Erlotinib-induced Hepatotoxicity—Clinical Presentation and Successful Management: A Case Report

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ABSTRACT

Drug-induced liver injury (DILI) is a common occurrence in clinical practice in the present era because of frequent use of drugs and increase in patients who have increased susceptibility to DILI (because of underlying non-alcoholic steatohepatitis [NASH], chronic hepatitis C, chronic hepatitis B and alcoholic liver disease). DILI is the most common reason for withdrawal of an approved drug from the market. The overall mortality rate among patients hospitalized for DILI is approximately 10%. Erlotinib, a tyrosine kinase inhibitor of epidermal growth factor receptor (EGFR) is indicated for treatment of patients with locally advanced or metastatic non-small cell lung cancer and pancreatic cancer. The most common adverse effects associated with erlotinib use are rash and diarrhea. Liver function test (LFT) abnormalities are commonly associated with erlotinib use. Grade 2 (ALT elevations >2.5 – $5\times$ upper limit of normal [ULN]) LFT abnormalities are observed in around 4% of patients while Grade 3 (ALT >5 – $20\times$ ULN) are not reported. We report a case of acute hepatitis due to administration of erlotinib in 81-year-old gentleman diagnosed as having non-small cell lung cancer with metastasis to mediastinal lymph nodes and started on erlotinib 150 mg/day. This type of deep jaundice is very rare, and timely diagnosis and withdrawal of the drug saved the life of the patient. It is recommended that liver functions be closely monitored in those with hepatic impairment, who are also on other cytochrome P450 3A4 inhibitors such as ketoconazole, clarithromycin, voriconazole, etc. In conclusion, we report a case of DILI

secondary to erlotinib with significant hyperbilirubinemia ($>5\times$ ULN; grade 4) in absence of concomitant P450 inhibitor intake and liver metastases. As erlotinib is now commonly incorporated into treatment of advanced lung and pancreatic cancer, it is important that clinicians are aware of this potential complication in practice especially in elderly patients.

INTRODUCTION

Drug-induced liver injury (DILI) is a common occurrence in clinical practice in present era because of frequent use of drugs and increase in patients who have increased susceptibility to DILI (because of underlying non-alcoholic steatohepatitis [NASH], chronic hepatitis C, chronic hepatitis B, alcoholic liver disease or advanced age). In a recent multicenter study in USA the proportion of acute liver failure cases caused by drugs (excluding paracetamol) was 11.1%.¹ A single center study from India showed 5.7% incidence of anti-tubercular treatment induced acute liver failure.² DILI is the most common reason for withdrawal of an approved drug from the market. The overall mortality rate in patients hospitalized for DILI is approximately 10%.³

Erlotinib an inhibitor of tyrosine kinase domain of epidermal growth factor receptor (EGFR) is indicated for treatment of patients with locally advanced or metastatic non-small cell lung cancer and pancreatic cancer. The most common adverse effects associated with erlotinib use are rash and diarrhea. Liver function test (LFT) abnormalities are frequently associated with erlotinib use generally leading to grade 2 alanine aminotransferase (ALT) abnormalities (ALT elevations >2.5 – $5\times$ upper limit of normal [ULN]) with relatively normal serum bilirubin. Proportionate elevation in bilirubin (grade 2 or 3 toxicity) has not been reported.⁴ We report a case of grade 4 hyperbilirubinemia ($>5\times$ ULN) due to erlotinib use in addition to grade 2 ALT toxicity.

CASE REPORT

We report a case of acute hepatitis due to administration of erlotinib in 81-year-old gentleman diagnosed as having non-small cell lung cancer with metastasis to mediastinal lymph nodes and started on erlotinib 150 mg/day. Two weeks later he presented with generalized skin rash and

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Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; DILI: drug-induced liver injury; EGFR: epidermal growth factor receptor; GGT: gamma-glutamyl transpeptidase; INR: international normalized ratio; LFT: liver function test; NASH: non-alcoholic steatohepatitis; ULN: upper limit of normal

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profuse watery diarrhea 10–12 times in a day associated with reduced urine output. He had no history of fever, altered sensorium, hematemesis, or melena. There was no past history of jaundice. He was a social alcoholic consuming 20 g alcohol per day for last 7 years. His BMI was 31 Kg/m² and he had no history of coronary artery disease, type 2 diabetes mellitus, or thyroid disease. He was on multivitamins and calcium for almost 2 months. On admission he was conscious, oriented, had a resting pulse rate of 100 beats/min and blood pressure of 110/76 mmHg. On examination he was found to have deep icterus. Respiratory and cardiovascular system examinations were normal. Abdominal examination was normal with no hepatosplenomegaly or signs of chronic liver disease. Investigation showed hemoglobin of 10.4 g/dL, a total leukocyte count of 11,800/mm³ with a differential showing 83% neutrophils, 8% lymphocytes, 2% eosinophils, 4% monocytes and 3% basophils, and platelet count of 2.39 lac/mm³. His serum electrolytes were normal but blood urea nitrogen and serum creatinine were high. His LFT reports are mentioned in Table 1.

