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

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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...
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 hepatotoxicity: liver decompensation with hyperbilirubinemia, hypoalbuminemia, coagulopathy, and hepatic encephalopathy. Abdominal CT with contrast enhancement revealed no abnormal findings. The HBV

**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.
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, 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%). 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. The mechanisms of TKI-induced HBV reactivation remain unclear. Studies in chimpanzees demonstrated that CD8+ T cells mainly control HBV replication and viral clearance. 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. Erlotinib, an EGFR-TKI for NSCLC treatment, can reduce T-cell proliferation and Th1/Th2 cytokine production, and induce T cell anergy in vitro.

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. 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.

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**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.

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