Current Hepatitis B Screening Practices and Clinical Experience of Reactivation in Patients Undergoing Chemotherapy for Solid Tumors: A Nationwide Survey of Medical Oncologists

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Abstract

Purpose: Universal screening for chronic hepatitis B virus (HBV) before chemotherapy has been recommended by the Centers for Disease Control. We sought to determine the practice of Australian oncologists with regard to HBV screening in patients with solid tumors (STs) and their clinical experience of HBV reactivation (HBVR).

Methods: A survey was sent to all consultant members of the Medical Oncology Group of Australia. One hundred eighty-eight responses (63% response rate) were received. We also reviewed the incidence of HBV in patients with STs screened at the Peter MacCallum Cancer Centre (Melbourne, Australia).

Results: Fifty-three percent of medical oncologists screen for HBV, but only 19% screen all patients. The most common reasons given for performing screening were anecdotal experience of HBVR (46%) and perceived sufficient evidence for screening of some patient subgroups (42%). Sixty-five percent of those who screened did so only in subgroups, usually selecting patients on the basis of ethnicity (82%). Oncologists who did not screen most commonly cited inadequate evidence for a benefit of screening (72%). Twenty-two percent of oncologists had witnessed one or more HBVR events, representing one event per 45 years of respondents' practice. HBVR events reported (n = 54) consisted of asymptomatic liver test abnormalities only (44%), symptomatic hepatitis (28%), decompensated liver failure (19%), and death (7%). In 206 patients with STs screened for HBV, 1.0% (n = 2) were HBV surface antigen positive, and 14.9% hepatitis B core antibody positive.

Conclusion: The majority of Australian medical oncologists have not adopted universal HBV screening before chemotherapy. Further evidence of the benefit and cost effectiveness of universal screening in patients with STs will be required to alter practice.

Introduction

Chronic hepatitis B virus (HBV) is endemic in southeastern Asia, China, western Pacific Islands, and Africa, where > 8% of the population may have HBV surface antigen (HBSAg) positivity.[1] In contrast, the population prevalence in the United States is estimated as 0.3% to 0.5%,[1] and in Australia as 0.7% to 1.1%.[2,3] Many immunosuppressive therapies have been implicated in the reactivation of chronic HBV, whereby the latent virus replicates in hepatocytes without adequate immunosurveillance.[4] Such reactivation events span a clinical spectrum from asymptomatic liver function test (LFT) abnormalities to fulminant hepatitis and death. The first reports of HBV reactivation (HBVR) were in patients receiving treatment for hematologic malignancies.[5-7] High rates of HBVR, 38% to 54%, are now recognized in HBV-positive patients undergoing hematopoietic stem-cell transplantation and treatment for lymphoma.[8,9]

Less clear is the magnitude of risk for clinically significant HBVR with chemotherapy for solid tumors (STs). Compared to patients with hematologic malignancies, patients with STs have lower baseline perturbation of immune function and generally receive chemotherapy less intense in immunosuppressive capacity. Studies investigating reactivation risks in HBV-positive patients with mixed STs found rates of 14% among 50 patients[10] and 19% among 78 patients.[11] When patients with lymphoma are excluded from these series, reactivation rates drop to 8% and 15%, respectively. The highest reactivation rates published in patients with STs undergoing chemotherapy are in two studies from Hong Kong. The authors report rates of 41% among 41 patients with breast cancer[12] and 36% among 102 patients with hepatocellular carcinoma (HCC).[13]

With respect to interventions to prevent HBVR with chemotherapy, a number of small prospective studies have examined the benefit of prophylactic administration of the nucleoside analog lamivudine. The relative risk of HBVR has been reported as 0.0 to 0.21 with lamivudine use.[14] Large randomized controlled trials of prophylactic antiviral therapy are lacking, however, and newer antiviral agents may be preferable to lamivudine[15] but are yet to be tested at all in this setting.

