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ORIGINAL ARTICLE

Risk of hepatitis B reactivation in HBsAg-negative/HBcAb-positive patients with undetectable serum HBV DNA after treatment with rituximab for lymphoma: a meta-analysis

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Abstract
Background Hepatitis B surface antigen (HBsAg)-negative/hepatitis B core antibody (HBcAb)-positive patients with undetectable serum hepatitis B virus (HBV) DNA have experienced and resolved hepatitis B virus (HBV) infection. Lymphoma patients with resolved HBV infection have high risk of HBV reactivation when treated with robust immunosuppressive agents, but the reported rate varies extensively between different studies. This study aims to estimate the risk of HBV reactivation in HBsAg-negative/HBcAb-positive patients receiving rituximab-containing chemotherapy for lymphoma.

Methods Databases were searched for papers published in English until 8 August 2016. The pooled risk of HBV reactivation was estimated using a random-effects model.
Results Data from 15 studies were retrieved, including a total of 1312 HBsAg-negative/HBcAb-positive lymphoma patients treated with rituximab-containing chemotherapy. The results revealed HBV reactivation rate of 9.0 % [95 % confidence interval (CI) 0.05–0.15]. In subgroup analysis, the reactivation rates for prospective and retrospective studies were 17 % ($I^2 = 87.3$ %; 95 % 0.08–0.39, $p < 0.001$) and 7 % ($I^2 = 43.1$ %; 95 % CI 0.05–0.11, $p = 0.07$), respectively.
Conclusions This meta-analysis confirms a measurable and potentially substantial risk of HBV reactivation in HBsAg-negative/HBcAb-positive patients with rituximab treatment for lymphoma. Prophylactic use of anti-HBV agents should be seriously considered for such patients.

Keywords Hepatitis B virus · Rituximab · Hepatitis B reactivation · Lymphoma

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Introduction

Rituximab (R) is a chimeric anti-CD20 monoclonal antibody that can induce B cell lysis by antibody-dependent cellular cytotoxicity, resulting in apoptosis of B-cell lymphoma cells [1]. Chemotherapy consisting of R, cyclophosphamide, doxorubicin, vincristine, and prednisolone is currently considered the standard chemotherapy for diffuse large B-cell lymphoma [2]. A growing body of evidence suggests that HBV reactivation is associated with use of rituximab [3]. It is well recognized that HBsAg-positive patients who receive immunosuppressive or cytotoxic chemotherapy have a substantial possibility of

developing HBV reactivation [4]. Cancer patients with "resolved" HBV infection [HBsAg negative and hepatitis B core antibody (HBcAb) positive] also carry a risk of chemotherapy-induced HBV reactivation [5]. In these patients, HBV may remain in covalently closed circular DNA in hepatocytes without obvious activity after clearance of HBsAg but could be reactivated when the immune system is suppressed by chemotherapy [6]. However, such reactivation rates vary extensively in different studies, ranging from 0 to 41.5 % [3, 7–20].

Therefore, we performed a systematic review of recent literature to estimate the risk of HBV reactivation in HBsAg-negative/HBcAb-positive patients receiving rituximab-based lymphoma therapy.

Materials and methods

Literature search strategy

We conducted searches using PUBMED and EMBASE (from 1996 to 8 August 2016) with the medical subject headlines of "Rituximab" and "Hepatitis B". Search results were limited to English-language publications.

Study selection and data extraction

We limited studies to those including HBsAg-negative/HBcAb-positive and rituximab-treated patients with lymphoma. Reviews, case reports, and case series with fewer than five patients were excluded. Author Z.T. reviewed the titles and abstracts of all the identified studies. Authors X.L., Y.L., and Y.Q. reviewed the full text of all potentially eligible studies. Author S.W. reviewed the inclusion criteria of the reference list of studies to identify additional studies that met the eligibility criteria. Authors D.X., J.L., and X.L. designed the study and revised the manuscript.

The primary outcome of this meta-analysis was the rate of HBV reactivation in HBsAg-negative/HBcAb-positive patients treated for lymphoma using rituximab. HBV reactivation was defined as increase in alanine aminotransferase (ALT) >40 U/L with an increase in HBV DNA from baseline (including change from undetectable to detectable), and/or HBsAg seroconversion from negative to positive, and absence of clinical or laboratory features of acute infection with hepatitis A virus, hepatitis C virus, or other systemic infections.

