original report

Cost Effectiveness of Universal Hepatitis B Virus Screening in Patients Beginning Chemotherapy for Sarcomas or GI Stromal Tumors

Glorijoy Tan
Ke Zhou
Chee Hian Tan
David B. Matchar
Mohamad Farid
Richard Quek
Joanne Ngeow

abstract

Purpose The value of screening for hepatitis B virus (HBV) infection before chemotherapy for non-hematopoietic solid tumors remains unsettled. We evaluated the cost effectiveness of universal screening before systemic therapy for sarcomas, including GI stromal tumors (GISTs).

Patients and Methods Drawing from the National Cancer Centre Singapore database of 1,039 patients with sarcomas, we analyzed the clinical records of 485 patients who received systemic therapy. Using a Markov model, we compared the cost effectiveness of a screen-all versus screen-none strategy in this population.

Results A total of 237 patients were screened for HBV infection. No patients developed HBV reactivation during chemotherapy. The incremental cost-effectiveness ratio per quality-adjusted life-year (QALY) of offering HBV screening to all patients with sarcomas and patients with GISTs exceeded the cost-effectiveness threshold of SG$100,000 per QALY. This result was robust in one-way sensitivity analysis. Our results show that only changes in mortality rate secondary to HBV reactivation could make the incremental cost-effectiveness ratio cross the cost-effectiveness threshold.

Conclusion Universal HBV screening in patients with sarcomas or GISTs undergoing chemotherapy is not cost effective at a willingness to pay of SG$100,000 per QALY and may not be required.

J Glob Oncol 2.

Glorijoy Tan, **Chee Hian Tan**, **Mohamad Farid**, **Richard Quek**, and **Joanne Ngeow**, National Cancer Centre Singapore; **Glorijoy Tan** and **Chee Hian Tan**, Tan Tock Seng Hospital; and **Ke Zhou**, **David B. Matchar**, **Mohamad Farid**, **Richard Quek**, and **Joanne Ngeow**, Duke–National University of Singapore Graduate Medical School, Singapore.

Supported in part by a National Medical Research Council Transition Award (J.N.) and by the National Cancer Centre Singapore Division of Medical Oncology, which provided seed funding for retrieval of archival data.

G.T. and K.Z. contributed equally to this work. M.F., R.Q., and J.N. are joint senior authors.

Authors' disclosures of potential conflicts of interest and contributions are found at the end of this article.

Corresponding author: Joanne Ngeow, MBBS, MRCP, MPH, National Cancer Centre Singapore, Division of Medical Oncology, 11 Hospital Drive, 169610, Singapore 6436 8000; e-mail: joanne.ngeow.y.y@singhealth.com.sg.

INTRODUCTION

Hepatitis B virus (HBV) reactivation (HBVr) is a well-recognized complication of immunosuppressive therapy in patients chronically infected with HBV, defined as those positive for hepatitis B surface antigen (HBsAg). HBVr is associated with a range of complications, and in patients with cancer, this can lead to delay or premature discontinuation of chemotherapy and compromise oncologic outcomes. The use of particular therapies in certain tumors renders specific groups of patients susceptible to HBVr.[1,2] B lymphocyte–depleting agents, such as rituximab, the monoclonal antibody against CD20, are especially immunosuppressive. Their use in the treatment of B-cell non-Hodgkin lymphoma, in concert with steroids, causes HBVr in up to half of HBsAg-positive patients with lymphoma treated with rituximab-based regimens.[3-5] Several prospective trials have shown reductions in rates of HBVr and HBV flare with use of prophylactic antiviral therapy in this population.[6,7] Universal screening for HBV in treatment of B-cell non-Hodgkin lymphoma is thus effective. It has also been shown to be cost effective[8] and is now universally recommended when initiating therapy in patients with lymphoma.[9]

The data for universal HBV screening in solid tumors are less clear. A cost-effectiveness analysis by Day et al[10] using a model based on the treatment of solid tumors revealed a pooled cost-effectiveness ratio of nearly $150,000 per life-year saved. The study included only patients undergoing chemotherapy for early breast cancer or advanced non–small-cell lung cancer. The absence of directly immunosuppressive treatment and the less favorable natural history and treatment outcomes in advanced solid tumors compared with lymphoma have been offered as reasons for this disparity. However, the heterogeneity in biology, prognosis, and therapeutic regimens used for various solid tumors probably necessitates tumor-specific evaluations of the cost effectiveness of universal HBV screening. This is especially important to systematic evaluation in an

HBV-endemic region like Singapore, where the high prevalence of chronic HBV infection (3.6%)[11] would, according to the latest ASCO provisional clinical opinion update, necessitate that all patients be screened before starting systemic therapy.[9]

Sarcomas are heterogeneous yet uncommon tumors of mesenchymal origin that comprise 1% of adult malignancies.[12] In the setting of advanced disease, they are often treated with myelosuppressive cytotoxics, either singly or in combination; objective response rates are modest, with median survival of only 12 months.[13] GI stromal tumors (GISTs) are a striking exception to this rule, having become the prototype for successful targeting of oncogene-addicted cancers. With the development of imatinib, a potent inhibitor of the cKIT oncoprotein constitutionally activated in the majority of GISTs, median survival in patients with advanced GISTs is now 5 years.[14] Other than several case reports documenting HBVr with the use of imatinib,[15,16] to our knowledge, there has been no systematic evaluation of the value of HBV screening when treating sarcoma. Compared with other solid tumors, the doses and drugs used for systemic therapy in treatment of sarcoma are typically much higher. It would thus be of clinical interest to study this population of patients who receive therapy that is expectantly more myelotoxic. In this study, we sought to evaluate the incidence of HBVr in patients receiving chemotherapy for sarcomas or GISTs using data from this database, and to assess the cost effectiveness of universal screening for HBV infection before treatment initiation.

PATIENTS AND METHODS

We identified 1,039 patients who were diagnosed with biopsy-proven bony or soft tissue sarcomas or GISTs between January 1, 1992, and December 31, 2013, who were receiving medical treatment at the National Cancer Centre Singapore. Patients who did not receive any systemic therapy during this period were excluded from the study, leaving 274 evaluable patients with sarcomas and 211

Table 1 – Demographic and Clinical Characteristics of Patients With Sarcomas or GISTs Who Received Chemotherapy (N = 485)

Characteristic	All Patients (N = 485)		Patients With Sarcomas (n = 274)*		Patients With GISTs (n = 211)	
	No.	%	No.	%	No.	%
Sex						
Male	250	51.5	128	46.7	122	57.8
Female	235	48.5	146	53.3	89	42.2
Age, years						
Median	53.1		48.7		58.1	
Range	4.6-89.0		4.6-89.0		16.2-89.0	
Race						
Chinese	361	74.4	191	69.7	170	80.6
Malay	36	7.4	16	5.8	20	9.5
Indian	19	3.9	15	5.5	4	1.9
Other	69	14.2	52	19.0	17	8.1
Chemotherapy intent						
Neoadjuvant	50	10.3	44	16.1	6	2.8
Adjuvant	167	34.4	83	30.3	84	39.8
Palliative	268	55.3	147	53.6	121	57.3
Unscreened	248	51.1	135	49.3	84	39.8
Screened	237	48.9	139	50.7	127	60.2
Chronic HBV carrier (HBsAg positive)	13	5.5	6	4.3	7	8.3
Previous HBV infection (HBcAb positive and HBsAg negative)	28	11.8	15	10.8	11	13.1
Screened negative (HBsAg negative ± HBcAb negative)	196	82.7	118	84.9	66	78.6

Abbreviations: GIST, GI stromal tumor; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B virus surface antigen; HBV, hepatitis B virus.
*Subgroup data listed in Appendix Table A1.