Guidelines recommending HBV screening for all patients before any form of immunosuppressive therapy were issued by the US Centers for Disease Control in 2008.[1] In 2009, the American Association for the Study of Liver Diseases (AASLD) amended their guidelines for prechemotherapy screening from testing only patients thought to be high risk of harboring chronic HBV[16] to universal testing.[15] Similar recommendations have been in place in Australia since 2006[17-19] but, anecdotally, do not appear to have been widely adopted among medical oncologists. A national survey of oncologists was therefore conducted, with the goals of determining (1) the current rate of HBV screening before chemotherapy for STs, the patient groups screened (if any), and the reasons underlying these

practices; (2) the number of career HBVR events witnessed by medical oncologists and basic details of these events. Concurrent with this, data concerning HBV carriage rate were collected from patients with STs at our own institution (the Peter MacCallum Cancer Centre, Melbourne, Australia).

Methods

National Survey

An electronic survey invitation was sent to members of the Medical Oncology Group of Australia. This society is the representative body of Australian medical oncologists and has almost universal membership. Doctors in training, hematologists, pediatric oncologists, and retired members were excluded. The survey comprised two parts, the first investigating current HBV screening practices, and the second the oncologists' experience of HBVR events among their patients.

Most survey questions were in a multiple-choice format. Where response options were considered mutually exclusive, only a single option could be selected, whereas other questions allowed the selection of multiple responses. Free text responses under the option "other" were available for some questions. The survey contained skip functions to tailor question flow to participants' responses. The first three questions requested basic oncology practice demographics (years of practice, state and region of practice). Pilot testing of the survey was undertaken by three medical oncologists who were not involved in its development.

The initial electronic survey invitation was sent by e-mail in June 2009. E-mail reminders were then sent at 1- and 2-month intervals. In September 2009, the survey was sent in paper form by postal mail to oncologists not known to have participated electronically. Both forms of the survey allowed anonymous participation. Duplicate survey responses were prevented by the electronic survey tool, and the mailed paper survey version was introduced to oncologists as an invitation only to those who had not already responded electronically. Ethics approval for the survey was granted by the Ethics Committee of our own institution and by the Medical Oncology Group of Australia Executive Committee.

Statistical Analyses

Responses to the electronic and paper survey versions were pooled. Statistical analyses were completed using SAS version 9 (SAS Institute, Cary, NC). Heterogeneity in screening practices was assessed by Pearson's exact χ^2 P values for region and state, and by an exact two-sided Cochran-Armitage trend test for years in practice.

Prevalence of Chronic HBV in Patients With STs

A policy of universal screening with HBSAg and hepatitis B core antibody (HBcAb) before chemotherapy was introduced in our institution in April 2009. To allow a 2-month policy introduction period, patients prescribed a new chemotherapy regimen between June 1 and November 30, 2009, were the subjects of this analysis. Patients undergoing HBV screening were identified by cross-referencing of all new electronic chemotherapy prescriptions for STs in this period and institution-wide HBV serology testing.

Results

Survey Participants

One hundred eighty-eight of 300 medical oncologists completed the survey, yielding a response rate of 63%. Responses were received from oncologists in every Australian state. Eighty-three percent of respondents practiced within a major city, and the remainder within a regional area. No oncologist practiced solely within a rural area. Respondents' years in consultant oncology practice were as follows: 0 to 5 years (25%), 6 to 10 years (21%), 11 to 15 years (21%), 16 to 20 years (11%), > 20 years (21%); median duration was 12 years (range, 1 to 40 years). The cumulative total of all participants' consultant oncology practice was 2,451 years.

Survey Part 1: HBV Screening Practices

Survey questions and results for all respondents are as shown in Table 1. Fifty-three percent (SE 4%) of medical oncologists ever screen for chronic HBV infection before chemotherapy. Among those oncologists who perform screening (n = 100), many had been doing so before the publication of universal screening guidelines, including 29% for > 5 years. The majority (65%) who conducted screening did so only in selected patient subgroups. Universal screening was practiced by 35% of those ever screening, representing 19% of all participating oncologists.

