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Original Research

Incidence of hepatitis B reactivation during epidermal growth factor receptor tyrosine kinase inhibitor treatment in non–small-cell lung cancer patients

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KEYWORDS
Non–small-cell lung cancer;
Hepatitis B reactivation;
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Abstract ***Background:*** Reactivation of hepatitis B virus (HBV) is a documented risk during cytotoxic chemotherapy in patients with lung cancer. Cases of HBV reactivation in non–small-cell lung cancer (NSCLC) patients receiving epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment have been reported; however, the incidence of HBV reactivation in patients treated with EGFR TKIs has not yet been reported.
Materials and methods: We enrolled 171 patients who were diagnosed as having NSCLC from 2011 through 2017 and who also had positive hepatitis B surface antigen (HBsAg). All patients had received EGFR TKIs as anticancer treatment for at least 2 weeks during their treatment course. Reactivation of HBV is defined as one of the following: an increase in HBV DNA by at least 10-fold compared to baseline or an absolute increase to >10^5 IU/mL with abnormal liver function.
Results: The median duration of EGFR TKI treatment was 10.5 months (95% confidence interval: 8.2–12.8). Sixteen (9.36%) patients met the criteria of HBV reactivation during EGFR

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TKI treatment, with an annual incidence of 7.86%. HBV reactivation occurred during erlotinib treatment in 6 patients, followed by 5 patients with gefitinib treatments, 3 patients with osimertinib treatment and 2 with afatinib treatment. No independent risk factor for HBV reactivation was identified.

Conclusion: NSCLC patients receiving EGFR TKI treatment may have a clinically meaningful risk of HBV reactivation during the treatment period. Thus, monitoring liver function, HBV viral load and serology of HBV (i.e., HBeAg and anti-HBc) during EGFR TKI therapy is recommended for NSCLC patients with positive HBsAg.

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1. Introduction

Hepatitis B virus (HBV) infection is a worldwide medical problem; it was estimated that more than 2 billion people had chronic HBV infection [1]. This is an important issue in Asian populations due to the relatively higher prevalence of HBV infection in Asia than in other areas. In Taiwan, the prevalence of HBV infection is as high as 15%, especially for those older than 40 years old [2]. HBV infection may behave as a chronic infection, resulting in liver cirrhosis and hepatocellular carcinoma, or as a more aggressive infection, reactivating and inducing fulminant hepatitis, which leads to a high risk of mortality.

Many studies have reported that patients with haematological malignancy had a high risk of HBV reactivation while receiving cytotoxic and targeted therapy [3,4]. The highest risk group is patients with lymphoma receiving an anti-CD20 antibody-containing regimen. One study reported the incidence of HBV reactivation after receiving an anti-CD20 antibody-containing regimen was as high as 41.5%, even in patients with resolved HBV infection or an undetectable HBV viral load [5]. Besides haematological malignancies, more and more patients with solid tumours were reported as developing HBV reactivation during chemotherapy, including those with lung cancer [6], which causes the most cancer-related deaths worldwide (1.59 million deaths in 2012) [7]. In addition to chemotherapy, some studies reported tyrosine kinase inhibitors (TKIs) may also induce HBV reactivation [8]. After the Iressa Pan-Asia Study(IPASS), epidermal growth factor receptor (EGFR) TKIs became first-line anticancer treatment for advanced non–small-cell lung cancer (NSCLC) harbouring an activated EGFR mutation [9–12]. However, whether EGFR TKIs can induce HBV reactivation is as yet uncertain.

Therefore, the objective of this study was to identify the incidence of HBV reactivation in patients with NSCLC receiving EGFR TKIs as anticancer therapy. We also wanted to investigate the risk factors of HBV reactivation during EGFR TKI therapy.

