Analysis of the immunity effects after enhanced hepatitis B vaccination on patients with lymphoma

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ABSTRACT
The purpose of the study was to evaluate the immunity effects after vaccinating different doses and frequencies of hepatitis B vaccines by calculating the seroconversion rates of HBsAb in patients with lymphoma. Clinical data of 315 patients from January 2010 to August 2018 were analyzed. According to different doses and frequencies, the patients were divided into three groups: low-dose group, high-dose group, and high-dose and high-frequency group. The highest seroconversion rate of HBsAb was 82.3% in the high-dose and high-frequency group \((p < .05)\). Multivariate logistic regression analysis showed that the dose and frequency of vaccination \((p < .001, \text{OR} = 2.663)\), sex \((p < .006, \text{OR} = 3.106)\), the Ann Arbor stage \((p < .001, \text{OR} = 0.195)\) and whether the chemotherapy regimen contained ibrutinib or not \((p < .008, \text{OR} = 8.115)\) are independent factors affecting the immunity effects of hepatitis B vaccine in patients with lymphoma. Increasing doses and frequencies of hepatitis B vaccination may improve the immune response in patients with lymphoma.

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Introduction
Hepatitis B virus (HBV) infection is prevalent all over the world and China is a highly endemic area. Malignant lymphoma, one of the ten most common malignant tumors in our country, which occupies the first place in hematological malignancies, will gradually increase with the aging of the population. Domestic and international studies have shown that patients with non-Hodgkin lymphoma (NHL) have higher HBV infection rate than the general population \([1]\) and the infection rate of HBV in patients with B-NHL is higher than that of T-NHL \([2]\). Compared with the general population, NHL patients had a lower positive rate of protective antibody HBsAb and a higher rate of loss of HBsAb. Similarly, HBV infection increases the incidence of NHL, especially diffuse large B-cell lymphoma (DLBCL) \([3]\). After chemotherapy, oral ulceration and impaired immune function in lymphoma patients with neutropenia will lead to a decrease in their resistance to infection and be susceptible to HBV cross-infection. In addition, patients with lymphoma are more likely to cause HBV hematogenous infection due to transfusion of blood products and sharing of blood cell extractors before autologous hematopoietic stem cell transplantation (auto-HSCT). Finally, lymphoma patients with HBV infection are at risk of HBV reactivation during chemotherapy or immunotherapy \([4]\).

At present, inoculation of hepatitis B vaccine is not only the most direct and effective way to prevent HBV infection \([5]\) but also can effectively prevent the reactivation of HBV after chemotherapy by increasing the titer of HbsAb in patients with lymphoma before chemotherapy \([6,7]\). 2017 Italian consensus guidelines, ‘Recommendations for screening, monitoring, prevention, prophylaxis and therapy of hepatitis B virus reactivation in patients with hematological malignancies and patients who underwent hematologic stem cell transplantation,’ strongly recommend that all patients with HBV-negative hematological disorders should be vaccinated against hepatitis B, 1–2 weeks before chemotherapy, and their HBsAb titers should be monitored regularly \([8]\). However, in the context of humoral and cellular immune disorders in most lymphoma patients, drug application such as glucocorticoids, rituximab, ibrutinib and auto-HSCT might play a role in the diminished response to hepatitis B vaccine inoculation, which will lead to the problems of low seroconversion rate and antibody peak value,
rapid disappearance of antibody and short maintenance time after immunization [9]. Up to now, there is no uniform standard of injection doses and frequencies for hepatitis B vaccine inoculated to patients with lymphoma at home and abroad. The purpose of this study is to provide reference for exploring the optimal method of hepatitis B vaccination in patients with lymphoma through the observation of seroconversion rates of HBsAb by increasing the doses and frequencies of hepatitis B vaccine, and investigate the immunity effects after enhanced hepatitis B vaccination and analyze the influencing factors.

