HBV-infected patients with NHL may be related to immunosuppression and increased HBV replication (He et al., 2008; Niitsu et al., 2010). In the current study, 56.7% of patients experienced damaged liver function, which is generally consistent with local research (Nakamura et al., 1996). A high proportion of patients experienced severely damaged liver function: 20 patients (26.3%) had III degree damage and 33 patients (43.4%) had IV degree damage. This indicates that HBV carriers with NHL have a higher risk of damaged liver function after chemotherapy; therefore, these patients should receive extensive care. Changes in liver function should be regularly monitored and reexamined during chemotherapy. If any abnormalities are noted, then re-examination of the patient's HBV-DNA replication state should be performed. Well-timed administration of liver-aiding and anti-HBV drugs is also particularly important. Accumulation of chemotherapy cycles also increases the probability of severely damaged liver function. Therefore, the unique adverse effects of chemotherapy in each patient should be given considerable attention. Consequently, adjustment of patients' chemotherapy regimens is clinically significant.

There is currently no specific index for forecasting the incidence and severity of damaged liver function after chemotherapy in HBV carriers with NHL. In this study, logistic single factor analysis of the relationships between various clinical factors and damaged liver function after chemotherapy revealed that gender, age, nationality, treatment situation, and HBeAg expression were not related to the occurrence of damaged liver function after chemotherapy. However, administration of chemotherapy drugs that contain anthracyclines and glucocorticoids was associated with an increased probability of damaged liver function. Our analysis found that NHL chemotherapy regimens contain immunosuppressants and glucocorticoids, which are intermittently administered in most cases, thereby enhancing the possibility of virus activation. Cyclophosphamide- and anthracycline-based chemotherapeutics, such as doxorubicin, are mainly metabolized in the liver, which may continually damage liver cells. Also, during immunosuppression, HBV reproduces in large quantities in liver cells, which enhances the virus load. When chemotherapy is administered intermittently, or after it is stopped, patients gradually recover immune function. Liver cells, which contain HBV, exhibit strong immune-mediated reactions, resulting in severely damaged liver function (Keam et al., 2011; Dyson et al., 2014). Reactivation of HBV replication is related to glucocorticoids. HBV-DNA contains a response component to glucocorticoids that plays a role in reactivating HBV-DNA, resulting in liver function damage. Chemotherapy regimens for other solid tumors usually do not contain glucocorticoids, so damaged liver function is less likely to occur (Cheng et al., 2003). Cheng (1996) used chemotherapy regimens that did not contain glucocorticoids, such as ACE (doxorubicin, cyclophosphamide, and etoposide), VIM (etoposide, ifosfamide, and methotrexate), and ACO (adriamycin, cyclophosphamide, and vincristine), to reduce the risk of damaged liver function in HBV infected patients with NHL. The results of our multifactorial analysis show that separate use of glucocorticoids is a risk factor that contributes to the

occurrence of damaged liver function after chemotherapy in HBV carriers with NHL. Similar to the report by Yeo et al. (2004), our study about the influence of anthracycline-based drugs on liver function is inconclusive and needs to be explored further.

For HBV carriers with NHL, precautions like examining HBV markers before chemotherapy, closely monitoring various indexes related to damaged liver function, quantitatively examining HBV-DNA, and administering preventive antiviral drugs during chemotherapy are necessary to prevent damaged liver function. Such precautions not only reduce the risk of damaged liver function, they also ensure the ability to continuously administer chemotherapy to NHL patients (Fermé, 2002; Lau et al., 2003; Lalazar et al., 2007). It is important to promptly monitor HBV-DNA levels to determine whether HBV activity is present, instead of starting the next course of chemotherapy after performing only a simple blind liver protection technique, in order to prevent severe hepatitis in NHL patients with damaged liver function after chemotherapy.

Conflicts of interest

The authors declare no conflict of interest.

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