2. Materials and methods

2.1. Patients and populations

For this retrospective study, all patients aged 18 years or older with a diagnosis of NSCLC from January 1, 2011, to December 31, 2017, at the National Taiwan University Hospital (NTUH) were identified. Eligibility criteria included the following: positive hepatitis B surface antigen (HBsAg) and having received EGFR TKIs (gefitinib, erlotinib, afatinib or osimertinib) as anticancer treatment during their treatment course. Exclusion criteria included the following: total duration of TKI treatment less than 2 weeks or therapy with investigational EGFR TKIs (such as CO1686, EGF816 or HS-10296). Baseline clinical characteristics, including age at diagnosis, sex, EGFR mutation type, kind of EGFR TKIs used, baseline liver function test, prior use of steroid or chemotherapy, history of anti-HBV therapy, liver metastasis or not, tumour histology and total duration of TKI treatment, were recorded by retrospective chart review. We also contacted the Taiwan Death Registry to check the survival status of patients who were lost to follow-up during the study period. If the patient had died, we recorded the date of death and calculated the overall survival (OS) of the patient. This investigation was approved by the NTUH Research Ethics Committee.

2.2. Definition of HBV reactivation and hepatitis flare up

Reactivation of HBV is defined as one of following: increase in HBV DNA by at least 10-fold compared to baseline or an absolute increase to $>10^5$ IU/mL combined with abnormal liver function for those with normal baseline liver function and no baseline HBV viral load data [13–15]. Hepatitis flare up was defined ALT level >100 IU/mL. If the patient met the criteria of

HBV reactivation, the duration of EGFR TKI treatment following HBV reactivation was then not calculated. The incidence calculation was not counted twice after HBV reactivation.

2.3. Statistical analysis

Categorical variables are reported as proportions. The compared data were analysed using Chi-square analysis or Fisher's exact test. $P < 0.05$ was considered significant. Logistic regression was applied to estimate odds ratios and confidence intervals (CIs). Patient OS was assessed using the Kaplan–Meier method. The log-rank test was used for comparison of survival curves of different characteristics. Statistical analysis was conducted using SPSS 25 for Windows. The data cut-off date was January 31, 2018.

3. Results

3.1. Patient characteristics

From January 1, 2011, to December 31, 2017, 7337 patients were diagnosed as having lung cancer at NTUH. Of these patients, 190 had positive HBsAg and received EGFR TKIs as anticancer treatment, including 148 who received EGFR TKIs as first-line treatment. After excluding patients with a total duration of EGFR TKIs less than 2 weeks and those receiving investigational EGFR TKIs, 171 patients were enrolled in this study (Fig. 1). The median follow-up time for these patients was 26.2 months (95% CI: 22.7–29.6). The patients were predominantly younger than 65 years (63.2%), female (57.3%), with a histology of adenocarcinoma (90.1%), with EGFR mutations

