


ORIGINAL ARTICLE

Clinical practice of hepatitis B screening in patients starting with chemotherapy: A survey among Dutch oncologists

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Abstract

Objective: Screening for hepatitis B virus (HBV) before chemotherapy is recommended by international guidelines; still, the HBV screening rate is low, and patients remain at risk for HBV reactivation (HBVr). Because HBVr is a serious and preventable condition, we conducted a survey to evaluate the screening behaviour of oncologists in the Netherlands.

Methods: We conducted an anonymous digital survey by email to all practicing medical oncologists. The surveys were sent in two sessions, the first one in 2017 and the second one in 2019. Questions included HBV screening procedures, reasons for screening and experience with HBVr.

Results: Among the 110 respondents, 29 (27%) followed a standardised protocol. Overall, 13 (12%) oncologists screened all patients, 76 (70%) only screened patients they considered as high risk and 19 (18%) did not screen anyone. Fourteen percent of the respondents experienced a HBVr in one of their patients.

Conclusion: This survey suggests that universal HBV screening is not common practice and usually patients considered as at risk for HBVr are screened, while this group is not always properly identified. Introduction of a national protocol for HBV screening and adjustment of the Dutch oncology guidelines might contribute to a reduction of HBVr during chemotherapy.

KEYWORDS

chemotherapy, guidelines, hepatitis B virus, hepatitis B virus reactivation, screening, survey

1 | INTRODUCTION

In patients that will start with chemotherapy hepatitis B virus (HBV) screening should be considered. Patients with chronic HBV infection, but also patients with a resolved HBV infection, are at risk for reactivation of HBV (HBVr) during immunosuppressive therapy (Hwang et al., 2015). HBVr during chemotherapy can lead to acute liver failure and delay of cancer treatment; the mortality directly related to HBVr can be as high as 25% (Di Bisceglie et al., 2015).

The risk of HBVr depends on both patient and therapeutic characteristics. The prevalence of chronic HBV infection is less than 2% in most Western European countries. However, a higher percentage is reached in certain subgroups like non-Western immigrants or people with high risk behaviour. The prevalence of a resolved HBV infection in the Netherlands was 3.5% in 2007, but prevalence's up to 20% in selected patient groups in multi-ethnic neighbourhoods have been found (Hahné et al., 2011; Veldhuijzen et al., 2009). Furthermore, many persons are unaware of their positive HBV status (Hwang et al., 2015).

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For the risk assessment of HBVr, immunosuppressive therapy is generally categorised in three categories; high risk (>10%), moderate risk (1–10%) and low risk (<1%) (Reddy et al., 2015). The B-cell-depleting agent rituximab is probably the best known high risk therapy, but also antracyclines and long-term use of moderate to high-dose steroids are associated with a high risk of HBVr (Lok & Bonis, 2018).

Screening for HBV before start of chemotherapy for both solid and haematological tumours is recommended by most international guidelines; see Table 1. In Dutch oncology guidelines, HBV screening before start of chemotherapy is not mentioned, while international reported HBVr rates in patients with solid tumours range between 8% and 41% (Day et al., 2011). We hypothesized that HBV screening rates are low within the Netherlands, while HBV is avoidable with the currently available antiviral therapy. Therefore, we set up this survey to investigate the HBV screening behaviour before start of chemotherapy by oncologists in the Netherlands. We hope that with the results of this survey, we can optimise the HBV screening process in cancer patients and eventually further prevent HBVr.

2 | METHODS

The oncology secretariats of all hospitals located in the Netherlands were contacted by phone and distribution of the anonymous digital survey followed by e-mail to all practicing medical oncologists ($n = 326$). The surveys, see Table S1, were sent in two sessions between 2017 and 2019. The first survey was sent to both medical oncologists and to haemato-oncologists within three regions (North Holland, South Holland and Utrecht). The second survey was sent only to medical oncologist in the remaining Dutch regions. In the second survey, we added some questions concerning reasons for screening and policy in case of a positive screening result.

