Received: 30 November 2021 | Accepted: 24 January 2022

DOI: 10.1111/1759-7714.14346

CASE REPORT

WILEY

Acute fulminant hepatitis associated with osimertinib administration in a lung cancer patient with chronic hepatitis B: The first mortality case report

You-Kuang Kang[1] | **Fan-Chun Meng**[2]

[1]Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

[2]Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan

Correspondence
Fan-Chun Meng
Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, Tri-Service General Hospital,
No. 325, Cheng-Kung Road,
Sec. 2, Taipei 114, Taiwan.
Email: drking0724@gmail.com

Abstract

Osimertinib is the most efficient first-line drug, with least adverse effects, for metastatic non-small-cell lung carcinoma (NSCLC) harboring epidermal growth factor receptor (*EGFR*) mutations with exon 19 deletion or exon 21 L858R mutations. Herein, we present a 68-year-old woman who had chronic hepatitis B with aggressive NSCLC and received osimertinib as cancer treatment for 4.5 months. This is the first report of mortality due to osimertinib-related acute fulminant hepatitis. Clinicians should routinely arrange for hepatitis B virus (HBV) screening and prescribe antiviral drugs to patients with chronic HBV infection before osimertinib administration.

KEYWORDS

hepatitis B virus, non-small-cell lung carcinoma, osimertinib

INTRODUCTION

Osimertinib is a targeted third-generation tyrosine kinase inhibitor (TKI) used to treat patients with non-small-cell lung carcinoma (NSCLC) harboring metastatic epidermal growth factor receptor (*EGFR*) mutations. According to the FLAURA and AURA3 trials, osimertinib is the most efficient TKI with the least adverse effects. Based on our literature review, we noted that osimertinib is associated with a relatively higher hepatitis B virus (HBV) reactivation rate than other EGFR-TKIs.[1] We present a case of acute fulminant hepatitis (AFH) in a 68-year-old Taiwanese woman with chronic HBV receiving osimertinib. To our knowledge, this is the first report of mortality due to osimertinib-related AFH.

Case report

A 68-year-old woman, who experienced passive smoking, had a history of hypertensive cardiovascular disease and a cerebral infarction with left hemiparesis. She reported productive cough, poor appetite, and progressive dyspnea for 2 months. She was diagnosed with poorly differentiated adenocarcinoma of the right upper lobe of the lung, with lung to lung, pleura, and multiple bony metastases after chest computed tomography (CT) (Fig. 1(a),(b)), thoracocentesis, pleural biopsy, whole-body bone scanning, and brain magnetic resonance imaging. Examinations revealed an *EGFR* exon 19 deletion and chronic HBV infection positive for hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc). Other serology results are shown in Table 1.

The patient was treated with 250 mg oral gefitinib daily for 48 days and intravenous bevacizumab (7.5 mg/kg) 450 mg/3 weeks for six cycles. We switched gefitinib to osimertinib 80 mg daily, as the National Health Insurance (NHI) covered the treatment of patients with NSCLC with exon 19 deletion and without brain metastasis. She did not receive antiviral prophylactic therapy for the chronic HBV infection. All serology findings were unremarkable (Table 1) after osimertinib administration for 2 months. Chest CT (Figure 2(a),(b)) after 3 months revealed a partial response of the lung tumor but osseous metastases progression in the thoracic spine.

At approximately 4.5 months, the patient reported poor appetite, oliguria, drowsy consciousness, and jaundice over

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.
© 2022 The Authors. *Thoracic Cancer* published by China Lung Oncology Group and John Wiley & Sons Australia, Ltd.