Cases and methods

Cases

Clinical data of 315 patients with lymphoma vaccinated with hepatitis B vaccine in the Second Affiliated Hospital of Fujian Medical University from January 2010 to August 2018 were analyzed retrospectively. All patients were diagnosed according to WHO criteria. Of the 288 patients with B-NHL (72.4%), 133 patients were diagnosed as DLBCL (42.2%). A total of 142 patients (45.1%) were male and 173 patients (54.9%) were female and the sex ratio was 1:1.22 with a median age of 53 years (range from 16 to 75 years). The five indexes of hepatitis B detected by ELISA (enzyme-linked immunosorbent assay, ELISA) before vaccination were all negative. According to different doses and frequencies of hepatitis B vaccination, the patients were divided into three groups: the low-dose group (10 μg for 0, 1, and 6 months, respectively), the high-dose group (20 μg for 0, 1, and 6 months, respectively), and the high-dose and high-frequency group (20 μg for 0, 1, 2, and 6 months, respectively). Details of clinical data are shown in Table 1.

Reagents and instruments

10 and 20 μg Recombinant yeast hepatitis B vaccine produced by Shenzhen Kangtai Biological Products Limited by Share Ltd. Five enzyme-linked immunosorbent assay kit for hepatitis B produced by Shandong Weifang Three Dimensional Bioengineering Group Co., Ltd and Switzerland Tecan Infinite F50 enzyme labeling instrument as a detection instrument. Hepatitis B virus surface antibody detection kit produced by Abbott Company of the United States and Abbott i4000SR automatic Chemiluminescence instrument as a detection instrument.

| Table 1. Clinical data of lymphoma patients vaccinated with hepatitis B vaccine. |
|---------------------------------------------------------------|
| Characteristics | n (%) |
| Inoculation doses and frequencies | |
| Low-dose group (10 μg for 0, 1, and 6 months, respectively) | 118 (37.5) |
| High-dose group (20 μg for 0, 1, and 6 months, respectively) | 118 (37.5) |
| High-dose and high-frequency group (20 μg for 0, 1, 2, and 6 months, respectively) | 79 (25.0) |
| Sex | |
| Male | 142 (45.1) |
| Female | 173 (54.9) |
| Age | |
| ~15 | 31 (9.8) |
| ~30 | 67 (21.3) |
| ~50 | 86 (27.3) |
| ~60 | 90 (28.6) |
| ~70 | 41 (13.0) |
| Pathological types | |
| Hodgkin’s lymphoma | 29 (9.2) |
| Non-Hodgkin’s lymphoma | 286 (90.8) |
| B cell type | 228 (72.4) |
| DLBCL | 133 (42.2) |
| Follicular lymphoma (FL) | 28 (8.9) |
| Small lymphocytic lymphoma (SLL) | 12 (3.8) |
| Mantle cell lymphoma (MCL) | 18 (5.7) |
| Marginal zone lymphoma (MZL) | 15 (4.8) |
| Lymphoplasmacytic lymphoma (LPL) | 9 (2.9) |
| Burkittlymphoma/leukemia (BL) | 13 (4.1) |
| T cell and NK cell type | 58 (18.4) |
| Peripheral T-cell lymphoma, NOS (PTCL) | 16 (5.1) |
| Angioimmunoblastic T-cell lymphoma (AITCL) | 14 (4.4) |
| Extramedial NK/T-cell lymphoma, nasal type (NK/TCL) | 24 (7.6) |
| Adult T-cell leukemia/lymphoma (ATLL) | 4 (1.3) |
| Stage of disease | |
| Stage I | 47 (14.9) |
| Stage II | 77 (24.4) |
| Stage III | 108 (34.3) |
| Stage IV | 83 (26.4) |
| B symptoms | |
| Yes | 105 (33.3) |
| No | 210 (66.7) |
| Chemotherapy regimen containing glucocorticoid | 243 (77.1) |
| Chemotherapy regimen containing rituximab | 151 (47.9) |
| Chemotherapy regimen containing lenalidomide | 90 (28.6) |
| Chemotherapy regimen containing ibrutinib | 19 (6.0) |
| Auto-HSCT | 20 (6.3) |

DLBCL: diffuse large B-cell lymphoma.