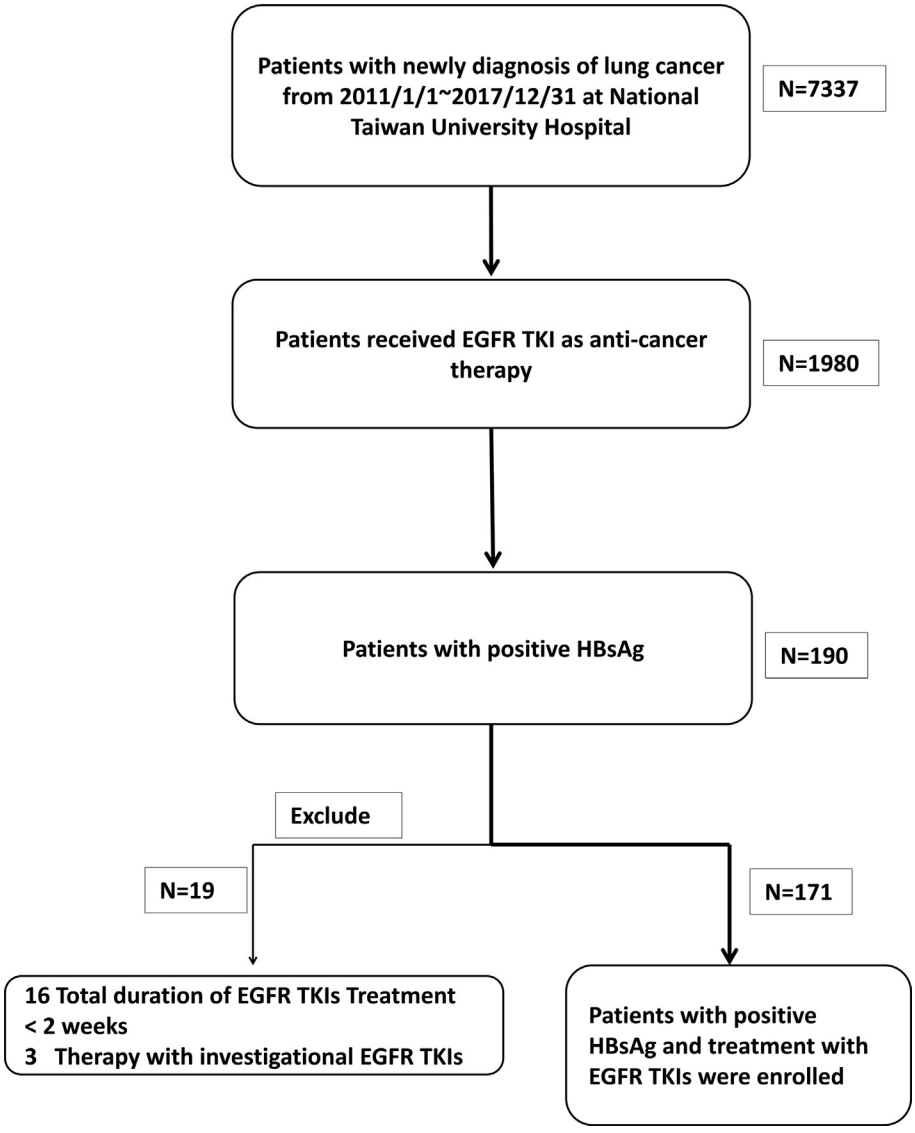

Fig. 1. Patient selection and exclusion criteria. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; HBsAg, hepatitis B surface antigen.

(81.9%) and normal hepatic enzyme before treatment (80.1%). The median age at diagnosis was 61.9 years. The most-used EGFR TKI was gefitinib (55.6%), followed by erlotinib (46.2%), afatinib (27.5%) and osimertinib (9.9%) (Table 1). Median total duration of EGFR TKI treatment was 10.5 months (95% CI: 8.2–12.8).

3.2. Patients with HBV reactivation

HBV reactivation occurred during erlotinib treatment in 6 patients, followed by 5 patients during gefitinib treatments, 3 patients during osimertinib treatment and 2 patients during afatinib treatment. Median time of onset of reactivation during EGFR TKI is 5.6 months (0.6–40 months) (Fig. 2). Most of the patients (13 of 16 patients) with HBV reactivation were diagnosed with the initial presentation of abnormal liver function during EGFR TKI treatment. There were only 3 patients whose liver function tests were within the normal limit at the time of HBV reactivation. These three patients received HBV viral load test as routine follow-up at hepatologist's clinic, and therefore, HBV reactivation was noticed incidentally. Among 16 patients with HBV reactivation, eight patients also met the criteria for hepatitis flare up. One patient had mild elevation of AST/ALT before anticancer therapy. Five patients had received anti-HBV therapy before EGFR TKI treatment for HBV prophylaxis during chemotherapy (Table 2), and one patient was coinfected with chronic hepatitis C. The median age was 72 years (40–92 years). Median OS was 44.5 months (95% CI: 2.9–86.1), and there was no significant difference between patients with and without HBV reactivation (median OS: 26.2 months, 95% CI: 22.7–29.6) (Fig. 3). There was also no HBV reactivation–related death.

3.3. Difference between patients with and without HBV reactivation

Of the 171 patients, 16 met the criteria for HBV reactivation and 8 had evidence of hepatitis flare up. Annual incidence of HBV reactivation was 7.86%. There was no significant difference in age, gender, EGFR mutation status, liver function before treatment, experience using chemotherapy, steroid or anti-HBV therapy before TKI treatment, liver metastasis or total duration of EGFR TKI treatment between the 'reactivation' and 'non-

Table 1
Baseline characteristics.