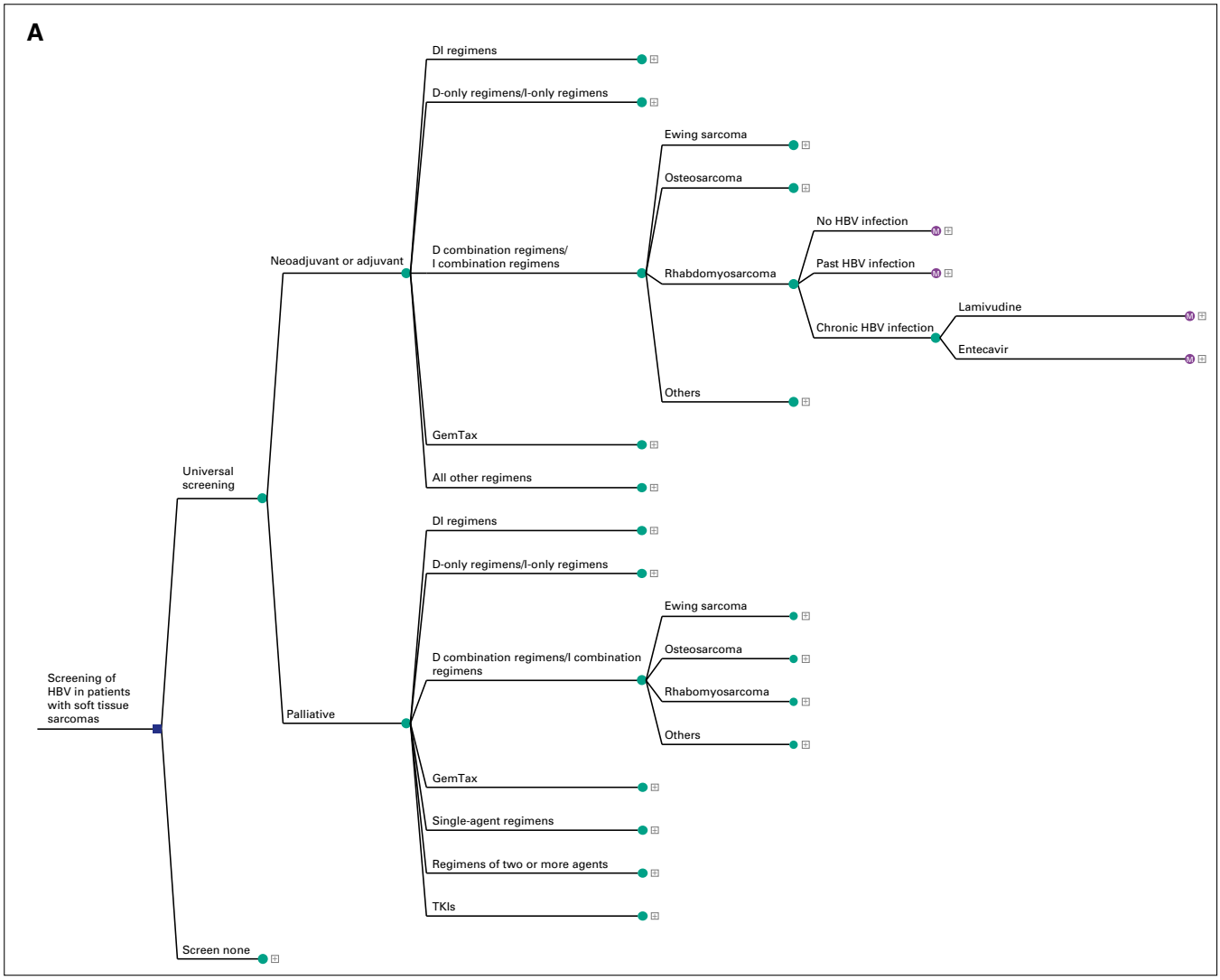


Fig 1 –
Model structure. (A) Diagram illustrates the structure of the Markov model of hepatitis B virus (HBV) screening in patients with sarcomas receiving chemotherapy. Square node denotes the two strategies in this study: universal screening and no screening. Patients under both strategies were classified according to intent of chemotherapy and type of drug combination used according to expected immunosuppressive effect. Regimens included doxorubicin only (D only), ifosfamide only (I only), doxorubicin and ifosfamide combination (DI), other doxorubicin or other

with GISTs (Table 1). The medical records of these patients were reviewed.

Definition of HBV Screening and HBVr

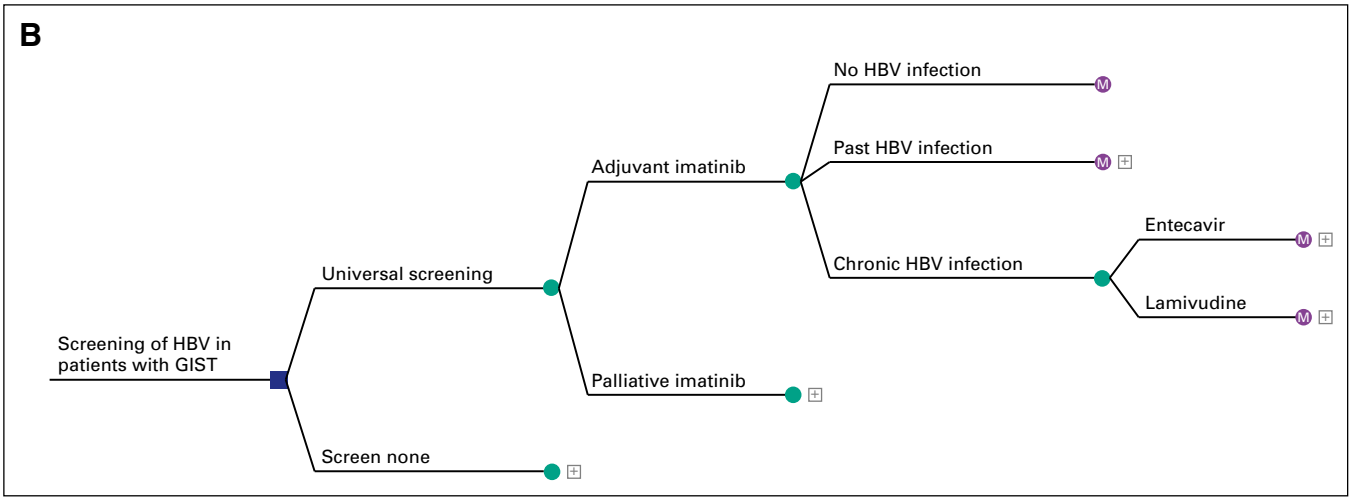
Patients were considered to have been screened when HBsAg testing was performed at any time before or up to within 6 months of initiation of systemic therapy. Chronic HBV infection is defined as being positive for HBsAg. Within the screened population, patients who were found to be HBV core antibody positive and HBsAg negative were considered to have had past HBV infection.

On the basis of a definition previously described by Lok et al,[17] hepatitis was defined as an abrupt rise in serum ALT of more than three-fold the upper limit of the laboratory reference range or an absolute increase of ALT to more than 100 U/L compared with prechemotherapy values.

Hepatitis attributable to an HBVr was defined as the presence of hepatitis as described earlier, as well as a rise in HBV DNA of 10-fold or more compared with prechemotherapy values or an absolute increase of more than 10^5 copies/mL.[18] Base-case values for HBVr and transition probabilities of hepatitis were estimated from our clinical cohort of 485 patients. The ranges of these parameters were derived from review of the literature.