Statistical analysis

The probability of HBV reactivation was estimated using a random-effects model. For the meta-analysis, we used the Cochrane heterogeneity chi-square test to determine whether the pooled estimates showed significant statistical heterogeneity, defined to be significant for p value <0.05. The I^2 statistic was used as a measure of heterogeneity in the selected study, with $I^2 > 50$ % indicating significant heterogeneity.

Results

The selection process for trial inclusion is illustrated in Fig. 1. The literature search yielded 964 citations. After screening the titles and abstracts, 78 potentially eligible studies were taken into consideration, 15 of which were ultimately included (Table 1) [3, 7–20]. The selected studies included five prospective cohort studies [3, 7–10], nine retrospective studies [11–19], and one study with mixed prospective and retrospective design [20]. Among all 15 selected studies, 12 studies were completed in Asia (2 from Japan [12, 20], 8 from China [3, 8, 9, 11, 13–16], 1 from South Korea [19], and 1 from Singapore [7]), 2 from Europe [10, 17] (Italy), and 1 from North America (the USA) [18].

Figure 2 illustrates that the risk estimates for HBV reactivation ranged from 0 to 41.5 %. Using the random-effects model, the pooled standardized HBV reactivation rate ($n = 15$ studies) was 9.0 % (121 reactivations in 1312 patients; 95 % CI 0.05–0.15). However, significant heterogeneity was present ($I^2 = 84$ %; $p < 0.001$).

The source of statistical heterogeneity was explored by analyzing the data by study type (prospective versus retrospective studies). When the analysis was limited to the prospective studies, the HBV reactivation rate was 17 % (Fig. 3; $I^2 = 87.3$ % $p < 0.001$; 95 % CI 0.08–0.39). When the analysis was limited to the retrospective studies, the HBV reactivation rate was 7 % (Fig. 4; $I^2 = 43.1$ %; $p = 0.07$; 95 % CI 0.05–0.11).

Discussion

Lymphoma patients with "resolved" HBV infection carry a substantial risk of chemotherapy-induced HBV reactivation, but the reactivation rate varies extensively between different studies, ranging from 0 to 41.5 %. Increasing attention has been attracted to whether prophylactic anti-HBV treatment should be administered to patients with resolved HBV infection before rituximab treatment. In this study, we estimated a pooled rate of HBV reactivation rate of 9 % in these patients. The fairly high reactivation rate suggests that antiviral prophylaxis should be taken into consideration for all HBcAb-positive patients regardless of HBsAg status.

It is well recognized that treatment with prophylactic nucleos(t)ide analogs (NAs) should be recommended in chronic hepatitis B (CHB) patients with lymphoma during

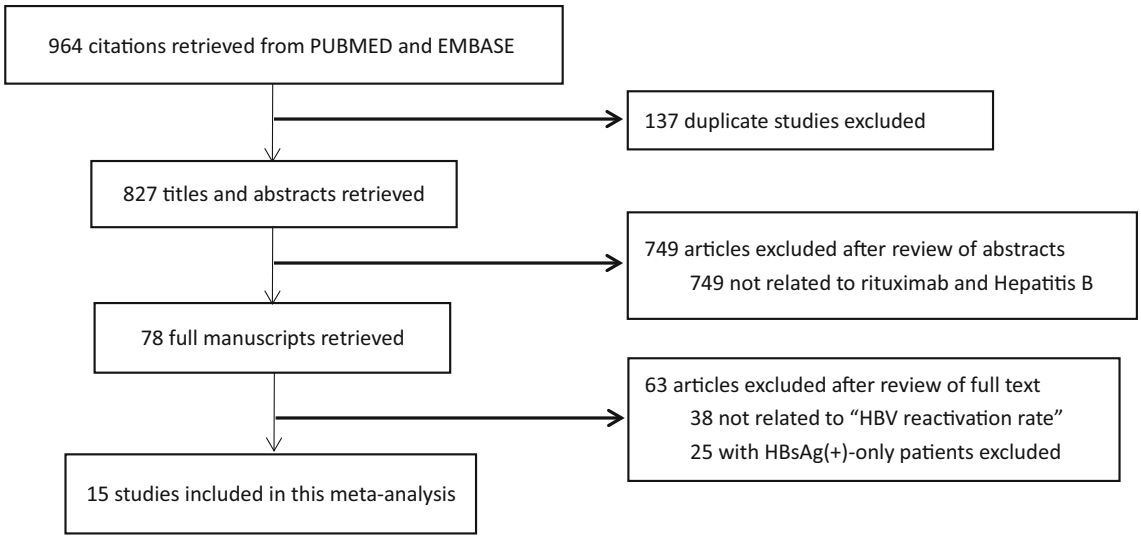

Fig. 1 Flowchart of article selection

Table 1 Studies with HBV reactivation among HBsAg-negative/HBcAb-positive patients after use of rituximab for lymphoma