Characteristic	Without HBV Reactivation No. (%)	With HBV Reactivation No. (%)	P-value
Age (36–92 years)			
<65 y/o	101 (65.2%)	7 (43.8%)	0.091
≥65 y/o	54 (34.8%)	9 (56.2%)	
Gender			
Female	87 (56.1%)	11 (68.8%)	0.331
Male	68 (43.9%)	5 (31.2%)	
Liver metastasis			
Yes	13 (8.4%)	0 (0%)	0.228
No	142 (91.6%)	16 (100%)	
Use of anti-HBV agent before EGFR TKI treatment			
Yes	66 (42.6%)	5 (31.2%)	0.381
No	89 (57.4%)	11 (68.8%)	
Liver function before EGFR TKI treatment			
Normal	126 (81.3%)	11 (68.8%)	0.231
Abnormal	29 (18.7%)	5 (31.2%)	
EGFR mutation status			
With mutation	125 (80.6%)	15 (93.7%)	0.195
Wild type or unknown	30 (19.4%)	1 (6.3%)	
Anticancer treatment			
Gefitinib	85 (54.8%)	10 (62.5%)	0.557
Erlotinib	71 (45.8%)	8 (50%)	0.749
Afatinib	42 (27.1)	5 (31.2%)	0.723
Osimertinib	14 (9.0%)	3 (18.8%)	0.216
Chemotherapy[a] before TKI	60 (38.7%)	6 (37.5%)	0.925
Total duration of EGFR TKI treatment			
<10 months	73 (47.1%)	8 (50%)	0.825
≥10 months	82 (52.9%)	8 (50%)	
Pathology			
Adenocarcinoma	138 (89.0%)	16 (100%)	0.377
Squamous cell carcinoma	10 (6.5%)	0 (0%)	
NOS	7 (4.5%)	0 (0%)	

HBV, hepatitis B virus; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; NOS, not otherwise specified.
[a] Chemotherapy includes cisplatin, carboplatin, pemetrexed, Navelbine, gemcitabine, paclitaxel, docetaxel.

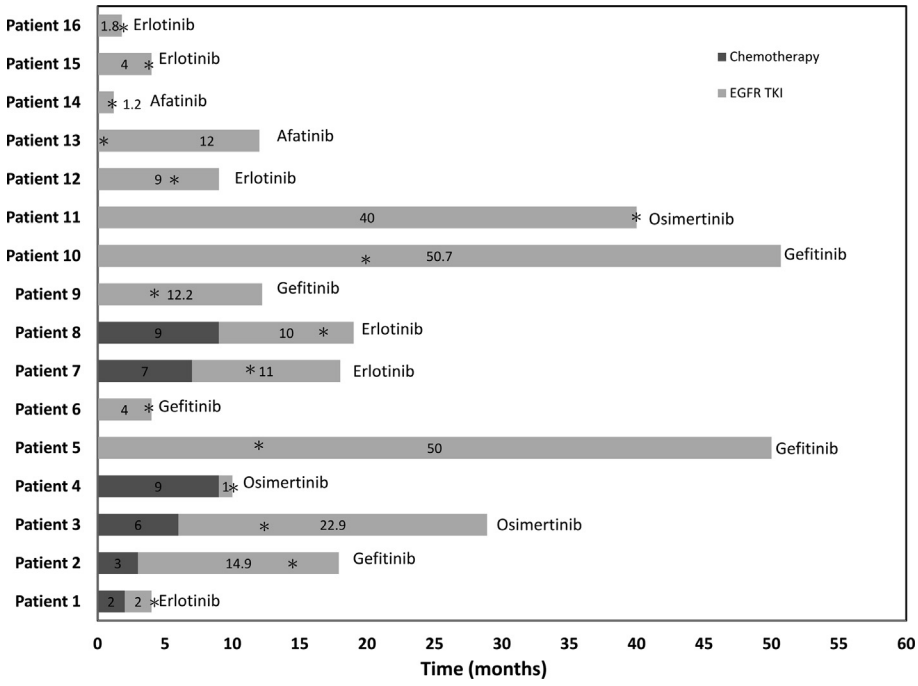

Fig. 2. Duration of TKI therapy. ∗Timing of HBV reactivation. EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Table 2
Profile of patients with HBV reactivation.