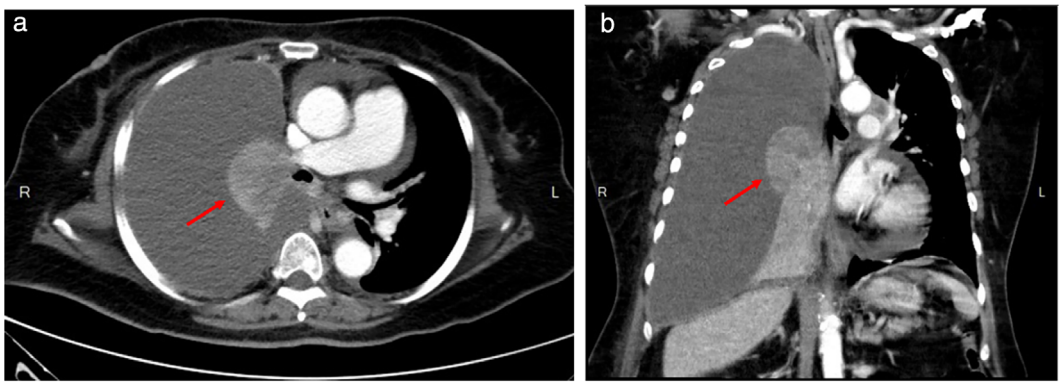

FIGURE 1 Initial chest CT with contrast enhancement revealed a mass lesion (3.55 cm) over the right upper lung with a massive right-sided pleural effusion, bilateral mediastinal lymph node enlargement, and a nodular lesion over the left upper lung

TABLE 1 Serum analysis of the patient before the cancer treatment, 2 months after treatment with osimertinib, at the beginning of admission, and 2 days before the patient expired

	Reference range	Before any treatment	Two months after treatment with osimertinib	At the beginning of admission	Two days before the patient expired
WBC (10^3/μL)	4500–11 000	7810	6150	9410	9980
Hb (g/dL)	12.0–16.0	11.8	11.5	14.2	11.9
Platelet (10^3/μL)	150–400	265	152	81	61
BUN (mg/dL)	7–25	14	42	34	21
Creatinine (mg/dL)	0.5–0.9	1.1	1.1	1.4	1.5
AST (U/L)	<40	13	17	391	315
ALT (U/L)	<41	8	9	481	417
Na (mmol/L)	136–145	142	142	138	140
K (mmol/L)	3.5–5.1	4.0	4.2	4.2	4.5
TG (mg/dL)	<200	146	None	77	None
TC (mg/dL)	<200	125	None	56	None
HDL (mg/dL)	>65	49	None	5	None
LDL (mg/dL)	<100	60	None	38	None
ALKP (mg/dL)	35–104	None	None	95	None
GGT (U/L)	5–36	None	None	50	None
Total bilirubin (mg/dL)	0.3–1.0	0.3	None	20.6	28.2
Direct bilirubin (mg/dL)	<0.2	None	None	9.9	11.9
PT (sec.)	8.0–12.0	10.3	None	55.1	63.8
APTT (sec.)	23.9–35.5	29.1	None	68.1	76.1
INR	1.0	1.0	None	6.10	7.82
Ammonia (μg/dL)	31–123	None	None	None	294
Lipase (U/L)	11–82	None	52	185	100
Albumin (g/dL)	3.5–5.7	3.6	None	2.7	None
CRP (mg/dL)	<0.8	2.47	<0.10	<0.10	0.88
LDH (U/L)	140–271	186	None	None	None

Abbreviations: ALKP, alkaline phosphatase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CRP, C-reactive protein; GGT, gamma-glutamyl transpeptidase; Hb, hemoglobin; HDL, high density lipoprotein; INR, international normalized ratio; LDH, lactate dehydrogenase; LDL, low density lipoprotein cholesterol; PT, prothrombin time; TC, total cholesterol; TG, triglyceride; WBC, white blood cell count.

the upper trunk and face for 1 week. She was admitted to our ward. Osimertinib was discontinued as we detected the onset of grade 4 hepatoxicity: liver decompensation with hyperbilirubinemia, hypoalbuminemia, coagulopathy, and hepatic encephalopathy. Abdominal CT with contrast enhancement revealed no abnormal findings. The HBV