The most common reasons given for performing any HBV screening were belief in an adequate evidence base for screening of selected patient subgroups, anecdotal experience of HBV reactivation, and hospital-based policy (Table 1). In the subgroup conducting universal screening specifically (n = 35), a predominance of hospital-based policy as a rationale for screening was seen (71% *v* 39% overall), as well as an increased belief in adequate evidence for global screening (23% *v* 10%). Other results for screening rationales in this group were belief in adequate evidence for selected screening (17%), guidelines of a professional society (26%), and anecdotal experience of HBVR (46%). In oncologists who screened selectively, patients were chosen for HBV testing most commonly on the basis of ethnicity (Table 1).

Among the 47% of oncologists who never performed HBV screening before chemotherapy, most (72%) cited inadequate evidence for a benefit of screening as the basis of their current practice (Table 1). Thirty-three percent of oncologists selected "other" as the basis of their choice not to screen for HBV and entered free text comments. Review by the authors found that most free text comments conformed to a belief in inadequate evidence of the need to perform screening.

Associations were sought between ever performing HBV screening and respondent demographics. Practice in a major city, compared with a regional area, was significantly associated with HBV screening (58% *v* 30%, respectively; $P = .005$), as

Table 1. Screening Practices for Chronic Hepatitis B Infection in Patients Starting Chemotherapy for Solid Tumors

Question	No. (N = 188)	%
1. In your current practice, do you ever screen for hepatitis B infection in patients starting chemotherapy for solid tumors? (Please note that screening differs from investigation of abnormal physical examination, blood test, or imaging results)		
Yes	100	53
No	88	47
"No" responders proceeded to question 9		
2. How long have you been screening for hepatitis B infection?		
< 1 yr	16	16
1-2 yr	29	29
2-5 yr	26	26
> 5 yr	29	29
3. What is your rationale for screening patients? (can choose multiple)		
Adequate evidence base for global screening	10	10
Adequate evidence base for screening in selected subgroups	42	42
Guidelines of professional society	16	16
Hospital-based recommendations or policy	39	39
Anecdotal experience of hepatitis B reactivation	46	46
Other	13	13
4. Do you screen all patients or selected subgroups?		
All patients	35	35
Selected subgroups	65	65
"All patients" responders proceeded to question 7		
5. Do you select patients for screening on the basis of (can choose multiple)		
Tumor type?	19	29
Chemotherapy regimen?	21	32
Patient ethnicity?	53	82
Other patient factors?	29	45
All responses other than "tumor type" proceeded to question 7		
6. In which tumors do you screen for hepatitis B before chemotherapy? (can choose multiple)		
Breast cancer	8	42
Lymphoma	12	63
Other	7	37
7. Which pathology tests do you request when screening? (can choose multiple)		
Hepatitis B surface antigen	72	72
Hepatitis B anti-core antibody	43	43
Hepatitis B surface antibody	40	40
Unsure, eg, as per pathology laboratory protocol	29	29
I also screen for hepatitis C infection	56	56
I also screen for HIV infection	16	16
8. In detected hepatitis B–positive patients does your management involve (can choose multiple)		
Monitoring only?	11	11
Antiviral treatment, eg, lamivudine?	56	56
Referral to a specialist unit, eg, infectious diseases or liver unit?	88	88
Other?	3	3
Only oncologists answering "No" to question 1:		
9. What is your rationale for not screening patients (can choose multiple)?		
Inadequate evidence for a benefit of screening	63	72
Unsatisfactory cost-benefit ratio for screening	20	23
Concern about delaying or unduly complicating chemotherapy	4	5
Other	29	33

Table 2. Career History of Witnessed Hepatitis B Virus Reactivation Events Attributable to Chemotherapy

Question	No. (N = 188)	%
1. Have you witnessed any cases of hepatitis B reactivation in patients undergoing chemotherapy for solid tumors, for whom you were the primary treating oncologist?		
Yes	42	22
No	146	78
Only those oncologists answering "Yes" to question 1:		
2. How many cases have you witnessed for which you were the primary treating oncologist?		
1	33	79
2	5	12
3	2	5
4	0	0
5	0	0
> 5	1	2

was fewer years in practice ($P = .01$). There was also an association with state of practice ($P = .01$), but this was attributable to zero of eight medical oncologists screening in one particular state; there was no significant difference in the screening rate between other Australian states.