Viral markers for hepatitis A (IgM anti-HAV), hepatitis E (IgM anti-HEV), hepatitis B (HBsAg) and for hepatitis C (anti-HCV) were negative. There was no evidence of hemolysis. Blood and urine cultures were negative. Ultrasound showed normal-sized liver with normal echotexture, portal vein size of 10 mm, normal spleen size and no ascites. Upper gastrointestinal endoscopy did not reveal any varices. Patient did not agree for liver biopsy. Erlotinib was discontinued on admission and he was treated with volume resuscitation, loperamide, antibiotics (ofloxacin and metronidazole for 5 days) and supportive care. Gradually the rash disappeared and diarrhea improved. As mentioned in the Table 1, LFTs returned towards baseline with time and he was discharged in a stable condition.

The other possible differential diagnosis considered in this patient included acute viral hepatitis, alcoholic hepatitis and metastatic disease to the liver which were excluded

by negative viral markers, normal gamma-glutamyl transpeptidase levels and a positron emission tomography CT scan showing no evidence of liver metastasis, respectively.

DISCUSSION

Erlotinib is predominantly metabolized in the liver via cytochrome P450 system, by the enzyme P450 3A4, and excreted in the bile.⁴ No significant LFT abnormalities were noted at dose of 150 mg/day in advanced non-small cell lung cancer in the TRIBUTE study⁵ and Shepherd study.⁶ In a case report of erlotinib-induced elevation of aminotransferase levels,⁷ it was observed that the bilirubin level remained within normal limits, while in our patient the bilirubin was significantly elevated (>5× ULN; grade 4 hyperbilirubinemia). In phase I study by Hidalgo et al,⁴ grade 1 hyperbilirubinemia occurred in patients with advanced solid tumors while transaminases remained unchanged. In a study of 488 patients liver enzyme elevations were mainly transient or associated with liver metastases while in our case, it occurred in absence of metastasis. Grade 2 (>2.5–5.0× the ULN) ALT elevations occurred in 4% while grade 3 (>5–20× the ULN) elevations were not observed in erlotinib-treated patients.⁸ Philip et al,^{9,10} observed grade 3 ALT toxicity in 1 of the 42 patients (0.2%) with advanced biliary malignancies and 1 of the 38 patients with advanced hepatocellular carcinoma treated with erlotinib. In a study by Moore et al,¹¹ it was shown that there is no increase in the incidence of grade 3 elevation of aminotransferases when erlotinib is added to gemcitabine as compared to gemcitabine alone. In a phase II clinical trial consisting of 80 patients ≥70 years of age treated with erlotinib for advanced non-small cell lung cancer, mainly grade 1 and 2 liver toxicities were noted and grade 4 liver toxicity was not observed.¹² To our knowledge there are two case reports of erlotinib-induced hepatotoxicity leading to death.^{13,14}

It is recommended that liver functions be closely monitored in those with hepatic impairment, who are also on

Table 1 Biochemical parameters before and after erlotinib therapy.

Tests	Pre-erlotinib			Post-erlotinib		
	Day 0	Day 14		Day 4	Day 7	Day 10
Bilirubin-total (mg/dL)	1.2	13.6	Erlotinib stopped	8.8	3.7	3
Bilirubin-direct (mg/dL)	0.8	6.6		5.3	1.9	1.4
AST (IU/L)	34	97		160	115	63
ALT (IU/L)	28	70		117	122	82
Alkaline phosphatase (IU/L)	94	102		108	100	95
GGT (IU/L)	26	27		39	69	66
INR	1.1	1.41		1.52	1.44	1.39
Blood urea nitrogen (mg/dL)	14	34		32	31	20
Serum creatinine (mg/dL)	0.9	2.96		2.74	2.41	1.45

AST: aspartate aminotransferase, ALT: alanine aminotransferase, GGT: gamma-glutamyl transpeptidase, INR: international normalized ratio.

Case Report

other cytochrome P450 3A4 inhibitors such as ketoconazole, clarithromycin, voriconazole, etc. These drugs may increase both the action of erlotinib and erlotinib-induced toxicity by inhibition of cytochrome P450 3A4. Our patient was not on any other drugs that could increase the risk of hepatotoxicity of erlotinib. Elderly are at more risk to develop erlotinib-induced hepatotoxicity due to impaired hepatic metabolism, and lower doses are advised to begin with in these patients as hepatotoxicity is dose-dependent.¹⁵ Index case was octogenarian receiving the usual 150 mg/day dose and this might be one factor for significant hepatotoxicity. In conclusion, we report a case of DILI secondary to erlotinib with significant hyperbilirubinemia ($>5\times$ ULN; grade 4) in absence of concomitant P450 inhibitor and liver metastases. Although we did not prove cause-and-effect relationship between erlotinib and hepatotoxicity by rechallenging the drug due to ethical concerns, normalization of LFT abnormalities after stoppage of erlotinib and absence of other known causative factors indicates relation between the two. As erlotinib is now commonly incorporated into treatment of advanced lung and pancreatic cancer, it is important that clinicians are aware of this potential complication in practice especially in elderly patients.

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