Modeling Approach

We created a Markov model (Fig 1) to examine the cost effectiveness of a screen-all strategy versus a screen-none strategy in patients with sarcomas or GISTs who were beginning neoadjuvant, adjuvant, or palliative chemotherapy. The sarcoma and GIST populations were analyzed using separate models.



ifosfamide combinations (other D/other I), gemcitabine and taxane combination (GemTax), other single-agent regimens, and combination regimens of two or more agents. We further subdivided the other D/other I group into various subtypes as follows: rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, and others. Each subgroup of patients was further categorized depending on whether patients were chronically infected with HBV, had HBV infections that resolved, or had never been infected with HBV. Only one such breakdown is shown in the diagram because the rest shared the same structure. All patients were observed until death. The difference between the universal screening arm and no-screening arm are was that patients with chronic HBV were treated with lamivudine or entacavir prophylaxis. Circle M indicates the time point when follow-up started. Only the universal screening arm is shown because the other arm has an identical structure. (B) Diagram illustrates the structure of the Markov model of HBV screening in patients with GI stromal tumors (GISTs) receiving chemotherapy. The only difference from (A) is that

Patients under both strategies were categorized according to clinical indications for chemotherapy (ie, neoadjuvant, adjuvant, or palliative chemotherapy) and further categorized based on chemotherapy regimen according to the myelosuppressive effect expected. The population of patients who received palliative chemotherapy was subdivided into various chemotherapy groups similarly.

Within the screen-all strategy, patients were screened for HBsAg before initiation of chemotherapy. HBV prophylaxis was then administered to patients who were chronic HBV carriers using either oral lamivudine (100 mg once per day) or entecavir (0.5 mg once per day) at the start of chemotherapy and continued for 6 months beyond completion. None of the patients within the screen-none strategy received antiviral prophylaxis.

Each patient moved from various states within a Markov model, as illustrated in Figure 1. These health states included mortality risks associated with other medical conditions, HBV infection, and cancer. The input data for mortality related to other medical conditions was obtained from a life table, whereas cancer-specific mortality was obtained from trial data. Mortality rate from HBVr was modeled as a cause of death independent of cancer or other medical conditions.

Model Inputs

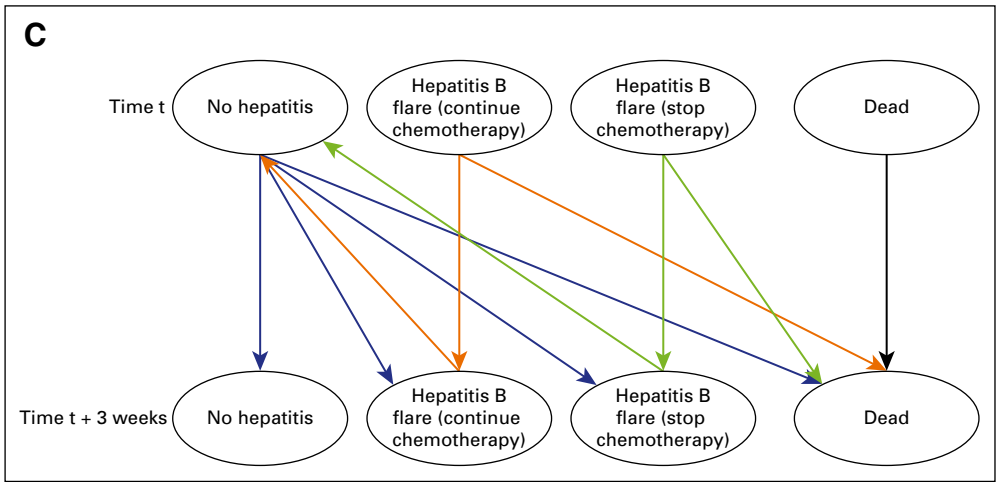
The proportion of patients falling into each category was estimated with retrospective analysis of our cohort of patients with sarcomas or GISTs. The clinical probabilities used were based on our clinical cohort of 485 patients. Probability estimates of HBVr for sensitivity analysis were derived from systematic review of the literature (Table 2).

Cost-Effectiveness Analysis

All costs were adjusted to 2015 Singapore dollar values (cost details listed in Appendix Table A2). Effectiveness was quantified in terms of quality-adjusted life-years (QALYs), which are the sum of products of health state utility and the duration in each health state. Costs and QALYs were discounted at 3%.[30] We calculated incremental cost-effectiveness ratios (ICERs), defined as the additional cost in Singapore dollars per gain in QALYs in patients using the more expensive strategy over the less expensive strategy. We used an ICER of SG$100,000 per QALY instead of $50,000 per QALY as the cost-effectiveness threshold, because it was thought to reflect inflation and economic growth in the past two decades,[31] and it has been used in other published cost-effectiveness analyses.[32] Cost effectiveness was calculated from the societal perspective limited to direct medical costs.

To account for uncertainty in parameter estimates, we conducted a one-way sensitivity analysis by examining ICERs with different inputs of each parameter within plausible range. We also performed a probabilistic sensitivity analysis by simultaneously sampling values for all parameters from their plausible ranges and calculating the distribution of ICERs for 10,000 iterations. Beta and gamma distributions were used to represent probability parameters and cost parameters, respectively.[33] All analyses were performed using TreeAge Pro 2015 (TreeAge Software, Williamstown, MA).

patients with GISTs were classified according only to intent of chemotherapy. (C) All patients, except for patients without HBV infection, may develop hepatitis, which may be followed by discontinuation of chemotherapy, continuation of chemotherapy despite reactivation, resolution of hepatitis, or death. Patients without hepatitis may die as a result of cancer or other causes. Patients with hepatitis flare may die as a result of hepatitis, cancer, or other causes. The Markov cycle length was assigned to be 3 weeks, which is the duration of one cycle of chemotherapy. TKI, tyrosine kinase inhibitor.



RESULTS

There were 274 patients with sarcomas and 211 patients with GISTs who received systemic therapy. Among all 485 patients who received chemotherapy, 237 (48.9%) were screened for HBV infection before initiation of chemotherapy (Table 1). Of the screened population, 13 patients (5.5%) were found to be chronic HBV carriers, and 28 (11.8%) were found to have had past HBV infection (subgroup analysis summarized in Appendix

Table 2 – Clinical Event Probabilities and Utilities

Variable	Base Case	Range	Reference
Clinical event probabilities			
Prevalence of chronic HBV infection, %	3.9	2.9-4.2	Ang[11]
Prevalence of past HBV infection, %	11.8	4.4-38.9	Ang[11]
Risk of HBVr with lamivudine, %	21.7	12-39.3	Kim,[4] Li,[19] Seetharam,[20] Chen[21]
Risk of HBVr with entecavir, %	2.2	0-6.3	Kim,[4] Li,[19] Seetharam,[20] Chen[21]
Rate of stopping chemotherapy because of HBVr	0.33	Not varied	Day[22]
Proportion of HBVr resulting in death, %	7	3.5*-71	Day,[10] Kawsar[23]
Relative risk of HBVr			
No entecavir *v* entecavir	7.5	1-58.5	Huang[6,7]
No lamivudine *v* lamivudine	5.3	1.7-16.4	Huang,[7] Yeo[24]
Duration of chemotherapy, weeks			
Sarcomas	18	10-25	Judson[13]
GISTs, adjuvant	130	18-156	Dematteo,[25] Joensuu[26]
GISTs, palliative	130	18-520	Blay[27]
Utility			
Sarcomas			
Neoadjuvant or adjuvant intention chemotherapy	0.42	0.34-0.50	Guest[28]
Palliative intention chemotherapy	0.07	0.01-0.12	Guest[28]
GISTs			
Neoadjuvant or adjuvant intention chemotherapy	0.743	0.712-0.775	Poole[29]
Palliative intention chemotherapy	0.513	0.414-0.612	Poole[29]

Abbreviations: GIST, GI stromal tumor; HBV, hepatitis B virus; HBVr, hepatitis B virus reactivation.
*Assumed to be half of the base-case value.