Patient	Age	AST/ALT before TKI treatment	Change of HBV viral load (IU/mL)	AST/ALT during HBV reactivation	Anti-HBV before TKI	TKI during HBV reactivation	Anti-HBV therapy after HBVR
Patient 1	81	Normal	81000000[a]	2X	Nil	Erlotinib	Nil
Patient 2	74	Normal	0 ≥ 730	Normal	Yes	Gefitinib	Nil
Patient 3	56	Normal	0 ≥ 18100000	5X	Yes	Osimertinib	Yes
Patient 4	75	1.5X	0 =＞ 112000	10X	Yes	Osimertinib	Yes
Patient 5	40	Normal	11300 =＞1240000	2X	Nil	Gefitinib	Yes
Patient 6	81	Normal	552000[a]	10X	Nil	Gefitinib	Nil
Patient 7	74	Normal	113 =＞ 2100	2X	Yes	Erlotinib	Nil
Patient 8	58	Normal	0 =＞ 500	Normal	Yes	Erlotinib	Nil
Patient 9	92	Normal	1090000[a]	5X	Nil	Gefitinib	Yes
Patient 10	59	Normal	＞170000000[a]	2X	Nil	Gefitinib	Yes
Patient 11	43	Normal	101 =＞1600	Normal	Nil	Osimertinib	Nil
Patient 12	81	Normal	＞170000000[a]	5X	Nil	Erlotinib	Yes
Patient 13	63	Normal	43700=＞2050000	2X	Nil	Afatinib	Yes
Patient 14	70	Normal	426000[a]	＞10X	Nil	Afatinib	Yes
Patient 15	77	Normal	586-＞5740000	＞10X	Nil	Erlotinib	Yes
Patient 16	47	Normal	＞170000000[a]	＞10X	Nil	Erlotinib	Yes

AST/ALT, aspartate aminotransferase/alanine aminotransferase; TKI, tyrosine kinase inhibitor; HBV, hepatitis B virus; HBVR, hepatitis B virus reactivation.
[a] No baseline HBV viral load.

reactivation' groups (Table 1). No patient in the 'reactivation' group had a smoking history. Treatment with the 3rd generation EGFR TKI osimertinib had a relatively high incidence of HBV reactivation (17.6%, p = 0.258), although without achieving a significant difference and only small numbers (Tables 1 and 3).

3.4. Patients without receiving chemotherapy before EGFR TKI treatment

Among 171 patients, 105 patients were identified receiving 'pure' EGFR TKIs as anticancer treatment and did not receive chemotherapy before any-line TKI treatment. This is in order to exclude cytotoxic effect by chemotherapy on HBV reactivation. Ten patients (9.52%) met the criteria for HBV reactivation and 6 had evidence of hepatitis flare up. Antiviral therapy was prescribed by the hepatologist for eight patients after HBV reactivation.

4. Discussion

This is the first study to investigate the incidence of HBV reactivation in NSCLC patients receiving EGFR TKIs.

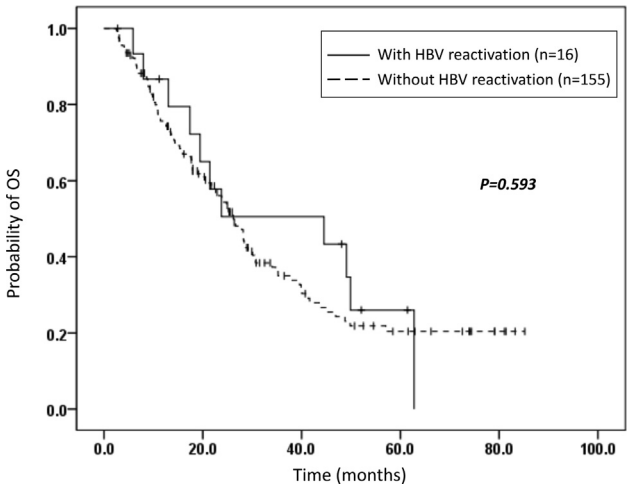

Fig. 3. Kaplan–Meier survival curves of overall survival of patients with and without HBV reactivation (P = 0.593, log-rank test). OS, overall survival; HBV, hepatitis B virus.