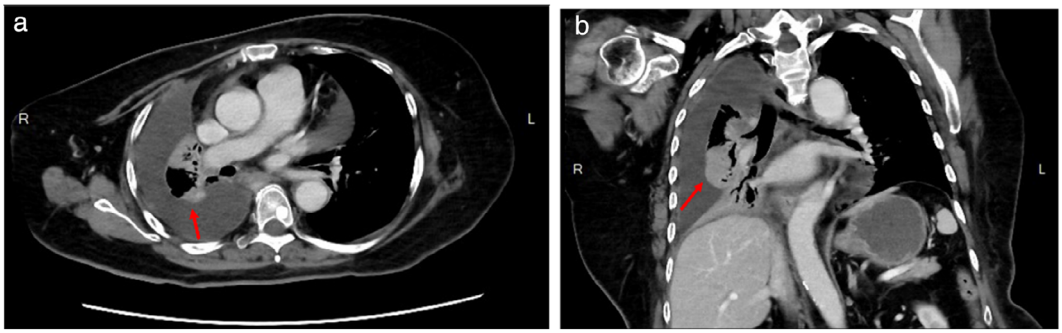

FIGURE 2 Follow-up chest CT with contrast enhancement after treatment with osimertinib for 3 months revealed a partial response of the lung tumor but disease progressive of the osseous metastases on the thoracic spine

DNA viral load was 98 368 750 IU/mL. Osimertinib-related AFH was considered; the patient was prescribed oral entecavir (0.5 mg daily). However, persistent hyperbilirubinemia, hyperammonemia, coagulopathy, encephalopathy, oliguria, and hypoxia were noted on day 5. Her family opted for hospice care. The patient died on day 7.

DISCUSSION

Osimertinib binds to select *EGFR* mutants, including exon 20, T790M, exon 21 L858R, and exon 19 deletion mutants. Based on the FLAURA trial,[2] osimertinib became the first-line treatment for metastatic NSCLC with *EGFR* mutations; it demonstrated better progression-free survival and response duration than gefitinib or erlotinib. Grade 3 or higher adverse events were fewer in the osimertinib group than in the EGFR-TKI group (34% vs. 45%) and drug-induced liver injury was lower (0% vs. 1%). In the AURA3 trial, grade ≥ 3 adverse events related to elevated liver function were not more commonly observed in the osimertinib-treated group than in the platinum-pemetrexed chemotherapy group (1% vs. 1%).[3] The FLAURA and AURA3 trials excluded patients with hepatitis B or positive HBsAg; there were no cases of HBV reactivation or associated death.

Considering the fewer adverse events of EGFR-TKI therapy, recommendations to prevent and treat HBV reactivation are frequently neglected. The Taiwan NHI covers only the antiviral prophylactic therapy for chronic HBV patients receiving chemotherapy as cancer treatment. We underestimated the incidence of osimertinib-induced HBV reactivation, thus we did not prescribe an antiviral drug to the patient during anticancer therapy. In 2002, the prevalence of chronic HBV infection in Taiwan was 13.7%, and over two-thirds (68.46%) had past exposure.[4] A retrospective study enrolled 171 Taiwanese patients with positive HBsAg and NSCLC who had received EGFR-TKIs as anticancer treatment.[1] Osimertinib resulted in a higher, but not significant ($p = 0.258$), incidence of HBV reactivation (17.6%) than other EGFR-TKIs (afatinib 10.6%, gefitinib 10.5%, erlotinib 10.1%). No independent risk factor for HBV reactivation was identified; there were no HBV reactivation-related deaths.

The mechanisms of TKI-induced HBV reactivation remain unclear. Studies in chimpanzees demonstrated that CD8+ T cells mainly control HBV replication and viral clearance.[5] TKIs targeting various tyrosine kinases are effective antileukemic agents, which may suppress the HBV-specific CD8+ T cells to control HBV infection. For example, imatinib, a selective Bcr/Abl TKI for chronic myeloid leukemia treatment, can inhibit antigen-specific T-cell activation and proliferation in vitro.[6,7] Erlotinib, an EGFR-TKI for NSCLC treatment, can reduce T-cell proliferation and Th1/Th2 cytokine production, and induce T cell anergy in vitro.[8] Further studies are needed to evaluate the mechanism of osimertinib-induced HBV reactivation.