Survey Part 2: Clinical Experience of HBVR

Fifty-four reactivation events in patients undergoing chemotherapy for STs were reported by the 188 respondents. Twenty-two percent of oncologists (n = 42) had been the primary treating physician for a patient with HBVR, of whom the majority (79%) had witnessed a single event (Table 2). One oncologist reported witnessing more than five events; however, the survey accommodated detailed recording of a maximum of five events. Division of participants' 2,451 cumulative years of practice by the 54 HBVR events resulted in one event witnessed per 45.4 years, with the potential for minor variance in this finding had recording of more than five HBVR cases by one respondent been allowed.

The clinical details of recalled HBVR events are as shown in Table 3. Events occurred most frequently in patients of Asian ethnicity (46%), most commonly consisted of abnormal liver enzymes only (44%), and did not result in interruption of chemotherapy (44%). However, 10 episodes of decompensated liver failure and four deaths were reported. Reactivation occurred across a range of malignancies and chemotherapy regimens.

Single-Institution HBV Screening in Patients With STs

Of the patients beginning chemotherapy for STs during the 6-month study period, 206 (35.2%) were tested for HBSAg. One hundred eighty-one of these (30.9%) were also tested for HBcAb. Two patients were HBSAg positive (1.0%), and 27 were HBcAb positive (14.9%). One of the two HBSAg-positive patients had been previously diagnosed with chronic HBV, whereas the other was newly diagnosed.

Table 3. Clinical Characteristics of Patients With Hepatitis B Virus Reactivation Attributable to Chemotherapy

Characteristic	No. (Total 54)	%
Patient ethnicity		
Aboriginal	0	0
African	0	0
Asian	25	46
Caucasian	16	30
Pacific Islander	8	15
Other	3	6
Not stated	2	4
Tumor type		
Breast cancer	15	28
Lymphoma	13	24
Other	20	37
Not stated	6	11
Severity of reactivation		
Asymptomatic elevation in LFT	24	44
Symptomatic hepatitis	15	28
Decompensated liver failure	10	19
Death	4	7
Not stated	1	2
Was chemotherapy delayed?		
No	24	44
Yes, but treatment continued	13	24
Chemotherapy was ceased	16	30
Not stated	1	2
Which chemotherapy had the patient been receiving?*		
Anthracycline-based	16	30
Cisplatin-based	3	6
Fluoropyrimidine-based	4	7
Lymphoma regimens†	12	22
Other‡	8	15
Not stated	11	20

Abbreviation: LFT, liver function test.
* Free text responses entered by participants, categorized to chemotherapy class by the authors.
† Including rituximab alone (3 cases) and with chemotherapy (7 cases).
‡ Cyclophosphamide, methotrexate, fluorouracil (3); methotrexate (2); gemcitabine (1); fludarabine (1); temozolomide (1).

Discussion

The goal of this study was to determine current HBV screening practices among Australian medical oncologists and their experience of HBVR. Our nationwide study surveyed medical oncologists only and achieved a response rate of 63%, significantly higher than two previous US surveys that were not restricted to medical oncologists.[20,21] Similar to the prior studies, part 1 of this survey investigated the detail of screening practices and clinical management of chronic HBV during chemotherapy; however, we also inquired about the rationale behind these practices.