In this study, we found that NSCLC patients receiving EGFR TKI treatment had a clinically meaningful risk of HBV reactivation during treatment (9.36%). There was no significant difference in age, gender, baseline liver function, liver metastasis, prior therapy with chemotherapy or anti-HBV medication, pathology or total duration of TKI treatment between the 'reactivation' and 'non-reactivation' groups. Fortunately, no patient died due to HBV reactivation–related complications.

The reported incidence of HBV reactivation during chemotherapy varied, ranging from 20% to 60% [16,17]. These results included mostly patients with lymphoma and breast cancer. In patients with lung cancer receiving chemotherapy, the incidence of HBV reactivation without anti-HBV prophylaxis was about 22%, relatively lower than for patients with lymphoma or breast cancer [6]. This may be partially explained by the chemotherapy regimen. Anthracycline (for breast cancer) and anti-CD20 antibody-containing regimens (for non-Hodgkin lymphoma) are now the most widely known cytotoxic and biologic agents that induce HBV reactivation. These 2 agents are not standard treatment for NSCLC. In the most recent decade, EGFR TKIs have become the first-line treatment for patients with NSCLC harbouring an EGFR mutation. This great advance in NSCLC treatment is especially important in Asia because about 50% of patients with NSCLC harbour an EGFR mutation (estimated to be 57% in Taiwan) [18]. With the high prevalence of HBV in Taiwan, whether EGFR TKIs induce HBV reactivation or not then becomes a very important issue. Until now, there is only one case report describing a 62-year-old woman who suffered from HBV reactivation after withdrawal of erlotinib [19]. No other related study or case report has been published. Our study is the first to show an HBV reactivation rate of 9.36% (16 of 171 patients) with an annual incidence of 7.86% during EGFR TKI treatment. Eight of 16 patients with HBV reactivation met the criteria of hepatitis flare. Ten of 16 patients were suggested to receive antiviral therapy by a hepatologist. According to the guidelines of the American Gastroenterological Association, those with an anticipated incidence of HBV reactivation of 1–10% and >10% are categorised as a moderate-risk group and a high-risk group, respectively [20]. Therefore, monitoring HBV status during EGFR TKI treatment seems needed.

In addition to chemotherapy regimens, some other risk factors have also been reported to be related to HBV reactivation, including male gender, young age, elevation of ALT at baseline, positive HBeAg and a high HBV viral load prior to treatment [4,21]. HBV viral load or HBeAg (hepatitis B e-antigen) is not included in the initial HBV screening in Taiwan; therefore, we lacked data on baseline HBV viral load and HBeAg. Although steroid is usually used for premedication with chemotherapy among our patients, the duration of steroid use

Table 3
HBV reactivation: univariate and multivariate analysis.

Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*P* value	Odds ratio	95% CI	*P* value
Age (≥65 y/o)	2.41	0.85–6.81	0.097	2.32	0.80–6.74	0.121
Gender (male)	0.58	0.19–1.75	0.324	0.55	0.17–1.75	0.311
Abnormal liver function before EGFR TKIs	1.99	0.64–6.12	0.256	2.07	0.65–6.65	0.220
Use of anti-HBV agent before EGFR TKIs	0.61	0.20–1.85	0.385			
EGFR mutation[a]	3.6	0.46–28.3	0.148			
Gefitinib	1.37	0.48–3.96	0.555			
Erlotinib	1.18	0.42–3.31	0.749			
Afatinib	2.32	0.40–3.73	0.726			
Osimertinib	3.5	0.59–9.15	0.258	2.04	0.49–8.61	0.330
Chemotherapy[b] before TKIs	0.95	0.33–2.75	0.924	1.18	0.38–3.66	0.776
Total duration of EGFR TKIs treatment>10 months	0.89	0.32–2.49	0.825			