Methods of immunization

Hepatitis B vaccine was injected intradermally at the left and right deltoid muscles of the upper arm according to the immunization program one to two weeks before chemotherapy.

Evaluation methods

One month after the end of the whole course of immunization, venous blood samples were collected to detect the quantitative level of HBsAb and calculate the seroconversion rate. Vaccine efficacy was defined as the concentration of HBsAb ≥10 mIU/mL determined by chemiluminescent microparticle
immunoassay after the course of immunization was completed.

**Statistical methods**

SPSS 19.0 software was used for statistical analysis to calculate the seroconversion rate of HBsAb. The influence factors of immunity effect of hepatitis B vaccine were analyzed by \( \chi^2 \) test or Fisher probabilities. \( p < .05 \) was regarded as significant.

**Results**

**Clinical data of lymphoma patients vaccinated with hepatitis B vaccine**

A total of 315 patients with lymphoma were vaccinated with hepatitis B vaccine, including 118 patients (37.5%) in each of the low-dose group (10 µg for 0, 1, and 6 months, respectively) and high-dose group (20 µg for 0, 1, and 6 months, respectively) and 79 patients (25.0%) in high-dose and high-frequency group (20 µg for 0, 1, 2, and 6 months, respectively). The main clinical data are shown in Table 1.

**Comparison of outcomes between three groups**

All patients successfully completed hepatitis B vaccination and no obvious adverse reactions were observed in each group. After vaccination, 242 patients were HBsAb positive and a seroconversion rate was 76.8%. In low-dose group, 81 patients were HBsAb positive and a seroconversion rate was 68.6%. In high-dose group, 96 patients were HBsAb positive and a seroconversion rate was 81.4%. In high-dose and high-frequency group, 65 patients were HBsAb positive and a seroconversion rate was 82.3%. The high-dose and high-frequency group had the highest seroconversion rate of HBsAb, followed by high-dose group and the low-dose group had the lowest seroconversion rate of HBsAb. There were significant differences among the three groups (\( \chi^2 = 0.028, p < .05 \)). The results showed that HBsAb seroconversion rate increased with the increase of inoculation dose and frequency. See Table 2.

| Doses and frequencies of inoculation | Positive [n (%)] | Negative [n (%)] | \( \chi^2 \) value | \( p \)-Value |
|--------------------------------------|------------------|------------------|-------------------|----------------|
| Low-dose group (10 µg for 0, 1, and 6 months, respectively) | 81 (68.6) | 37 (31.4) | 7.116 | .028 |
| High-dose group (20 µg for 0, 1, and 6 months, respectively) | 96 (81.4) | 22 (18.6) | 65 (82.3) | 14 (17.7) |

**Comparison of outcomes between response and non-response patients**

There were also significant differences in the seroconversion rate of HBsAb in terms of age, gender, pathological type, the Ann Arbor stage, whether or not treated with glucocorticoid, rituximab, ibrutinib or auto-HSCT (\( p < .05 \)). No significant differences were observed between patients with B symptoms or without, and the same were found between patients treated with lenalidomide or without (\( p > .05 \)). See Table 3.

**Multivariate analysis of influencing factors on immunity effects of hepatitis B vaccine in patients with lymphoma**

Taking the above statistically significant indexes as independent variables and HBsAb seroconversion rate as the dependent variable, unconditional logistic regression analysis was used to screen the related factors affecting the immunity effects of hepatitis B vaccine in patients with lymphoma. The results showed that the dose and frequency of vaccination (\( p < .001, OR = 2.663 \)), sex (\( p < .006, OR = 3.106 \)), the Ann Arbor stage (\( p < .001, OR = 0.195 \)) and whether the chemotherapy regimen contained ibrutinib or not (\( p < .008 \), OR = 8.115) are independent factors affecting the immunity effects of hepatitis B vaccine in patients with lymphoma. Intensive vaccination, female, early Ann Arbor stage and chemotherapy without ibrutinib can significantly improve the HBsAb seroconversion rate of hepatitis B vaccine in patients with lymphoma. However, age, pathological type, whether the chemotherapy regimen contained glucocorticoid, rituximab or not and whether treated with autologous hematopoietic stem cell transplantation or not were independent factors affecting the immunity effects of hepatitis B vaccine in patients with lymphoma (all \( p > .05 \)). See Table 4.