The respondents were asked for their specialty registration (medical oncologist, haemato-oncologist or oncologist in training) and their hospital setting (academic, teaching or non-teaching hospital). Multiple choice questions addressed HBV screening procedures, reason for screening or not screening, policy in case of a positive test result and experience with HBVr. Some questions could be answered with more than one answer or free text fields for additional comments. We used descriptive statistics to analyse the results of the survey.

TABLE 1 Hepatitis B virus screening recommendations for immunosuppressed patients

Organisations	Year published	Recommendation	Screening tests
American Society of Clinical Oncology (Hwang et al., 2015)	2015	Screen patients who have risk factors for HBV infection or for whom immunosuppressive therapy associated with HBV reactivation is planned.	HBsAg, anti-HBc
European Society of Medical Oncology (Tilly et al., 2015)	2015	Screen patients with diffuse large B-cell lymphoma	HBsAg, anti-HBc, anti-HBs
American Association for the Study of Liver Diseases (Terrault et al., 2018)	2018	Testing should be performed in all persons before initiation of any immunosuppressive, cytotoxic, or immunomodulatory therapy.	HBsAg, anti-HBc
European Association for the Study of the Liver (European Association For The Study Of The Liver, 2017)	2017	All candidates for chemotherapy and immunosuppressive therapy should be tested for HBV markers prior to immunosuppression (Evidence level I, grade of recommendation 1)	HBsAg, anti-HBs, anti-HBc
American Gastroenterology Association (AGA) (Reddy et al., 2015)	2015	The AGA recommends screening for HBV in patients at moderate or high risk who will undergo immunosuppressive drug therapy. The AGA suggests against routinely screening for HBV in patients who will undergo immunosuppressive drug therapy and are at low risk.	HBsAg, anti-HBc followed by a sensitive HBV DNA test if positive
Asian Pacific Association for the Study of the Liver (Sarin et al., 2016)	2015	Persons needing immunosuppressive or cancer chemotherapy.	HBsAg, anti-HBc
Centers for Disease Control and Prevention (Abara et al., 2017)	2017	Screen all patients requiring immunosuppressive therapy.	HBsAg, anti-HBc, anti-HBs
The National Comprehensive Cancer Network (Baden et al., 2016)	2016	Any patient expected to receive immunosuppressive therapy or chemotherapy should be screened prior to treatment.	HBsAg, anti-HBc, anti-HBs

Abbreviations: anti-HBc, antibodies to hepatitis B core antigen; anti-HBs, antibodies to hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

3 | RESULTS

We received 110 responses (34% response rate) of whom 77 (70%) were oncologists, 25 (23%) haemato-oncologists and 8 (7%) oncology residents. Sixty five (60%) of the respondents worked at a teaching hospital, 29 (26%) respondents worked at an academic hospital and 16 (15%) at a non-teaching hospital; see Table S1. Nine respondents did not complete the entire survey.

Twenty nine (27%) of the respondents followed a standard protocol for HBV screening; see Figure 1a. Interestingly, 64% of the haemato-oncologists and only 13% of the medical oncologists followed a protocol. Universal HBV screening is performed by 13 (12%) of the respondents, high risk based screening by 76 (70%) of the respondents and 19 (18%) respondents reported that they never screen patients before start of chemotherapy (Figure 1b). All haemato-oncologists performed HBV screening (either universal or high risk based), while none of the medical oncologists performed universal screening and 19 (18%) never screen before start of therapy.

For respondents that perform universal HBV screening, the most chosen reason is that they follow the guidelines. Conversely, responders performing only high risk screening say that universal screening is not mentioned in oncology guidelines. Also, lack of evidence for universal screening and the negligible risk of HBVr are common answers. The medical oncologists that never perform HBV screening before chemotherapy responded that the risk of HBVr in

solid tumours is very low and that HBV screening is not mentioned in guidelines.