The practice guidelines published by the American Society of Clinical Oncology recommend that all patients anticipating systemic anticancer therapy should be tested for HBsAg, anti-HBc, and anti-HBs before treatment.[9,10] Patients with chronic HBV and receiving systemic anticancer therapy should be administered antiviral prophylaxis during anticancer therapy and for at least 12 months after; additionally, the baseline HBV DNA viral load and the HBV DNA viral load every 6 months during antiviral therapy should be checked.

This is the first report of mortality due to chronic HBV reactivation with AFH after osimertinib administration. It may persuade clinicians to consider routine HBV screening, and antiviral prophylaxis should be prescribed for patients with chronic HBV before osimertinib therapy.

Patient consent statement

Written informed consent was obtained from the patient for publication of this case.

ACKNOWLEDGMENTS

No support/funding was claimed or received by any author from any source for this study.

CONFLICT OF INTEREST

The authors report no conflict of interest.

ETHICS APPROVAL

Not applicable.

DATA AVAILABILITY STATEMENT

The datasets analyzed during the current study care available from the corresponding author on reasonable request.

ORCID

You-Kuang Kang https://orcid.org/0000-0002-3761-9179

REFERENCES

1. Yao ZH, Liao WY, Ho CC, Chen KY, Shih JY, Chen JS, et al. Incidence of hepatitis B reactivation during epidermal growth factor receptor tyrosine kinase inhibitor treatment in non-small-cell lung cancer patients. Eur J Cancer. 2019;117:107–15.
2. Soria JC, Ohe Y, Vansteenkiste J, Reungwetwattana T, Chewaskulyong B, Lee KH, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. N Engl J Med. 2018; 378:113–25.
3. Mok TS, Wu YL, Ahn MJ, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer. N Engl J Med. 2017;376:629–40.
4. Lin CL, Kao JH. Perspectives and control of hepatitis B virus infection in Taiwan. J Formos Med Assoc. 2015;114:901–9.
5. Thimme R, Wieland S, Steiger C, Ghrayeb J, Reimann KA, Purcell RH, et al. CD8+ T cells mediate viral clearance and disease pathogenesis during acute hepatitis B virus infection. J Virol. 2003; 77(1):68–76.
6. Seggewiss R, Loré K, Greiner E, Magnusson MK, Price DA, Douek DC, et al. Imatinib inhibits T-cell receptor–mediated T-cell proliferation and activation in a dose-dependent manner. Blood. 2005; 105(6):2473–9.
7. Cwynarski K, Laylor R, Macchiarulo E, Goldman J, Lombardi G, Melo J, et al. Imatinib inhibits the activation and proliferation of normal T lymphocytes in vitro. Leukemia. 2004;18(8):1332–9.
8. Zeboudj L, Maître M, Guyonnet L, Laurans L, Joffre J, Lemarie J, et al. Selective EGF-receptor inhibition in CD4+ T cells induces anergy and limits atherosclerosis. J Am Coll Cardiol. 2018;71(2):160–72.
9. Hwang JP, Feld JJ, Hammond SP, Wang SH, Alston-Johnson DE, Cryer DR, et al. Hepatitis B virus screening and management for patients with cancer prior to therapy: ASCO provisional clinical opinion update. J Clin Oncol. 2020;38:3698–715.
10. Hwang JP, Lok AS, Fisch MJ, Cantor SB, Barbo A, Lin HY, et al. Models to predict hepatitis B virus infection among patients with cancer undergoing systemic anticancer therapy: a prospective cohort study. J Clin Oncol. 2018;36:959–67.

How to cite this article: Kang Y-K, Meng F-C. Acute fulminant hepatitis associated with osimertinib administration in a lung cancer patient with chronic hepatitis B: The first mortality case report. Thorac Cancer. 2022;13:1091–4. https://doi.org/10.1111/1759-7714.14346