Table 3 – Cost, Effectiveness, and ICER at Base Case

Screening Strategy	Mean Survival (years)	Incremental Survival (years)	Cost (SG$)	Incremental Cost (SG$)	Effectiveness (QALYs)	Incremental Effectiveness (QALYs)	ICER (SG$/QALY)
Sarcomas							
All patients							
None	4.30	—	14,926	—	0.831	—	—
Universal	4.31	0.01	15,240	314	0.833	0.002	226,771
Adjuvant or neoadjuvant							
None	7.22	—	17,587	—	1.677	—	—
Universal	7.23	0.01	17,979	392	1.680	0.003	138,071
Palliative							
None	1.783	—	12,622	—	0.0987	—	—
Universal	1.786	0.003	12,870	248	0.0989	0.0002	1,855,517
GISTs							
All patients							
None	11.50	—	120,881	—	2.975	—	—
Universal	11.53	0.03	123,448	2,567	2.982	0.0074	393,900
Adjuvant or neoadjuvant							
None	19.79	—	134,060	—	4.76	—	—
Universal	19.83	0.04	136,368	2,308	4.77	0.01	216,138
Palliative							
None	5.35	—	111,100	—	1.651	—	–
Universal	5.36	0.01	113,859	2,759	1.654	0.003	805,121

Abbreviations: GIST, GI stromal tumor; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

Tables A1 and A3). This is consistent with the national incidence of HBV in Singapore.[11]

Base-Case Analysis

Table 3 lists the results of the base-case analysis. If HBV screening and prophylaxis were not offered, patients with sarcomas or GISTs who received chemotherapy would be expected to survive 4.3 and 11.5 years, respectively, which translated into 0.831 and 2.98 QALYs, respectively, when adjusted for utility and discounted for gains in the future. The difference in QALYs is attributable to the longer survival time and higher health state utility of patients with GISTs compared with patients with sarcomas. However, costs related to chemotherapy and treatment of HBVr are also higher for patients with GISTs than for those with sarcomas (SG $120,881 *v* SG$14,926), which is attributable to longer duration of chemotherapy and higher accumulated risks for HBVr among patients with GISTs.

In the base case, screening for both patients with sarcomas and patients with GISTs exceeded the SG$100,000 threshold by at least two-fold. Offering HBV screening led to greater improvements in QALYs for patients with GISTs than for those with sarcomas (0.007 *v* 0.002 QALYs), but at a higher incremental cost (SG$2,567 *v* SG$314); the net effect was that the ICER of offering HBV screening to all patients with sarcomas was smaller than that of offering screening to those with GISTs (SG $226,771 *v* SG$393,900 per QALY).

When the cost effectiveness of screening subgroups of patients based on therapeutic intentions was examined, screening those who received chemotherapy for adjuvant or neoadjuvant intentions was much more cost effective than palliative intentions (SG$138,071 *v* SG$1,855,517 per QALY for patients with sarcomas and SG$216,138 *v* SG $805,121 per QALY for patients with GISTs). However, even the smallest ICERs of these subgroup analyses was still higher than the cost-effectiveness threshold of SG$100,000 per QALY.

Sensitivity Analyses

One-way sensitivity analyses were conducted to determine the input parameters to which the

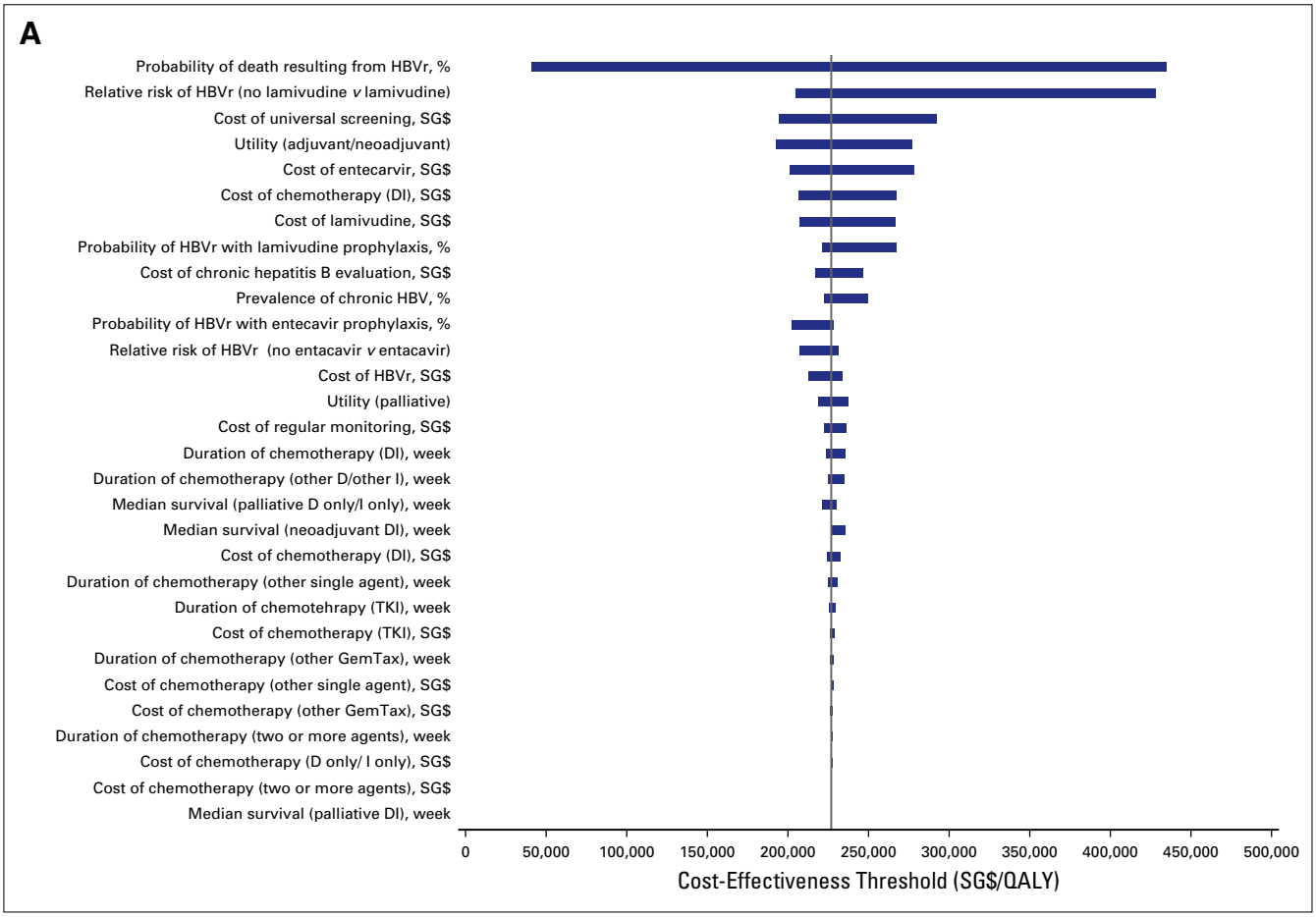


Fig 2 –
One-way sensitivity analysis. Diagram illustrates the range of incremental cost-effectiveness ratios (ICERs) of hepatitis B virus (HBV) screening in patients with (A) sarcomas or (B) GI stromal tumors (GISTs) when the value of each parameter is varied within plausible range when keeping the other variables constant. The axes cross at the base-case ICER (SG $226,771 per quality-adjusted life-year [QALY] for patients with sarcomas and SG$393,900 per QALY for patients with GISTs). Although the ICERs remained greater than the cost effectiveness of SG $100,000 per QALY when the values for most parameters were changed, HBV screening became cost effective when mortality risk resulting from