**Discussion**

Hepatitis B virus infection is associated with high morbidity and mortality in patients with lymphoma [10,11]. Vaccination of hepatitis B vaccine is the most
direct and effective way to prevent hepatitis B virus infection. Existing studies have shown that the level of HbsAb in patients with lymphoma is a protective factor for HBV reactivation. The higher the HBSab level, the lower the risk of HBV reactivation [12,13]. Therefore, it is of great significance to improve the level of HbsAb in patients with lymphoma by vaccinated with hepatitis B vaccine before chemotherapy.

Table 3. Comparison of clinical characteristics between response and non-response patients with lymphoma after vaccination with hepatitis B vaccine.

| Clinical characteristics | Positive [n (%)] | Negative [n (%)] | χ² value | p-Value |
|--------------------------|------------------|------------------|----------|---------|
| Sex                      |                  |                  |          |         |
| Male                     | 97 (68.3)        | 45 (31.7)        | 10.531   | .001    |
| Female                   | 145 (83.8)       | 28 (16.2)        |          |         |
| Age groups (years)       |                  |                  | 12.965   | .111    |
| ~15                      | 28 (90.3)        | 3 (9.7)          |          |         |
| ~30                      | 56 (83.6)        | 11 (16.4)        |          |         |
| ~50                      | 64 (74.4)        | 22 (25.6)        |          |         |
| ~60                      | 65 (72.2)        | 25 (27.8)        |          |         |
| ~70                      | 27 (65.9)        | 14 (34.1)        |          |         |
| Pathological types       |                  |                  | 29.423   | .002    |
| Hodgkin’s lymphoma       | 27 (93.1)        | 2 (6.9)          |          |         |
| non-Hodgkin’s lymphoma   | 218 (76.2)       | 68 (23.8)        |          |         |
| B cell type              |                  |                  |          |         |
| DLBCL                    | 92 (69.2)        | 41 (30.8)        |          |         |
| FL                       | 28 (100.0)       |                  |          |         |
| SLL                      | 12 (100.0)       |                  |          |         |
| MCL                      | 13 (72.2)        | 5 (27.8)         |          |         |
| MZL                      | 13 (86.7)        | 2 (13.3)         |          |         |
| LPL                      | 9 (100.0)        |                  |          |         |
| BL                       | 12 (92.3)        | 1 (7.7)          |          |         |
| T cell and NK cell type  |                  |                  |          |         |
| PTCL                     | 8 (50.0)         | 8 (50.0)         |          |         |
| AITCL                    | 10 (71.4)        | 4 (28.6)         |          |         |
| NK/TCL                   | 18 (75.0)        | 6 (25.0)         |          |         |
| ATLL                     | 3 (75.0)         | 1 (25.0)         |          |         |
| Stage of disease         |                  |                  | 8.271    | .041    |
| Stage I                  | 41 (87.2)        | 6 (12.8)         |          |         |
| Stage II                 | 62 (80.5)        | 15 (19.5)        |          |         |
| Stage III                | 79 (73.1)        | 29 (26.9)        |          |         |
| Stage IV                 | 58 (69.9)        | 25 (30.1)        |          |         |
| B symptoms               |                  |                  | 3.218    | .73     |
| Yes                      | 77 (73.3)        | 28 (26.7)        |          |         |
| No                       | 174 (82.9)       | 36 (17.1)        |          |         |
| Chemotherapy regimen containing glucocorticoid |                  |                  | 5.973    | .015    |
| Yes                      | 179 (73.7)       | 64 (26.3)        |          |         |
| No                       | 63 (87.5)        | 9 (12.5)         |          |         |
| Chemotherapy regimen containing rituximab |                  |                  | 8.655    | .003    |
| Yes                      | 105 (69.5)       | 46 (30.5)        |          |         |
| No                       | 137 (83.5)       | 27 (16.5)        |          |         |
| Chemotherapy regimen containing lenalidomide |                  |                  | 0.863    | .353    |
| Yes                      | 70 (77.8)        | 20 (22.2)        |          |         |
| No                       | 165 (73.3)       | 60 (26.7)        |          |         |
| Chemotherapy regimen containing ibrutinib |                  |                  | 9.854    | .002    |
| Yes                      | 9 (47.4)         | 10 (52.6)        |          |         |
| No                       | 233 (78.7)       | 63 (21.3)        |          |         |
| Auto-HSCT                |                  |                  | 5.714    | .017    |
| Yes                      | 11 (55.0)        | 9 (45.0)         |          |         |
| No                       | 231 (78.3)       | 64 (21.7)        |          |         |

