Letter to the Editors

Three cases of severe hepatic impairment caused by erlotinib

Yi-Sheng Huang, She-Juan An, Zhi-Hong Chen & Yi-Long Wu

Guangdong Lung Cancer Institute, Guangdong General Hospital and Guangdong Academy of Medical Sciences, China

Lung cancer is the second-most common cancer in men and women, accounting for about 13% of all diagnosed cancers. It is, however, the leading cause of cancer-related deaths in industrialized countries, exceeding the mortality from breast, colorectal, and prostate cancer combined.

Erlotinib is an orally administered, quinazoline-based agent that competes with adenosine triphosphate for binding to the intracellular catalytic domain of the epidermal growth factor receptor (HER1/EGFR) tyrosine kinase, inhibiting phosphorylation. Inhibition of tyrosine kinase activity prevents HER1/EGFR phosphorylation and its associated downstream signaling events, and it may block tumorigenesis that is mediated by inappropriate HER1/EGFR signaling [1]. In November 2004, the U.S. Food and Drug Administration (FDA) approved erlotinib as a single-agent treatment for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure with at least one standard chemotherapy regimen.

Erlotinib is better tolerated and causes fewer adverse reactions than cytotoxic drugs. The most common adverse reactions in patients are rash (acneform eruptions) and diarrhoea [2]. The majority of hepatotoxicity presents as mild or moderate hepatic dysfunction; severe hepatic impairment has been documented rarely. Here, we report three cases of severe hepatic impairment which was caused by erlotinib.

Erlotinib is cleared predominantly by the liver and is metabolized primarily by oxidation of CYP3A4, which is excreted in bile [3]. CYP3A4 exhibits remarkable interindividual activity as high as 20-fold. Genetic polymorphisms are a common source of these differences in the context of drug metabolism [4]. There are three mutations of CYP3A4 in the Chinese population that have been reported to attenuate CYP3A4 activity. These mutations include A13989G, C15820G and an A17776 insertion [5].

Additionally, CYP2D6 belongs to the cytochrome P450 oxidase family and is responsible for the majority of the interindividual variability in drug metabolism. There are four phenotypes of CYP2D6: poor metabolizer (PM), intermediate metabolizer (IM), extensive (normal) metabolizer

(EM), and ultrarapid metabolizer (UM). If a substrate of the enzyme is given to a patient as medication, and if the patient has impaired CYP2D6, the patient will accumulate the drug and experience severe side effects. In contrast, for the UM patient, drug concentrations might be too low to have a therapeutic effect. Thus, assessing the patient's phenotype will help determine the optimal dose of a drug.

One mutation in the CYP2D6 coding sequence that frequently occurs in the Chinese population is C188T(CYP2D6*10) [6]. Therefore, we analyzed DNA samples from two subjects by polymerase chain reaction and direct sequencing of three mutations in the CYP3A4 coding sequence and one mutation in the CYP2D6 coding sequence. Primer design, polymerase chain reaction, and CYP3A4 and CYP2D6 sequencing were performed as described [5, 6].

Case report

Case 1

A 31 year-old nonsmoking Chinese male was admitted to Guangdong General Hospital on May 4 2007 due to chest distress and shortness of breath that had persisted for 2 weeks. A computed tomography (CT) scan of his chest revealed the presence of bilateral pleural effusion, hydropericardium and ascites. No abnormality was found in his medical history. On physical examination, the patient had an ECOG performance score of 3, and diminished breath sounds of the bilateral lower lung and moist rales in the right upper lung were detected.

On May 8 2007, laboratory tests revealed that his alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), and direct bilirubin (DBIL) concentrations were 53 U l^{-1} , 52 U l^{-1} , $15.2 \mu\text{mol l}^{-1}$, and $5.4 \mu\text{mol l}^{-1}$, respectively. Titres were negative for hepatitis A, B and C. A pathological diagnosis through bronchofibroscopy (performed on May 11 2007) confirmed adenocarcinoma. A clinical diagnosis of adenocarcinoma

Table 1

Changes in ALT, AST, TBIL and DBIL concentrations before and after treatment with erlotinib

		Baseline	Peak value	Discontinue treatment	End result
ALT (U l⁻¹) 5–40	Case 1	53	896	596	Dead
	Case 2	18	745	622	Dead
	Case 3	49	1412	1945	Dead
AST (U l⁻¹) 8–40	Case 1	52	431	343	
	Case 2	20	800	618	
	Case 3	38	1250	1966	
TBIL (μmol l⁻¹) 7.0–19.0	Case 1	15.2	103	122.5	
	Case 2	14.2	222	201	
	Case 3	11.7	57.1	70	
DBIL (μmol l⁻¹) 2.0–7.0	Case 1	5.4	24	29.5	
	Case 2	5.8	114.1	103.7	
	Case 3	7	16.1	21.8	

of the right upper lung with clinical staging IV, cT4N2M1 (with pleura, liver and bone metastases) was made.