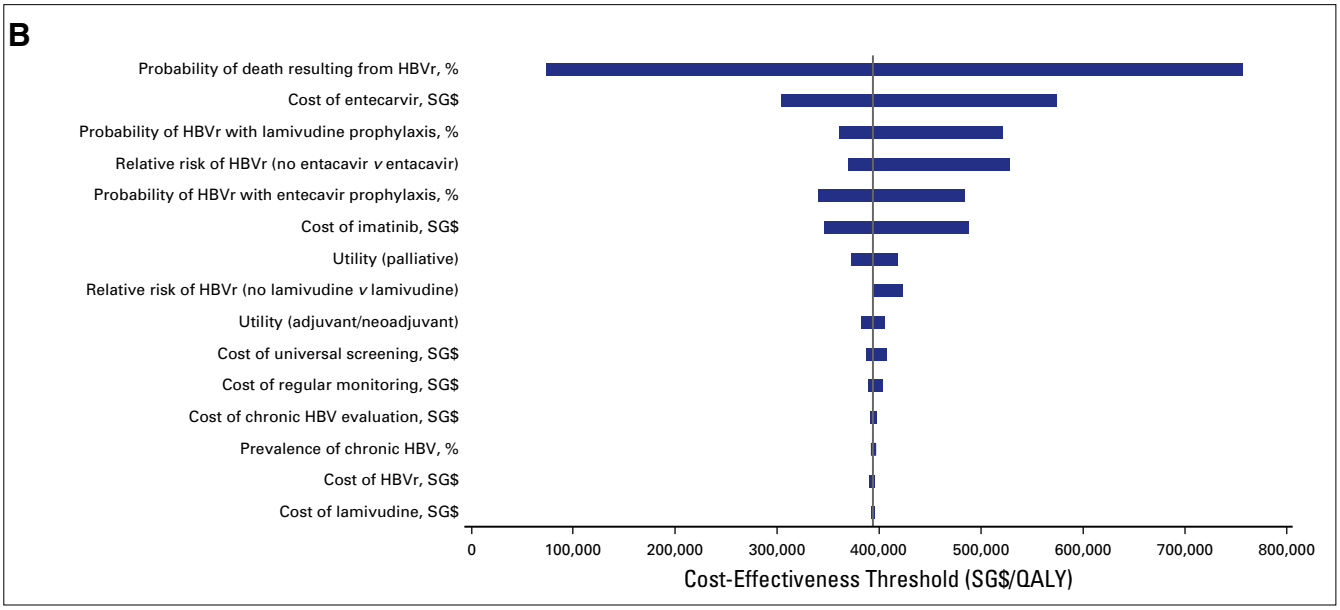
results were most sensitive. Our analysis of screening all patients with sarcomas revealed that only changes in mortality rate secondary to HBVr could make the ICER cross the cost-effectiveness threshold. Screening became increasingly cost effective with a high rate of death resulting from HBVr, and the rate at which it crossed SG $100,000 was 18% (Fig 2A). Similarly, the cost effectiveness of screening all patients with GISTs depended only on mortality rate secondary to HBVr. When mortality rate secondary to HBVr was greater than 38%, screening patients with GISTs for HBV became cost effective (Fig 2B).

Because there are no estimates of HBVr in patients with sarcomas or GISTs receiving chemotherapy in the literature, we examined conservative scenarios in which patients who received prophylaxis manifested no reactivation, whereas those who did not receive prophylaxis were subject to reactivation risk from 0% to 100%. Holding the other parameters at base-case value, the ICERs of conducting HBV screening in all patients with sarcomas and all patients with GISTs were greater than $190,000 and $280,000 per QALY, respectively, even when the risk of reactivation without prophylaxis was 100%.

Even at the higher bound of chronic HBV prevalence (4.2%), ICERs of screening patients with sarcomas or GISTs did not cross the cost-effectiveness threshold. The result was relatively robust to rates of reactivation with antiviral prophylaxis and utility states in both the palliative and neaoadjuvant or adjuvant arms. Probabilistic sensitivity analysis revealed that at a cost-effectiveness threshold of $100,000 per QALY, conducting HBV screening in patients with sarcomas and patients with GISTs before chemotherapy was not cost effective in 91.6% (Fig 3A) and 99.8% (Fig 3B) of the iterations, respectively.

DISCUSSION

The findings of this study lend support to the ASCO provisional clinical opinion that for patients who neither have HBV risk factors nor anticipate cancer therapy associated with a high risk of reactivation, current evidence does not support HBV screening before initiation of cancer therapy.[9] Even in a population in which HBV infection



HBV reactivation (HBVr) was greater than 18% for patients with sarcomas and 38% for those with GISTs. D, doxorubicin; I, ifosfamide.

is endemic, we have shown that it is not cost effective to practice universal screening for patients with sarcomas or GISTs.

Our analysis showed that the cost effectiveness of conducting HBV screening among patients with sarcomas or GISTs before chemotherapy depends on the probability of dying as a result of HBVr. The proportion of HBVr cases resulting in death may be affected by quality of health care infrastructure and availability of tertiary care that would vary geographically.

Our study used real-world data from a prospective clinical database with 485 patients, providing a more realistic application and analysis of the screen-all versus screen-none strategy. This is in contrast to previous cost-effectiveness analyses, which were purely based on input values derived from published literature. Our population was identified for study because there are no current available data regarding HBVr among patients with sarcomas or GISTs, making this the first comprehensive analysis to our knowledge of performing HBV screening in the sarcoma and GIST population. The population studied also encompassed a wide range of histologic subtypes, including both bony and soft tissue sarcomas, to accurately reflect the diversity of biologies and therapies. The systemic treatment of sarcomas involves the use of cytotoxic chemotherapy, either singly or in combination, associated with varying degrees of myelotoxicity. Conversely, GISTs are treated with small-molecule tyrosine kinase inhibitors. There is no evidence from our analysis that such therapies predispose patients with sarcomas or GISTs to HBVr, consistent with what has been shown for other solid tumors,[10] as distinct from the demonstrably immunosuppressive therapies used in the treatment of lymphoma and other hematologic malignancies.

Because of the scarcity of literature on HBVr in patients with sarcomas or GISTs and lack of reactivation within the database of data collected over 11 years, it was necessary to rely on data derived from published studies conducted among patients with lymphoma for our model inputs. We are aware of the clear association of anti-CD20–based therapy in lymphomas with HBVr as opposed to solid tumors, where such therapy is not used. As such, we could be confident that the ICERs we derived for sarcomas and GISTs would be underestimations, thus reinforcing the lack of cost effectiveness of HBV screening in sarcoma and GIST management.