If HBV screening was performed, we asked which diagnostic tests were used. Almost 40% answered that they were unsure which test to order. Most other respondents adequately tested for HBsAg, anti-HBc (some also standard anti-HBs), and in case of a positive test an additional HBV DNA test.

We asked additional questions to find out which patients were identified as high risk patients for HBVr; see Table 2. All three possible options are considered high risk patients for HBVr in accordance with literature. Patients from endemic HBV regions were considered as high risk patients by 73% of the respondents. Patients with high risk behaviour were considered as high risk patients by 66% of the respondents and patients with high risk medication by 75% of the respondents. In the free text answers about risk factors, antracyclines and steroids were recurring points of discussion as well as the different treatment between haematological and solid malignancies.

In hypothetical HBV positive cases presented in our survey, the most important results considered policy in patients with a chronic HBV infection and patients with a resolved HBV infection treated with high risk medication. In these patients, anti-viral prophylaxis should be started prior to start chemotherapy. We found that in patients with a resolved HBV infection treated with high risk medication, 24% of the respondents will not refer to a specialist or start anti-

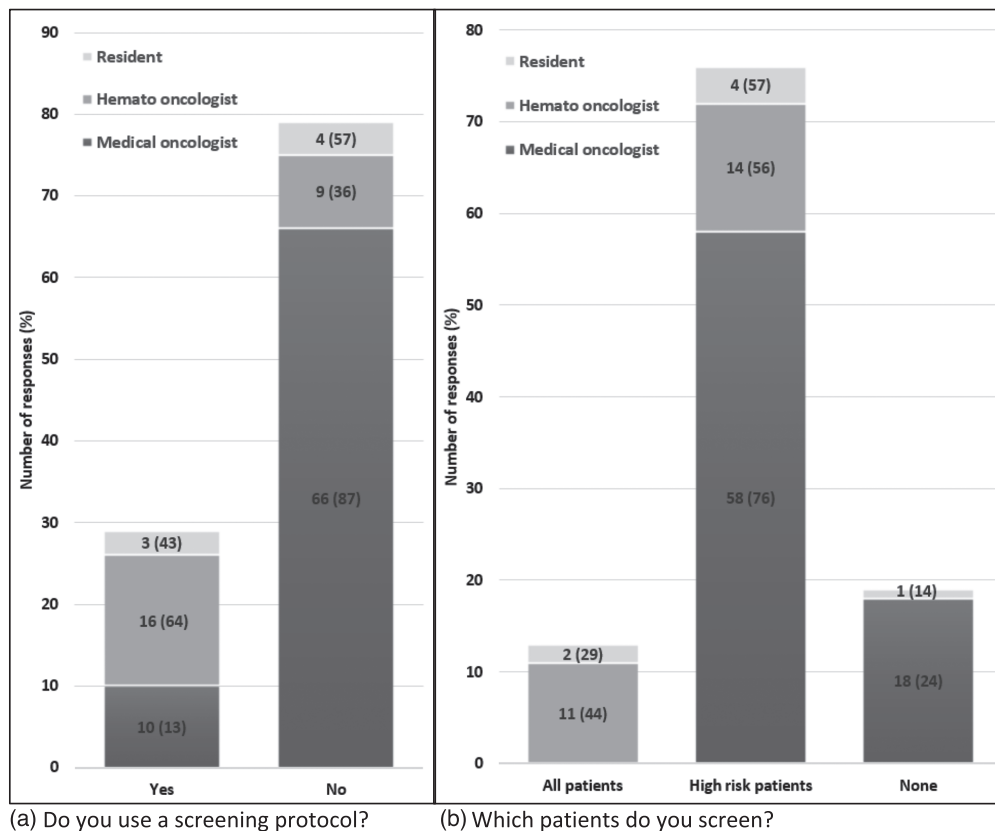


FIGURE 1 Hepatitis B virus screening. (a) Do you use a screening protocol? (b) Which patients do you screen?