Table 4. Logistic regression analysis of factors related to immunity effect of hepatitis B vaccine in patients with Lymphoma.

| Group                                      | Partial regression coefficient | Standard error | Wald statistic | p-Value | OR (95%CI) |
|--------------------------------------------|--------------------------------|----------------|----------------|---------|------------|
| The dose and frequency of vaccination      | 0.979                          | 0.265          | 13.617         | <.001   | 2.663 (1.583–4.480) |
| Sex                                        | 1.133                          | 0.411          | 7.596          | .006    | 3.106 (1.387–6.954) |
| The Ann Arbor stage                        | −1.637                         | 0.361          | 20.556         | <.001   | 0.195 (0.096–0.395) |
| Whether the chemotherapy regimen contained ibrutinib | 2.094                          | 0.789          | 7.041          | .008    | 8.115 (1.728–38.101) |
to prevent HBV reactivation after chemotherapy. The recombinant yeast hepatitis B vaccine commonly used now has good immunogenicity with protective effect depends on humoral immunity and cytotoxic T lymphocyte reaction and the long-term immune protection depends on the immune memory of B cells. Because of impaired humoral and cellular immune function in lymphoma patients, the immune response rate to the hepatitis B vaccine is poorer than general population according to the current inoculation methods [14]. Our study confirmed that the seroconversion rate of HBsAb in the low-dose group was lower than that in the general population reported so far. It is necessary to increase the dose and frequency of vaccination to improve the protection level of HbsAb due to the low response rate of lymphoma patients to hepatitis B vaccine can lead to HBV infection. Our study also showed that the seroconversion rate of HBsAb in the high-dose and high-frequency group was higher than that in the high-dose group and low-dose group, indicating that the immunity effects of hepatitis B vaccination in lymphoma patients could be maximized by increasing the dose and frequency of vaccination.