Our study has a number of limitations. Sarcomas are a heterogeneous group of tumors with a wide spectrum of disease progression, response to treatment, and overall survival. In spite of this heterogeneity, sarcomas do share some common clinical features (eg, hematogenous rather than lymphatic spread and proclivity for lung metastasis) that lend clinical value to studying and managing them as one entity. To further account for this heterogeneity, we opted to divide patients into chemotherapy groups, within which patients may have had differing histologic subtypes. To address this limitation, we further classified one subgroup of patients who received other doxorubicin or ifosfamide combinations into histologic subtypes to better represent their disease characteristics (details provided in Modeling Approach in Appendix). The resultant small subset of

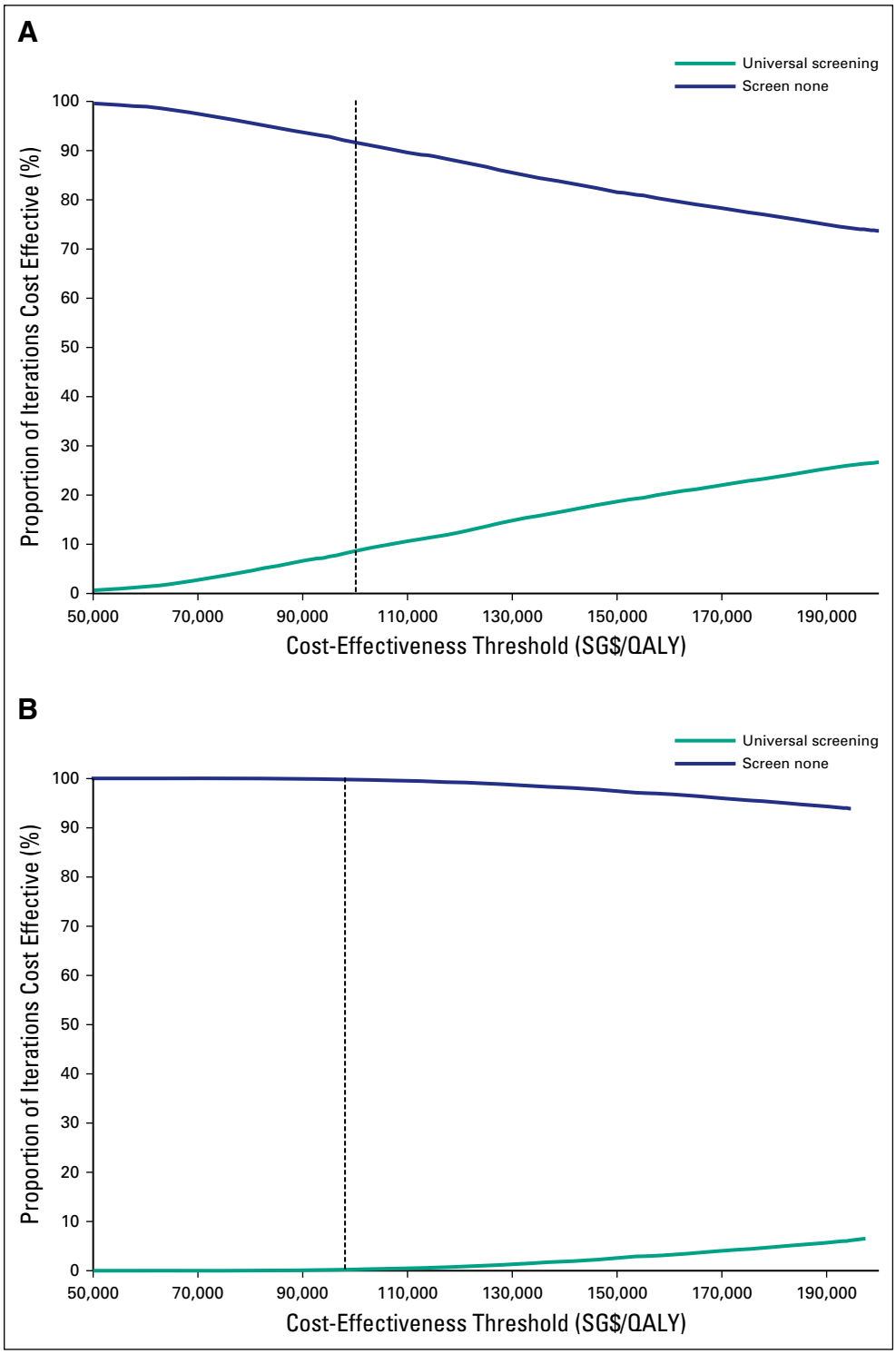


Fig 3 –
Probability sensitivity analysis. Diagram illustrates distributions of incremental cost-effectiveness ratios in 10,000 iterations of probabilistic sensitivity analysis in patients with (A) sarcomas or (B) GI stromal tumors (GISTs). With an increasing cost-effectiveness threshold, the universal screening approach is more likely to be cost effective. At a cost-effectiveness threshold of SG$100,000 per quality-adjusted life-year (QALY), 91.6% and 99.8% of the simulations suggested hepatitis B virus screening to be not cost effective for patients with sarcomas and GISTs, respectively.

chemotherapy groups may have masked the effect of more immunosuppressive therapies on reactivation rates. However, this was accounted for by sensitivity analysis in which we analyzed the results using the upper limits of reactivation rates described in the available literature. As such, the model output may be viewed as an estimate of the average cost effectiveness in any patients with sarcomas or GISTs. Our findings were consistent across both the neoadjuvant and palliative groups. The structure of our model is shown in Figure 1.

Although we found that the cost effectiveness of HBV screening was sensitive to the HBVr rate, it is notable that even at the highest reactivation rate,

the ICERs of HBV screening were still much higher than the cost-effectiveness threshold (Fig 2). We also performed a scenario analysis in which we assigned all the parameters taken from lymphoma literature to the extremes of their possible ranges to make screening as cost effective as possible. Even at the highest possible risk of HBVr with prophylaxis, we derived an ICER of SG$172,197 per QALY for sarcoma and SG$174,602 per QALY for GIST. In addition, it is worth noting that relative risks of HBVr (ie, effectiveness of prophylaxis in preventing HBVr) had similar or greater influence on ICERs compared with corresponding HBVr rates. However, range of ICERs yielded by different relative risk estimates stayed above the cost-effectiveness threshold. These results indicate that our conclusion would likely remain unchanged with a more accurate estimate of HBVr risk or effectiveness of prophylaxis.

We recognize that the prevalence of HBV carriage may differ across various populations, and certain at-risk groups such as intravenous drug abusers may have higher prevalence of HBV carriage and thus be at higher risk of HBVr. The prevalence of chronic HBV carriage in a needle-sharing community has been reported to be as high as 40.0% in Chinese populations.[34,35] Using these input values in our model generated an ICER of SG $168,167 per QALY with a prevalence of 40% for patients with sarcomas and SG$381,333 per QALY for patients with GISTs. Additionally, we conducted a sensitivity analysis by allowing the prevalence of chronic HBV infection to be as high as 88% (not 100%, because infection was resolved in 11.8% of patients who had a history of acute chronic infection). We found that the marginal reduction in ICER decreased as the prevalence of chronic infection rose and leveled off at more than SG$160,000 per QALY and SG $380,000 per QALY for sarcomas and GISTs, respectively, which were higher than the threshold of SG$100,000 per QALY. Therefore, we are confident that our conclusion will not be changed by the prevalence of chronic HBV infection.

The only parameter whose change may make HBV screening cross the cost-effectiveness threshold is the mortality risk resulting from HBVr. We found that if this risk exceeded 18% for patients with sarcomas and 38% for those with GISTs, conducting HBV screening would be cost effective. On the basis of clinical experience, the mortality rate resulting from HBVr is unlikely to be higher than 5% in our local contexts because of close monitoring and prompt treatment once HBVr is detected. We recognize, however, that HBVr-related mortality cannot be considered constant around the world.

Our study suggests that universal screening before chemotherapy for patients with sarcomas or GISTs is not cost effective at a willingness to pay of SG $100,000 per QALY and should not be advised as part of routine prechemotherapy assessment. An exception to this recommendation may be made in settings where mortality resulting from HBVr is substantial or if other risk factors exist.

DOI: 10.1200/JGO.2015.001669
Published online on jgo.ascopubs.org on February 17, 2016.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Financial support: Joanne Ngeow
Administrative support: Joanne Ngeow
Provision of study materials or patients: Richard Quek
Collection and assembly of data: All authors
Data analysis and interpretation: Glorijoy Tan, Ke Zhou, Chee Hian Tan, David B. Matchar, Mohamad Farid, Joanne Ngeow
Manuscript writing: All authors
Final approval of manuscript: All authors

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or jco.ascopubs.org/site/ifc.