The patient was treated with erlotinib (Tarceva®; F. Hoffmann-La Roche, China) 150 mg orally once daily as first-line therapy due to his poor performance status on May 15 2007. After 2 days of erlotinib treatment, ALT concentrations increased to 21.8 times the upper limit of normal [ULN], AST to 7 times ULN, TBIL to 1.8 times ULN and DBIL to 2.3 times ULN. The patient experienced grade 4 acute hepatic toxicity (severe hepatotoxicity) (Common Terminology Criteria for Adverse Events 3.0) [7]. On May 19 2007, his ALT increased to 22.4 times ULN, AST to 10.7 times ULN, TBIL to 5.4 times ULN, and DBIL to 3.4 times ULN.

A liver biopsy was not performed, and serum drug concentrations were not measured. Erlotinib was discontinued on May 19 2007, and his ALT and AST concentrations decreased to 14.9 times ULN and 8.6 times ULN, respectively, within 3 days, but TBIL and DBIL concentrations increased to 6.4 times ULN and 4.3 times ULN, respectively (on May 22). The values of the liver function tests are listed in Table 1. The patient deteriorated rapidly and died on May 25 2007.

Case 2

A 58 year-old nonsmoking Chinese male was diagnosed with adenocarcinoma of the left upper lobe by bronchofibroscopy, performed on October 26 2006. A clinical diagnosis was made of adenocarcinoma of the left upper lung with clinical staging IV, cT4N3M1 (with bone and brain metastases).

The patient accepted gamma-knife treatment for the brain metastases on October 31 2006 and received two cycles of chemotherapy with gemcitabine and cisplatin from November 22 2006 to December 13 2006. The response evaluation was stable.

An MRI scan of his brain on January 5 2007 revealed that the brain metastases were progressive. He then

Table 2

Results of analysis for three mutations in the CYP3A4 coding sequence

Mutation type	Case 2	Case 3
A13989G	Wild type	Wild type
C15820G	Wild type	Wild type
A17776 insertion	Wild type	Wild type

Table 3

Results of analysis for one mutation in the CYP2D6 coding sequence

Mutation type	Case 2	Case 3
C188T	TT-homozygous	CT-heterozygous

received whole-brain radiotherapy. From February 27 2007 to March 30 2007, he was given an additional two cycles of gemcitabine and cisplatin. His response assessment was still stable.

Disease progression occurred on August 6 2007, as assessed by chest CT scan. The PFS (progression-free survival) was 10 months. Titres were negative for hepatitis A, B and C. Laboratory tests performed on August 13 2007 showed that ALT, AST, TBIL, and DBIL concentrations were normal.

The patient began once daily oral erlotinib 150 mg as a second-line treatment on August 16 2007. After 7 days, laboratory tests showed that ALT concentrations increased to 18.6 times ULN, AST to 20 times ULN, TBIL to 11.7 times ULN, and DBIL to 16.3 times ULN. The patient experienced grade 4 acute hepatic toxicity (severe hepatotoxicity). Erlotinib was discontinued on the same day, but the patient deteriorated quickly. Laboratory tests on August 29 2007 revealed the following concentrations: ALT 622 U l⁻¹ (15.5 times ULN), AST 618 U l⁻¹ (15.5 times ULN), TBIL 201 μmol l⁻¹ (10.6 times ULN), and DBIL 103.7 μmol l⁻¹ (14.8 times ULN). Hepatic enzymes were slightly decreased (Table 1). The results of the gene analysis are shown in Tables 2 and 3. The patient died on August 29 2007.

Case 3

A 72 year-old nonsmoking Chinese male underwent a right upper lobectomy with lymphadenectomy under a thoracoscope on September 22 2004. Postoperative pathological findings showed a moderately differentiated adenocarcinoma. A positron emission tomography (PET) scan that was performed in March 2006 revealed metastases in the thoracic cavity and asymptomatic multiple brain metastases.