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitors.
[a] Compared to wild-type or unknown EGFR status.
[b] Chemotherapy includes cisplatin, carboplatin, pemetrexed, Navelbine, gemcitabine, paclitaxel, docetaxel.

is less than 1 week and these 2 groups are almost overlapping. We, therefore, did not analyse the risk of steroid for HBV reactivation separately. The other previously reported risk factors were then put into multivariable analysis. After both univariate and multivariable analysis, all prior reported risk factors, including receiving chemotherapy before EGFR TKI treatment, revealed no significant correlation with HBV reactivation. Why chemotherapy before EGFR TKI treatment did not increase the risk of HBV reactivation may be explained by anti-HBV therapy, which is reimbursed by the Bureau of National Health Insurance of Taiwan for patients with positive HBsAg during and until 6 months after cessation of chemotherapy.

Our study excluded 3 patients who took investigational third-generation EGFR TKIs from analysis. However, these 3 patients all suffered from HBV reactivation and hepatitis flare up during their treatment period of the investigational TKIs. Our study included 17 patients who received osimertinib as anticancer treatment, and three of them suffered from HBV reactivation during osimertinib treatment. Among these 17 patients, two patients received osimertinib as first-line treatment and the others received osimertinib as second-line treatment or beyond. The total duration of EGFR TKI treatment of the 2 patients with first-line osimertinib treatment was 16.5 and 40 months, respectively (mean total duration = 28.3 months). The median total duration of EGFR TKI treatment of the other patients receiving osimertinib as second-line treatment or beyond was 26.3 months. There was no difference in total duration of EGFR TKI treatment between these two groups of patients.

In addition to EGFR TKIs, imatinib and nilotinib (both used for treatment of chronic myeloid leukaemia) have also been proposed to induce HBV reactivation and have been categorised as belonging to a moderate-risk group of HBV reactivation [22]. Why TKIs increase the risk of HBV reactivation remains unknown. However, lymphocytes play an important role in immune control of HBV replication [22]. TKIs that are designed to target critical pathways for immune activation and proliferation of lymphocytes may play a role in lymphocyte dysfunction and therefore induce HBV reactivation [23].

For patients with resolved HBV infection (i.e., anti-HBc positive, HBsAg negative), some immunosuppressants (e.g., rituximab) are still considered to carry a high risk of HBV reactivation [24]. A recent prospective trial showed high anti-HBc and low anti-HBs at baseline predicted a high risk of HBV reactivation [15]. Until now, there are no available data on the incidence of HBV reactivation during EGFR TKI treatment in patients with lung cancer and resolved HBV infection. However, one study reported a low risk of HBV reactivation in patients with chronic myeloid leukaemia and resolved HBV infection treated with TKIs [25].

As for the HBV screening strategy for patients planning to receive immunosuppressant drugs, there is still no universal consensus. The guidelines from the Asian Pacific Association for the Study of the Liver suggest HBV screening for all people requiring immunosuppressive therapy or cancer chemotherapy [26]. However, a study conducted in Australia revealed HBV screening is less cost-effective for patients with breast cancer under adjuvant chemotherapy or those with NSCLC under palliative therapy [27]. These differences may be partially explained by the differences in HBV prevalence in Asia (>8%) and Australia (2%). In low HBV prevalence area, we suggest regular liver function tests monitoring during EGFR TKI treatment. It helps us to find out the patients who may benefit from HBV screening and who are at risk of HBV reactivation.

In Taiwan, anti-HBV therapy is reimbursed by the Bureau of National Health Insurance of Taiwan for patients with positive HBsAg during and until 6 months after cessation of chemotherapy. This means that some patients may receive EGFR TKIs and anti-HBV treatment concomitantly if the time interval after the last chemotherapy is less than 6 months. However, if the time interval is more than 6 months after the last chemotherapy, anti-HBV therapy was then discontinued. Among five patients who had HBV reactivation and received anti-HBV therapy before EGFR TKI treatment, none of them received anti-HBV therapy at the time of HBV reactivation. The efficacy of anti-HBV prophylaxis then could not be concluded from our study.