Glorijoy Tan
No relationship to disclose

Ke Zhou
No relationship to disclose

Chee Hian Tan
No relationship to disclose

David B. Matchar
No relationship to disclose

Mohamad Farid
No relationship to disclose

Richard Quek
Honoraria: Novartis, Bayer, GlaxoSmithKline, Merck, Bristol-Myers Squibb
Consulting or Advisory Role: Novartis, Merck, Bristol-Myers Squibb, Bayer
Speakers' Bureau: Bayer, Merck
Travel, Accommodations, Expenses: Novartis, Roche
Other Relationship: Novartis, Janssen Pharmaceuticals, Bayer, GlaxoSmithKline, Pfizer

Joanne Ngeow
No relationship to disclose

REFERENCES

1. Ling WH, Soe PP, Pang AS, et al: Hepatitis B virus reactivation risk varies with different chemotherapy regimens commonly used in solid tumours. Br J Cancer 108:1931-1935, 2013
2. Hsu C, Tsou HH, Lin SJ, et al; Taiwan Cooperative Oncology Group. Chemotherapy-induced hepatitis B reactivation in lymphoma patients with resolved HBV infection: A prospective study. Hepatology 59:2092-2100, 2014
3. Seto WK, Chan TS, Hwang YY, et al: Hepatitis B reactivation in patients with previous hepatitis B virus exposure undergoing rituximab-containing chemotherapy for lymphoma: A prospective study. J Clin Oncol 32:3736-3743, 2014
4. Kim SJ, Hsu C, Song YQ, et al: Hepatitis B virus reactivation in B-cell lymphoma patients treated with rituximab: Analysis from the Asia Lymphoma Study Group. Eur J Cancer 49:3486-3496, 2013
5. Koo YX, Tan DS, Tan IB, et al: Hepatitis B virus reactivation and role of antiviral prophylaxis in lymphoma patients with past hepatitis B virus infection who are receiving chemoimmunotherapy. Cancer 116:115-121, 2010
6. Huang YH, Hsiao LT, Hong YC, et al: Randomized controlled trial of entecavir prophylaxis for rituximab-associated hepatitis B virus reactivation in patients with lymphoma and resolved hepatitis B. J Clin Oncol 31:2765-2772, 2013
7. Huang H, Li X, Zhu J, et al: Entecavir vs lamivudine for prevention of hepatitis B virus reactivation among patients with untreated diffuse large B-cell lymphoma receiving R-CHOP chemotherapy: A randomized clinical trial. JAMA 312: 2521-2530, 2014
8. Zurawska U, Hicks LK, Woo G, et al: Hepatitis B virus screening before chemotherapy for lymphoma: A cost-effectiveness analysis. J Clin Oncol 30:3167-3173, 2012
9. Hwang JP, Artz AS, Somerfield MR: Hepatitis B virus screening for patients with cancer before therapy: American Society of Clinical Oncology provisional clinical opinion update. J Oncol Pract 11:e487-e489, 2015
10. Day FL, Karnon J, and Rischin D: Cost-effectiveness of universal hepatitis B virus screening in patients beginning chemotherapy for solid tumors. J Clin Oncol 29:3270-3277, 2011
11. Ang LW, Cutter J, James L, et al: Seroepidemiology of hepatitis B virus infection among adults in Singapore: A 12-year review. Vaccine 32:103-110, 2013
12. Burningham Z, Hashibe M, Spector L, et al: The epidemiology of sarcoma. Clin Sarcoma Res 2:14, 2012
13. Judson I, Verweij J, Gelderblom H, et al: Doxorubicin alone versus intensified doxorubicin plus ifosfamide for first-line treatment of advanced or metastatic soft-tissue sarcoma: A randomised controlled phase 3 trial. Lancet Oncol 15:415-423, 2014
14. Blanke CD, Demetri GD, von Mehren M, et al: Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. J Clin Oncol 26:620-625, 2008
15. Walker EJ, Simko JP, Ko AH: Hepatitis B viral reactivation secondary to imatinib treatment in a patient with gastrointestinal stromal tumor. Anticancer Res 34:3629-3634, 2014
16. Lakhani S, Davidson L, Priebat DA, et al: Reactivation of chronic hepatitis B infection related to imatinib mesylate therapy. Hepatol Int 2:498-499, 2008
17. Lok AS, Liang RH, Chiu EK, et al: Reactivation of hepatitis B virus replication in patients receiving cytotoxic therapy: Report of a prospective study. Gastroenterology 100:182-188, 1991
18. Yeo W, Chan PK, Hui P, et al: Hepatitis B virus reactivation in breast cancer patients receiving cytotoxic chemotherapy: A prospective study. J Med Virol 70:553-561, 2003
19. Li HR, Huang JJ, Guo HQ, et al: Comparison of entecavir and lamivudine in preventing hepatitis B reactivation in lymphoma patients during chemotherapy. J Viral Hepat 18:877-883, 2011
20. Seetharam A, Perrillo R, Gish R: Immunosuppression in patients with chronic hepatitis B. Curr Hepatol Rep 13:235-244, 2014
21. Chen FW, Coyle L, Jones BE, et al: Entecavir versus lamivudine for hepatitis B prophylaxis in patients with haematological disease. Liver Int 33:1203-1210, 2013
22. Day FL, Link E, Thursky K, et al: Current hepatitis B screening practices and clinical experience of reactivation in patients undergoing chemotherapy for solid tumors: A nationwide survey of medical oncologists. J Oncol Pract 7:141-147, 2011
23. Kawsar HI, Shahnewaz J, Gopalakrishna KV, et al: Hepatitis B reactivation in cancer patients: Role of pre-chemotherapy screening and antiviral prophylaxis. Clin Adv Hematol Oncol 10:370-378, 2012
24. Yeo W, Chan PK, Ho WM, et al: Lamivudine for the prevention of hepatitis B virus reactivation in hepatitis B s-antigen seropositive cancer patients undergoing cytotoxic chemotherapy. J Clin Oncol 22:927-934, 2004
25. Dematteo RP, Ballman KV, Antonescu CR, et al: Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: A randomised, double-blind, placebo-controlled trial. Lancet 373:1097-1104, 2009
26. Joensuu H, Eriksson M, Sundby Hall K, et al: One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: A randomized trial. JAMA 307:1265-1272, 2012

27. Blay JY, Le Cesne A, Ray-Coquard I, et al: Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: The French Sarcoma Group. J Clin Oncol 25:1107-1113, 2007

28. Guest JF, Sladkevicius E, Gough N, et al: Utility values for advanced soft tissue sarcoma health states from the general public in the United Kingdom. Sarcoma [epub ahead of print on March 17, 2013]

29. Poole CD, Connolly MP, Chang J, et al: Health utility of patients with advanced gastrointestinal stromal tumors (GIST) after failure of imatinib and sunitinib: Findings from GRID, a randomized, double-blind, placebo-controlled phase III study of regorafenib versus placebo. Gastric Cancer 18:627-634, 2015

30. Siegel JE, Weinstein MC, Russell LB, et al: Recommendations for reporting cost-effectiveness analyses. JAMA 276: 1339-1341, 1996

31. van Hees F, Habbema JD, Meester RG, et al: Should colorectal cancer screening be considered in elderly persons without previous screening? A cost-effectiveness analysis. Ann Intern Med 160:750-759, 2014

32. Neumann PJ, Cohen JT, and Weinstein MC: Updating cost-effectiveness: The curious resilience of the $50,000-per-QALY threshold. N Engl J Med 371:796-797, 2014