In this survey, 53% of oncologists reported performing HBV screening, although only 19% reported conducting universal testing. Practice location showed evidence of an associa-

tion with ever screening versus not screening, with oncologists in major cities significantly more likely to test for HBV than those based in regional areas. Approximately 50% of chronic HBV infections in Australia afflict immigrants from Asia,[22] greatly disproportionate to the overall 25% immigrant population, and placing the largest concentration of chronic HBV in major cities where migration is heaviest.[23] This was recently confirmed within Victoria, where in a large serosurvey, the incidence of HBSAg positivity was 1.5% in metropolitan areas versus 0.3% in nonmetropolitan areas, and HBcAb positivity was 7.6% versus 1.2%, respectively.[3]

Support for universal screening was markedly low among surveyed oncologists, including among those who do test for HBV. Only 10% of those who performed any screening cited a belief in adequate evidence for global patient screening, and this figure was only marginally higher (23%) in those who actually conducted global screening. In the latter group, hospital-based policy was the main impetus for their practice (71%). To explore the argument for selective screening, we questioned participants with this practice regarding the patient subgroups chosen. Whereas patient ethnicity, tumor type, and treatment regimen were all selected as indicators by > 25% of oncologists, patient ethnicity was easily the strongest consideration, selected by 82%. "Other patient factors" was also chosen by 45%, and free text entries cited a range of known behavioral risk factors for HBV, most commonly a history of intravenous drug use. In screen-detected HBV-positive patients, 88% of oncologists would seek appropriate advice regarding treatment, and 56% would arrange antiviral prophylaxis. Only 11% of oncologists selected "monitoring only" as a management strategy, in contrast with a survey in the Washington, DC, area, where only 46% of oncologists would consider prophylaxis in chronic HBV carriers, and resolved HBV infection was considered a stronger indication for prophylaxis (selected by 52%).[21] Taken together, our survey findings suggest that participating oncologists who perform screening are aware of basic aspects of HBV epidemiology and clinical management, and have made a considered decision regarding their practice.

Many factors need to be considered in determining the benefit of a universal HBV screening policy. Key clinical aspects include the prevalence of chronic HBV in the population in question, the proportion of infections not already diagnosed, the risk of reactivation with the treatment proposed, and the potential clinical sequelae of reactivation events. Accurate data on these aspects of chronic HBV in patients with STs are surprisingly limited, and this limitation is particularly pertinent in Australia, where oncology and hematology practices are divided such that medical oncologists generally manage STs only, although this may include lymphomas.

With respect to the prevalence of chronic HBV in patients newly diagnosed with STs, incidence may vary from overall population results and even between tumor types. For example, similar geographical areas of endemicity for HBV and high nasopharyngeal carcinoma incidence[24] mean that an association between these tumors and higher HBV carriage is likely, and HBV is implicated in the genesis of HCC.[25] The two published studies that address HBV prevalence in patients beginning chemotherapy for mixed STs found a prevalence of 5.3% among 1,008 patients in Greece,[10] and 12.5% among 626 patients in Hong Kong (HCC excluded).[11] In the latter study, chronic HBV prevalence varied from 5% to 24% depending on tumor type. Data from a US cancer hospital were recently presented by Hwang et al[26] and included subcategorization for nonlymphoma STs. This retrospective study found a 3.8% rate of HBSAg positivity in patients with STs,[26] much higher than the overall US population prevalence; however, only 3% of the cohort were screened, making selection bias likely.