There are three main factors that affect the immunity efficacy of hepatitis B vaccine in lymphoma patients. The first one is organism factor. The seroconversion rate of HBsAb in female was higher than that in male [15] and the response rate of hepatitis B vaccine generally decreased with age, which was consistent with the results of our study. Another one is disease factor. The more advanced stage of lymphoma is, the more serious the suppression of the immune function. T lymphocytes, especially Th cells, play an important role in the secretion of specific antibodies by B lymphocytes. As a result, NK/T cell lymphoma often has more severe autoimmune dysfunction than Hodgkin’s lymphoma and B cell lymphoma [16]. Meanwhile, DLBCL often appears serious immunosuppression due to EB virus infection and R-CHOP regimen chemotherapy [17]. These factors contribute to insufficient HBsAb production from immunization. The B symptoms are positively correlated with the level of IL-6 which can stimulate the proliferation of T cells and activated B cells, secrete antibodies and improve the effect of hepatitis B vaccine inoculation [18]. Our study also showed that the HBsAb positive rate of NK/T cell lymphoma was lower than that of Hodgkin’s lymphoma and B cell lymphoma, and the HBsAb positive rate of DLBCL was lower than that of other pathological types of B cell lymphoma. Moreover, the later the Ann Arbor stage was, the lower the seroconversion rate of HBsAb was. However, the seroconversion rate of HBsAb was not affected by the presence or absence of B symptoms, which maybe due to the small sample sizes of our study and lymphoma patients with B symptoms which is currently considered to be a poor prognostic factor for malignant lymphoma usually opt for relatively high-intensity regimens (such as R-CHOP regimen). The third one is therapeutic factors. Shimba et al. [19] demonstrated that glucocorticoids decrease the activity of immune effector T cells by inhibiting systemic immunity, this state of tolerance prevents hepatitis B vaccination from producing sufficient HBsAb. Dervite et al. [20] showed that the direct induction of B cell apoptosis by rituximab leads to a decrease in the number of plasma cells differentiated from B cells, which in turn reduces antibody production and prevents hepatitis B vaccination from producing sufficient HBsAb. Tam CS [21] used the new targeted drug BTK inhibitor ibrutinib inhibits the proliferation and activation of B lymphocytes by blocking the signal transduction pathway of B cell receptor and results in the decrease of immune response to hepatitis B vaccination. Finally, auto-HSCT results in deeper and more persistent bone marrow suppression and immunosuppression than conventional chemotherapy, cause active immune nonresponse or weak response to hepatitis B vaccine due to high-intensity pre-conditioning [22]. All of these factors can be summarized as therapeutic factors, resulting in a decline in the immune response of hepatitis B vaccine. However, the new immunomodulator lenalidomide can activate T lymphocytes to improve the immunosuppressive status of lymphoma patients and increase the positive rate of hepatitis B vaccination [23]. In our study, patients treated with glucocorticoids, rituximab, and ibrutinib as well as patients undergoing auto-HSCT had lower HBsAb seroconversion rates than controls. There was no significant difference in the seroconversion rate of HBsAb between the patients treated with lenalidomide and the control group, which may be due to the small sample size of this study and the low dose of lenalidomide applied in the study.

The results of logistic regression analysis showed that the dose and frequency of vaccination, sex, the Ann Arbor stage and whether the chemotherapy regimen contains ibrutinib or not were independent factors affecting the immunity effects of hepatitis B vaccine in patients with lymphoma. Among them, intensive vaccination, female and chemotherapy regimen did not contain ibrutinib were positively correlated with the immunity effects of hepatitis B vaccine,
while the Ann Arbor stage was negatively correlated with the immunity effects of hepatitis B vaccine. The results showed that the dose and frequency of vaccination, sex, the Ann Arbor stage and whether the chemotherapy regimen contains ibrutinib or not could be used as the main predictors of the immunity effect of hepatitis B vaccine in patients with lymphoma. In particular, the chemotherapy regimen containing ibrutinib will significantly affect the immunity effect of hepatitis B vaccine in patients with lymphoma. However, this conclusion needs to be clarified by further prospective studies and control studies.

In this study, all patients with lymphoma after vaccination of hepatitis B vaccine did not appear obviously adverse reactions and had a good tolerance, which proved the effectiveness and safety of the vaccination. It is recommended that patients with lymphoma should be given hepatitis B vaccine as early as possible (20 μg for 0, 1, 2, and 6 months, respectively), as the results of the study also showed that the immunity effects of hepatitis B vaccine decreased with age. At present, the most protective HBV immunization program for lymphoma patients is rarely reported all over the world. The result of our study is of great significance for the prevention of HBV infection in patients with lymphoma and even other hematological diseases. However, our study was a retrospective study with small sample size, few available vaccine doses and short follow-up periods, large-scale prospective clinical trials involving in different doses and frequencies of vaccination as well as combined immunopotentiators are needed to further explore the optimal regimens for hepatitis B vaccination in patients with lymphoma.

Disclosure statement

Wei-Huang Zhuang and Ya-Ping Wang declare no conflict of interest. The authors alone are responsible for the content and writing of this paper.

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