33. Briggs AH, Goeree R, Blackhouse G, et al: Probabilistic analysis of cost-effectiveness models: Choosing between treatment strategies for gastroesophageal reflux disease. Med Decis Making 22:290-308, 2002

34. Wu Q, Zu J, Wei X, et al: Survey of hepatitis B infection and vaccination status among drug users in Xi'an [in Chinese]. Zhonghua Yu Fang Yi Xue Za Zhi 48:862-866, 2014

35. Xu CJ, Zhang CP, Luo BF, et al: Prevalence and characterization of hepatitis B and C virus infections in a needle-sharing population in northern China. BMC Public Health 15:460, 2015

APPENDIX

Modeling Approach

Patients under both strategies were categorized according to clinical indications for chemotherapy (ie, neoadjuvant, adjuvant, or palliative chemotherapy). Patients who received chemotherapy of neoadjuvant or adjuvant intent were further categorized based on chemotherapy regimen according to the myelosuppressive effect expected. For patients with sarcomas, these regimens included doxorubicin only, ifosfamide only, doxorubicin and ifosfamide combination, other doxorubicin or other ifosfamide combinations (other D/other I), gemcitabine and taxane combination, other single-agent regimens, and combination regimens of two or more combination agents. Given the heterogeneity of tumor subtypes of patients in the other D/other I category, we decided to further subdivide the other D/other I group into various subtypes as follows: rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, and others. This allowed a more accurate reflection of survival rates for each subgroup of patients. For patients with GISTs, the regimens were classified as tyrosine kinase inhibitors or others. The population of patients who received palliative chemotherapy was subdivided into various chemotherapy groups similarly.

Cost Details

Cost estimates for the various costs related to medical visits, medication, and laboratory tests were obtained from the National Cancer Centre Singapore laboratory and pharmacy billing database and are listed in Table A2. We assumed that charges in the bills were unbiased estimates of the service costs.

For patients who were screened to be hepatitis B surface antigen positive, baseline investigations for further evaluation included measurement of hepatitis B virus (HBV) DNA levels, liver function test, hepatitis B envelope antigen and antibody, abdominal ultrasound, international normalized ratio, and referral to a specialist. Recurring costs of regular monitoring with liver function tests, hepatitis B surface antigen, and HBV DNA were included at 3-month intervals during the potential reactivation period.

Costs incurred with HBV reactivation (HBVr) included standard biochemistry evaluation as well as evaluation for other possible causes of hepatitis. The cost of hospitalization related to HBVr was estimated using the national average hospitalization bill because there was no disease-specific publication related to HBVr in the local context.

Table A1 – Subgroup Data of Patients With Sarcomas Who Received Chemotherapy (n = 274)

Characteristic	Doxorubicin Only (n = 17)		Ifosfamide Only (n = 8)		Doxorubicin and Ifosfamide Only (n = 70)		Other Doxorubicin and Other Ifosfamide Combinations (n = 81)		Gemcitabine and Docetaxel Only		Tyrosine Kinase Inhibitor		Other Regimens (≥ two agents)		Other Regimens (single agent or unknown)	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Sex																
Male	4	23.5	5	62.5	35	50.0	40	49.4	3	20.0	4	57.1	7	46.7	30	49.2
Female	13	76.5	3	37.5	35	50.0	41	50.6	12	80.0	3	42.9	8	53.3	31	50.8
Age, years																
Median	49.2		61.4		48.5		36.5		51.8		58.8		44.1		63.1	
Range	20.9-63.8		34.7-73.6		16.8-68.5		4.7-67.6		24.1-68.2		23.9-83.2		17.7-73.5		4.6-89.0	
Race																
Chinese	14	82.4	6	75.0	52	74.3	46	56.8	10	66.7	5	71.4	12	80.0	46	75.4
Malay	2	11.8	1	12.5	4	5.7	5	6.2	1	6.7	0	0.0	0	0.0	3	4.9
Indian	0	0.0	0	0.0	5	7.1	5	6.2	1	6.7	0	0.0	1	6.7	3	4.9
Other	1	5.9	1	12.5	9	12.9	25	30.9	3	20.0	2	28.6	2	13.3	9	14.8
Chemotherapy intent																
Neoadjuvant	0	0.0	1	12.5	6	8.6	26	32.1	2	13.3	0	0.0	6	40.0	3	4.9
Adjuvant	6	35.3	1	12.5	24	34.3	32	39.5	5	33.3	2	28.6	2	13.3	12	19.7
Palliative	11	64.7	6	75.0	40	57.1	23	28.4	7	46.7	5	71.4	7	46.7	46.0	75.4
Unscreened	9	52.9	2	25.0	29	41.4	36	44.4	6	40.0	4	57.1	7	43.8	28	45.9
Screened	8	47.1	6	75.0	41	58.6	45	55.6	9	60.0	3	42.9	8	50.0	33	54.1
Chronic HBV carrier (HBsAg positive)	0	0.0	0	0.0	1	2.4	1	2.2	0	0.0	0	0.0	1	12.5	3	9.1
Previous HBV infection (HBcAb positive and HBsAg negative)	2	25.0	1	16.7	5	12.2	2	4.4	0	0.0	0	0.0	2	25.0	5	15.2
Screened negative (HBsAg negative ± HBcAb negative)	6	75.0	5	83.3	35	85.4	42	93.3	9	100.0	3	100.0	5	62.5	25	75.8

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

Table A2 – Cost Estimates

Variable	Base Case	Range*
Universal screening, SG$		
HBsAg	24	12-48
HBcAb	42	21-84
HBsAb	24	12-48
Chronic HBV evaluation, SG$		
HBV DNA	170	85-340
HBeAg, HBeAb	70	35-140
Liver function test	79	39.5-158
INR/PT/PTT	73	36.5-146
US HBS	176	88-352
Gastroenterologist referral	120	60-240
Antiviral medications		
Lamivudine for 1 month	87	43.5-174
Entecavir for 1 month	300	150-600
Monitoring, SG$		
HBsAg	24	12-48
HBV DNA	170	85-340
Liver function test	79	39.5-158
Hepatitis flare, SG$		
Hepatitis A, B, and C serology	165	82.5-330
Antinuclear, antimitochondrial antibody	71	35.5-142
Iron studies: Fe, transferrin, ferritin	72	36-144
Liver function test	79	39.5-158
INR/PT/PTT	73	36.5-146
CT AP	975	487.5-1,950
HBV DNA	170	85-340
HBeAg, HBeAb	70	35-140
Specialist referral	120	60-240
Hospitalization	6,000	3,000-12,000

Abbreviations: CT AP, computed tomography abdomen/pelvis; HBcAb, hepatitis B core antibody; HBeAb, hepatitis B envelope antibody; HBeAg, hepatitis B envelope antigen; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; INR, international normalized ratio; PT, prothrombin time; PTT, partial thromboplastin time; US HBS, ultrasound hepatobiliary system.
*Arbitrarily set to range from half of to two times the base-case values.

Table A3 – Patients Screened for HBV

	Patients With Sarcomas (n = 110)		Patients With GISTs (n = 127)	
HBV Status	No.	%	No.	%
Chronic HBV carriers	6	5.5	7	5.5
Prophylaxis administered	3	2.7	3	2.4
No prophylaxis administered	3	2.7	4	3.1
Previous HBV infection	17	15.5	11	8.7
Prophylaxis administered	3	2.7	1	0.8
No prophylaxis administered	14	12.7	10	7.9
HBVr	0	0.0	0	0.0

Abbreviations: GIST, GI stromal tumor; HBV, hepatitis B virus; HBVr, hepatitis B virus reactivation.