Study	Study design	Country or origin	Patients	Male (%)	Age, years (median, range)	Follow-up length, months (median, range)	Reactivation rate (%)
Seto [8]	Prospective	China	63	25 (39.7)	70.9 (38–90)	17.5 (1.5–26)	41.5
Hsiao [16]	Retrospective	Taiwan	317	NA	NA	NA	7.3
Chen [15]	Retrospective	China	55	30 (54.5)	58 (18–79)	61 (1–93)	10.9
Wu [14]	Retrospective	Taiwan	190	120/70	72 (22–91)	23.6 (3.4–116.3)	14.2
Lu [13]	Retrospective	China	150	92 (61.3)	57 (28–87)	28 (2–100)	2.7
Hsu [9]	Prospective	Taiwan	150	81 (54.0)	61 (27–84)	27.4 (1.1–45.7)	11.3
Persico [10]	Prospective	Italy	7	NA	NA	NA	28.9
Yeo [3]	Prospective	Hong Kong	21	NA	NA	NA	23.8
Koo [7]	Prospective	Singapore	62	37 (59.7)	67.2 (47–87)	32 (4.7–47.2)	3.2
Targhetta [17]	Retrospective	Italy	74	NA	NA	NA	2.7
Fukushima [20]	Retrospective and prospective	Japan	32	NA	NA	NA	9.1
Ji [11]	Retrospective	China	43	25/18	NA	22 (6–86)	2.3
Matsue [12]	Retrospective	Japan	56	37/19	71 (43–90)	24 (2–56)	5.4
Mendez-Navarro [18]	Retrospective	USA	25	NA	NA	NA	0.0
Oh [19]	Retrospective	Korea	67	41/26	66 (27–92)	NA	3.0

NA indicates that relevant data, i.e., sex, age, and follow-up duration, were not available in the original paper

chemotherapy [5]. Currently, NAs available for clinical intervention include entecavir, adefovir, telbivudine, and tenofovir in addition to lamivudine. In one systematic analysis including 52 articles and 3892 HBsAg-positive participants, Zhang et al. evaluated the prophylactic efficacy of the five oral NAs on chemotherapy-induced HBV reactivation [21]. They found that prophylactic therapy with tenofovir and entecavir may be the most potent interventions for prevention of HBV reactivation. On the other side, after HBV reactivation, entecavir showed good treatment efficacy for suppression of HBV and was highly recommended [22].

The definition of HBV reactivation was not completely identical across the 15 included studies. In this study, we

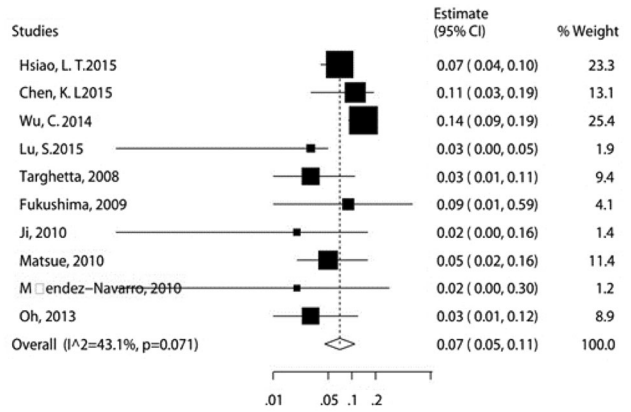

Fig. 2 Pooled rate of HBV reactivation among HBsAg-negative/HBcAb-positive patients after using rituximab for lymphoma

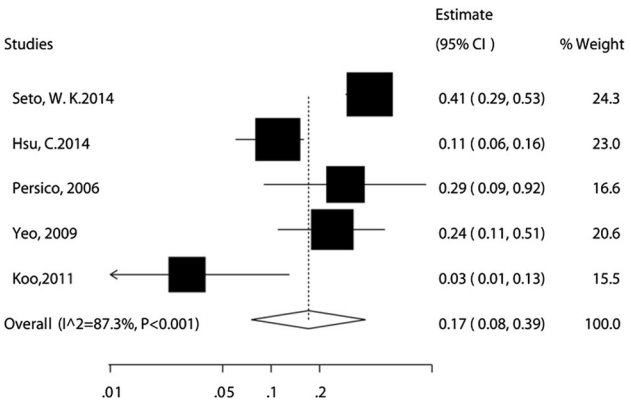

Fig. 3 Pooled rate of HBV reactivation among HBsAg-negative/HBcAb-positive patients after using rituximab for lymphoma. Analysis limited to prospective studies