We investigated HBV prevalence within our own institution, an inner-city tertiary care cancer hospital. In 206 patients with STs, the chronic HBV prevalence of 1.0% was similar to the Australian population incidence. Interestingly, however, evidence of prior HBV exposure, as determined by HBcAb positivity, was higher than population estimates; 14.9% versus 6.1 to 9.4%, respectively.[2-3] Whether this is attributable to a true higher incidence of HBV exposure in patients newly diagnosed with STs, is an artifact of small sample size, or is in part related to our hospital location is not clear. Current AASLD and Australian guidelines do not recommend antiviral prophylaxis during chemotherapy for patients with isolated HBcAb positivity, although monitoring of HBV seromarkers is recommended.[15,19] Despite reports of HBVR in HBSAg-negative, HBcAb-positive patients,[27,28] in large series the incidence of HBVR in this group is very low, even during treatment for lymphoma.[29,30]

Available data regarding the spectrum and proportions of potential clinical sequelae of HBVR in patients with nonlymphoma STs are limited. Alexopoulos et al imply that clinical hepatitis occurred in some (unspecified) of seven patients with HBVR, but all showed a complete recovery,[10] and Yeo et al describe several patients with coagulopathy but no liver-related mortality.[11] The study in breast cancer demonstrating the highest reactivation rate in STs[12] reported no episodes of icteric hepatitis or hepatic decompensation, and subsequent complete normalization of LFT in all patients. The best characterized spectrum of HBVR severity comes from the study of patients with HCC treated in a phase III anthracycline-based chemotherapy trial,[13] in which approximately half of the 36% of patients who experienced HBVR developed icteric hepatitis, and two thirds of those died as a result. This series is not representative of the larger cohort of patients with STs, however, given the likelihood of baseline advanced cirrhosis in these patients.

In an attempt to gather information on the frequency and nature of HBVR in patients with STs, the second part of this survey documented the clinical details of 54 HBVR events. Our findings were that HBVR is rare, with 78% of oncologists never having witnessed an event among their patients and, overall, one case described per 45 years of consultant practice. The spectrum of clinical manifestations of HBVR was similar to that expected in the context of the limited international literature, with minor events dominating (44% abnormal LFT only), but severe complications possible. Forty-four percent of reported

HBVR cases did not result in chemotherapy delay (possibly because of the common occurrence of HBVR after treatment completion[31]), whereas 24% of patients experienced delay but continued treatment, and 30% required cessation of chemotherapy. These findings are in line with the published series of HBVR in breast cancer, where these results were 29%, 35%, and 35%, respectively.[12] In our survey, reported HBVR cases were related to anthracycline-based chemotherapy regimens in 30% of patients, and lymphoma treatment protocols in 22%; including three patients who received rituximab alone. Only 7% of cases were related to fluoropyrimidine-based treatment and 6% to cisplatin-based treatment. Although the denominator for these treatment protocols is not known, anthracyclines,[11,32] corticosteroids,[32-34] and rituximab[35] have been previously implicated as treatment-related risk factors for HBVR.

Limitations of our method of data collection for investigating HBVR include the reliance on physician recall of HBVR events, the inability of the authors to confirm the diagnosis of HBVR in each reported case, and conversely the possibility that events were under-reported as a result of failure to recognize cases of HBVR. Although HBVR can be expected to be a memorable chemotherapy complication, 2% to 20% of the associated clinical details could not be recalled, with chemotherapy regimen being the most difficult. Despite these flaws, the cases reported are a valuable reflection of > 2,000 aggregate years of consultant oncology practice and add to the minimal data available on HBVR in patients with STs.

The main finding in this survey of a 19% universal prechemotherapy HBV screening rate among Australian oncologists is similar to the findings of the pooled hematologist and oncologist surveys from the United States, which reported respective universal testing rates of 13% and 14%.[20,21] Recently the American Society of Clinical Oncology issued a Provisional Clinical Opinion highlighting the insufficient evidence base for the recommendation of universal HBV screening by the Centers for Disease Control, and discussed many of the above shortcomings in data regarding HBVR risk in patients with STs and the use of antiviral prophylaxis.[36] This document concluded that clinical judgement should be exercised in the individualized application of prechemotherapy HBV testing until such time as an adequate evidence base exists to support a net benefit from universal screening. Our results regarding the practice of Australian medical oncologists suggest that they would largely agree with this conclusion. Further evidence of the benefit and cost effectiveness of universal HBV screening in patients with STs will be required to alter practice.

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