The patient was given gefitinib as first-line treatment because he refused chemotherapy. After 40 days of treat-

ment, the disease progressed, as measured by PET. The patient subsequently was given chemotherapy with gemcitabine and carboplatin for four cycles, then whole brain radiotherapy from May to July in 2007; the response was stable.

On September 26 2007, the patient was admitted to the hospital due to coughing and shortness of breath that had persisted for 1 week. A CT scan indicated the presence of metastases in the right lower lung, pleura, and liver. The diagnosis was lung adenocarcinoma with rT0N0M1 stage IV (metastases of pleura, right lower lung, liver, and brain). Laboratory tests on October 1 2007 revealed that ALT concentrations were 49 U l⁻¹, AST 38 U l⁻¹, TBIL 11.7 µmol l⁻¹ and DBIL 7 µmol l⁻¹.

The patient's liver function was re-examined after 6 days of treatment with erlotinib (150 mg orally once daily) on October 6 2007. ALT concentrations had increased to 35.3 times ULN, AST to 31.3 times ULN, TBIL to 3 times ULN, and DBIL to 2.3 times ULN. The patient experienced grade 4 acute hepatic toxicity (severe hepatotoxicity). He was urged to discontinue erlotinib on the same day.

The following day, his hepatic enzyme concentrations continued to rise, with ALT concentrations increased to 48.6 times ULN, AST to 49.5 times ULN, TBIL to 3.68 times ULN and DBIL to 3.1 times ULN (Table 1). The results of the gene analysis are shown in Tables 2 and 3. The patient died on October 8 2007.

Erlotinib is a targeted oral treatment for NSCLC. It is cleared predominantly by the liver and is metabolized primarily by oxidation of CYP3A4, which is excreted in the bile. Erlotinib is better tolerated and causes fewer adverse reactions than cytotoxic drugs [2].

According to the drug's product label, liver function test abnormalities (including elevated ALT, AST, and bilirubin) have been observed in patients who have received single-agent Tarceva 150 mg. Grade 2 (>2.5–5.0 times ULN) ALT elevations occur in 4% of Tarceva-treated patients, but grade 3 (>5.0–20.0 times ULN) elevations were not observed (Genentech, Inc. at 08/2007).

Additionally, the currently approved product information for Tarceva (erlotinib, Revision 6, published 05/02/08) in Europe states, under the section 'Undesirable effects,' that hepatobiliary disorders (liver function test abnormalities, including increased ALT, AST and bilirubin) were common (>1/10) in the studies PA.3 (Tarceva 100 or 150 mg plus gemcitabine in the phase III pancreatic cancer study) and BR.21 (>1/100, <1/10) (Tarceva 150 mg monotherapy during phase III NSCLC study). These instances were primarily mild or moderate in severity.

Furthermore, rare cases (>1/10 000, <1/1000) of hepatic failure (including fatalities) have been reported with erlotinib use. Confounding factors have included pre-existing liver disease and concomitant hepatotoxic medications (<http://www.emea.europa.eu/umandocs/Humans/EPAR/tarceva/tarceva.htm>). In three phase III randomized clinical

trials of erlotinib, no grade 3 liver function test abnormalities were reported [8–10]. There was, however, a patient with stage IV non-small cell lung cancer who died of fulminant hepatic failure as a result of treatment with erlotinib [11].

This report introduces three cases of severe hepatic impairment within 1 week of initiation of erlotinib therapy. All patients experienced grade 4 acute hepatic toxicity (Common Terminology Criteria for Adverse Events 3.0) [7]. The timing of the start of erlotinib and the onset of liver function test abnormalities are consistent with drug-related hepatocellular injury [12].

There was no indication of current viral hepatitis (negative for hepatitis B and C markers), infection or gallbladder disease. Other causes of hepatocellular injury (for example, other viruses or toxic exposure) are possible but unlikely, given the clinical histories. There was no use of other known hepatotoxic medications or herbs.

Although neither a liver biopsy nor an autopsy was performed, the available data only allowed a broad diagnosis of hepatocellular injury. We concluded that the liver function abnormalities and death were related to the drug.

In determining what causes severe hepatic toxicity, genetic polymorphisms are an important source of inter-individual differences in drug metabolism. There are three mutations in the CYP3A4 coding sequence and one mutation in the CYP2D6 coding sequence, which we investigated.