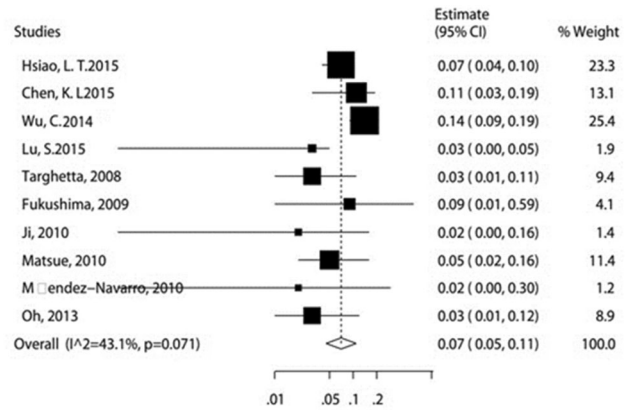

Fig. 4 Pooled rate of HBV reactivation among HBsAg-negative/HBcAb-positive patients after using rituximab for lymphoma. Analysis limited to retrospective studies

chose a rather loose definition of HBV reactivation, i.e., ALT >1 ULN with HBV DNA increase and/or HBsAg reappearance, in order to include those patients with mild HBV DNA increase but who still had substantial risk of suffering liver damage, liver failure, or even death. A previous meta-analysis reported a 6.3 % HBV reactivation rate [23], lower than the pooled rate (9.0 %) obtained in this study. In comparison with our study, the previous study used a stricter definition of HBV reactivation (ALT >3 ULN with HBV DNA increase and/or HBsAg reappearance), and analyzed fewer patients (578 patients versus 1312 patients in our study). These two factors may account for the difference in the estimated rate of HBV reactivation between the two studies.

HBV genotype is suggested to be a factor associated with the virulence and natural history of HBV, possibly impacting on nucleotide-analog-resistant mutations and the risk of cirrhosis, liver failure, and hepatocellular carcinoma [24]. In this meta-analysis, not all retrieved studies provided HBV genotype information. Therefore, it was hard to judge whether HBV genotype would affect the probability of reactivation during immunosuppression. However, one study reviewed that the HBV reactivation rates did not vary significantly between regions (Asia versus Europe) [23]. Given the fact that the genotype distribution varies by region, i.e., genotypes A and D predominate in Europe while genotypes B and C predominate in Asia, it is very unlikely that genotype is a factor influencing HBV reactivation.

The most important source of heterogeneity in this study was likely to be study design. Prospective studies normally use a more accurate definition of HBV reactivation with closer and systematic surveillance for HBV reactivation. As a result, it is likely that the prospective studies provide an estimate of the risk of HBV reactivation that is closer to the true risk. We supplemented recent studies and pooled nine retrospective and five prospective studies that met the inclusion criteria. The results showed that prospective studies tended to report higher rates of HBV reactivation compared with retrospective studies (17 versus 7 %). Besides, studies varied with regard to how long patients were monitored for HBV reactivation. Recent data suggest that the risk of HBV reactivation persists for months after rituximab therapy [25], thus studies that followed up patients for a longer time may be more likely to recognize HBV reactivation. In this review, the follow-up duration for the included studies ranged from 1.1 to 116.3 months.

There are two major limitations to our meta-analysis. One is the high heterogeneity among the retrieved studies, which might influence precise evaluation of the estimated rate of HBV reactivation. Another is that comparison of HBsAg-negative/HBcAb-positive/hepatitis B surface antibody (HBsAb)-negative patients with HBsAg-negative/HBcAb-positive/HBsAb-positive patients was not performed due to the lack of HBsAb information in some retrieved studies. Nevertheless, HBsAb positivity was recently reported to be associated with decreased risk of reactivation in patients with resolved HBV receiving rituximab chemotherapy for lymphoma without antiviral prophylaxis [26].

In summary, our meta-analysis confirms a measurable and potentially substantial risk of HBV reactivation in HBsAg-negative/HBcAb-positive patients with rituximab treatment for lymphoma. This study furthers knowledge on prophylactic use of anti-HBV agents in such patients.

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Compliance with ethical standards

Conflict of interest Zilin Tang, Xiaodong Li, Shunquan Wu, Yan Liu, Qiao Yan, Dongping Xu, and Jin Li declare that there are no conflicts of interest.

Human and animal rights statement This study was approved by the ethics committee of Beijing 302 Hospital. This article does not contain any studies with human or animal subjects.

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