Although EGFR TKI treatment may result in HBV reactivation, there is no significant difference in OS between patients with or without this reactivation. Also, no reported death has been caused by a HBV reactivation–related complication. One study showed there was no significant difference in OS relative to HBV infection status among patients with NSCLC harbouring an EGFR mutation using gefitinib as first-line treatment [28]. This may be partially explained by the use of effective anti-HBV medication and regular hepatic enzyme monitoring during outpatient department follow-up at NTUH.

To our knowledge, ours is the first study to investigate the incidence of HBV reactivation in patients with EGFR TKI treatment and reminds us that use of EGFR TKIs may carry a moderate to high risk of HBV reactivation. Close monitoring of hepatic enzymes and HBV viral load may be needed in patients with HBV infection receiving EGFR TKIs. This finding is especially important for patients in Asia, due to the high prevalence HBV infection and that more than 50% of patients with NSCLC harbour EGFR mutations.

However, our study has several limitations. First, the HBV status of more than 40% of patients during initial screening was unknown. Second, patients who received HBV screening were those who had abnormal liver

function during TKI treatment or who planned to receive chemotherapy. Both of the aforementioned limitations may have resulted in selection bias. Third, for patients receiving chemotherapy, anti-HBV therapy was prescribed until 6 months after cessation of chemotherapy. This indicates that some patients may have received anti-HBV therapy and EGFR TKI concomitantly. In consideration of this point, the incidence of HBV reactivation could be underestimated. Fourth, for patients with advanced disease, several lines of anticancer treatment usually were continued without interruption, except for those with a poor performance status. Thus, residual immunosuppressive effects from prior anticancer regimens could not be excluded. However, among 105 patients with only 'pure' EGFR TKI treatment, HBV reactivation still developed in 10 patients (9.52%). Therefore, EGFR TKI–related HBV reactivation could not be ignored. Finally, there were only about 35% patients in our study receiving serial follow-up of HBV viral load. This means we may miss the patients with 'silent' HBV reactivation and therefore underestimate the incidence of HBV reactivation.

In conclusion, NSCLC patients receiving EGFR TKI treatment may have a clinically meaningful risk of HBV reactivation during the treatment period. Thus, in high HBV prevalence area such as Taiwan, HBV screening before EGFR TKI treatment is recommended. For patients with known HBV infection, we suggest regular liver function tests monitoring (including AST/ALT) every 4 weeks. HBV viral load should be monitored before and every 3 months after EGFR TKI treatment or in patients with abnormal liver function tests. For patients with resolved HBV infection, whether EGFR TKI treatment increases the risk of HBV reactivation has not been determined and requires further study.

Conflict of interest statement

Dr. Liao reports personal fees from AstraZeneca, Roche, Boehringer Ingelheim, Eli Lilly, Pfizer, MSD Oncology, Novartis and Bristol-Myers Squibb, outside the submitted work. Dr. Ho has received grants from AstraZeneca (#ISSIRES0105) and honorarium for speech or participated in compensated advisory board of Boehringer Ingelheim, Eli Lilly, Roche/Genentech/Chugai, MSD, Pfizer, Novartis, BMS and Ono Pharmaceutical, outside the submitted work. Dr. Chen reports personal fees from AstraZeneca, Roche, Novartis, Pfizer, Eli Lilly, Merck Sharp and Dohme, Ono Pharmaceutical, Chugai Pharmaceutical and Boehringer Ingelheim, outside the submitted work. Dr. Shih reports personal fees from AstraZeneca, Roche, Boehringer Ingelheim, Pfizer, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, AbbVie, Ono Pharmaceutical, Chugai and Eli Lilly, outside the submitted work. Dr. Yang reports personal fees from AstraZeneca, during the conduct of the study, Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech, Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals, BMS, Ono Pharmaceuticals, Daiichi Sankyo, Hansoh Pharmaceuticals, Takeda Pharmaceuticals and Blueprint Medicines, outside the submitted work. The other authors declare no conflict of interest.

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