TABLE 2 Patients considered at risk for hepatitis B reactivation

	Total (91)	Medical oncologist (67)	Haemato-oncologist (19)	Resident (15)
Patients born in an HBV endemic region (or parents from endemic region)	66 (73)	49 (73)	14 (74)	3 (60)
Patient with high risk behaviour (iv-drug use, sexual risk behaviour etc.)	60 (66)	44 (66)	14 (74)	2 (40)
Patients with high risk medication	68 (75)	48 (72)	17 (89)	3 (60)

Abbreviations: HBV, hepatitis B virus; iv, intravenous.

viral prophylaxes. In chronic HBV-infected patients treated with low risk medication, 76% of the respondents would start anti-viral prophylaxis or refer to a specialist. This increased to 98% of the respondents when high risk medication was used. Within this cohort of oncologists, 14% experienced one or more HBVr in their patients.

4 | DISCUSSION

The results of our survey suggest that HBV screening before start of chemotherapy is not common practice. This is in line with previous studies investigating the HBV screening rate in the oncology population (Day et al., 2011; Lee et al., 2012; Tran et al., 2010).

In contrast to international guidelines that mention HBV screening before start of chemotherapy, HBV screening is not mentioned in Dutch oncology guidelines which is a reason to not perform (universal) HBV screening for several respondents. In contrast, guidelines for haematologists, infectious disease specialists and gastroenterologists do mention HBV screening before start of chemotherapy, likely explaining the difference we found in screening behaviour between haemato-oncologists and medical oncologists. In addition, rheumatologist seem to be aware of the risk of HBVr as they prescribe immunosuppressive therapy to their patients (Toka et al., 2019). This also illustrates that the expertise of different medical specialists is not always shared, which might be a missed opportunity to improve patient care.

A prospective study analysed different risk-assessment tools to predict the risk of HBV in American patients starting with anti-cancer therapy (Hwang et al., 2018). They found that, using a five-question HBV screening tool, the majority of patients still needed HBV testing before start of treatment and concluded that universal HBV screening is more efficient. In low endemic countries like the Netherlands, the risk of HBVr might be highest when high risk therapy is initiated; therefore, this must be a cornerstone in HBVr risk-assessment. However, as correct identification of patients at risk for HBVr is notoriously difficult, we and others advocate universal screening over high risk based screening (Hwang et al., 2012). In our study, the most notable result was that almost one quarter of the medical oncologists stated never to perform HBV screening, while 14% of the respondents reported an experience with HBVr.

Only a minority of the respondents, especially the medical oncologist, have a local protocol for HBV screening. We noticed that many respondents were not sure which tests to order for HBV screening.

Also, encountered with a positive HBV screening test in different cases, the respondents would act very diverse and sometimes even inadequate referring to the answers for chronic HBV infected patients.

Strength of this study is that next to the screening rates, also the reason for screening practice was questioned. Furthermore, we tried to get insight in general knowledge among oncologists about HBV and the risk of reactivation. For this, we asked oncologists which patients they consider to be at risk for HBVr and which HBV test they perform depending on patient characteristics.

A limitation is the relatively small sample size and low response rate, therefore we cannot rule out selection bias. However, if oncologist have experienced a HBVr in their practice, they are likely more prone to respond; hence, these study results may be even an over-estimation of the real screening rate.

In conclusion, introduction of an easy to find national HBV screening protocol for oncologists can provide clarity about whom to test, the required diagnostic tests, policy in case of a positive test result and appropriate follow-up during chemotherapy. An automatic warning or checklist, concerning HBV testing, when prescribing high risk medication could be helpful and some rheumatologists already use such a warning that prevents prescription of rituximab if HBV screening results are not available. We think that knowledge of international guidelines, adjustment of the Dutch oncology guidelines and a change of screening behaviour of the medical oncologists might contribute to a reduction of the risk of HBVr during chemotherapy.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

AUTHOR CONTRIBUTIONS

KL, JO, MC and FL designed the study. The survey, data collection and the first draft was written by KL. Analyses were performed by KL, MC and FL. All authors wrote and commented on previous versions of the manuscript and read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

All data will be available on request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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