Our results showed that there were wild types among the three mutations in the CYP3A4 coding sequence. One case was heterozygous for the C188T mutation in CYP2D6. Another case was homozygous for C188T. Homozygosity for C188T in CYP2D6 causes poor metabolism of CYP2D6. Such patients have elevated drug concentrations and experience severe side effects. However, erlotinib is metabolized primarily by oxidation of CYP3A4 rather than CYP2D6; the effect of CYP2D6 activity needs to be evaluated further, as does whether there are other mutations of CYP3A4 that decrease enzymatic activity.

Thus, some patients possibly are intolerant of erlotinib. Erlotinib exposure can increase the risk in patients with hepatic dysfunction in the short term. The half-life of erlotinib is longer and its clearance is inadequate in patients with hepatic impairment [13]. Therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) is recommended in clinical therapy. Dose reduction or interruption of erlotinib should be considered if liver function damage arises to prevent severe hepatic impairment from developing. The most critical aspect that we must determine is what causes the majority of the interindividual variability in the ability to metabolize erlotinib.

These three cases have been reported to the State Food and Drug Administration in China and to Roche Pharma (Schweiz) Ltd.

Competing interests

None declared.

REFERENCES

- 1 Akita RW, Sliwkowski MX. Preclinical studies with erlotinib (Tarceva). *Semin Oncol* 2003; 30 (3 Suppl. 7): 15–24.
- 2 Gridelli C, Bareschino MA, Schettino C, Rossi A, Maione P, Ciardiello F. Erlotinib in non-small cell lung cancer treatment: current status and future development. *Oncologist* 2007; 12: 840–9.
- 3 Kitada M, Kamataki T, Itahashi K, Rikihisa T, Kanakubo Y. Significance of cytochrome P450(P450HFLa) of human fetal livers in the steroid and drug oxidations. *Biochem Pharmacol* 1987; 36: 453–6.
- 4 Inaba T, Nebert DW, Burchell B, Watkins PB, Goldstein JA, Bertilone L, Tucker GT. Pharmacogenetics in clinical pharmacology and toxicology. *Can J Pharmacol* 1995; 73: 331–8.
- 5 Hsieh KP, Lin YY, Cheng CL, Lai ML, Lin MS, Siest JP, Huang JD. Novel mutations of CYP3A4 in Chinese. *Drug Metab Dispos* 2001; 29: 268–73.
- 6 Ling JJ, Shixiu PAN, Jianmin WU, Marti-Jaun J, Hersberger M. Genetic polymorphisms of CYP2D6 in Chinese mainland. *Chin Med J* 2002; 115: 1780–1784.
- 7 NCI. Common Terminology Criteria for Adverse Events v3.0 (CTCAE), 2006.
- 8 Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P, Seymour L; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; 353: 123–32.
- 9 Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, Kris MG, Tran HT, Klein P, Li X, Ramies D, Johnson DH, Miller VA; TRIBUTE Investigator Group. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol* 2005; 23: 5892–9.
- 10 Gatzemeier U, Pluzanska A, Szczesna A, Kaukel E, Roubec J, De Rosa F, Milanowski J, Karnicka-Mlodkowski H, Pesek M, Serwatowski P, Ramlau R, Janaskova T, Vansteenkiste J, Strausz J, Manikhas GM, Von Pawel J. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva lung cancer investigation trial. *J Clin Oncol* 2007; 25: 1545–52.
- 11 Liu W, Makrauer FL, Qamar AA, Jänne PA, Odze RD. Fulminant hepatic failure secondary to erlotinib. *Clin Gastroenterol Hepatol*. 2007; 5: 917–20.
- 12 Danan G, Benichou C. Causality assessment of adverse reactions to drugs – I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993; 46: 1323–30.
- 13 Miller A, Murry D, Owzar K, Hollis DR, Lewis LD, Kindler HL, Marshall JL, Villalona-Calero MA, Edelman MJ, Hohl RJ, Lichtman SM, Ratain MJ. Phase I and Pharmacokinetic study of erlotinib for solid tumors in patients with hepatic or renal dysfunction: CALGB 60101. *J Clin Oncol* 2007; 25: 3055–60.

RECEIVED

9 November 2008

ACCEPTED

23 April 2009

CORRESPONDENCE

Professor Yi-Long Wu, Guangdong General Hospital (GGH) & Guangdong Academy of Medical Sciences, 106 Zhongshan Er Road, Guangzhou 510080, China.
E-mail: syylwu@live.cn