

## LETTER

# Hepatic Failure and Hepatorenal Syndrome Secondary to Erlotinib: A Possible Etiology of Complications in a Patient with Pancreatic Cancer

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Dear Sir,

We would like to present a case in reference to an article entitled "Hepatic failure and hepatorenal syndrome secondary to erlotinib. Safety reminder" previously published in JOP as Pancreas News in November 2008 [1].

Erlotinib is an epidermal growth factor (EGFR) tyrosine kinase inhibitor which is highly expressed and mutated in certain cancers. It binds in a reversible fashion to the adenosine triphosphate (ATP) binding site of the receptor [2]. For the signal to be transmitted, two members of the EGFR family need to come together to form a homodimer. These then use the molecule of ATP to autophosphorylate each other, which causes a conformational change in their intracellular structure exposing a further binding site for binding proteins that cause a signal cascade to the nucleus. By inhibiting the ATP, autophosphorylation is not possible and the signal is stopped. It is approved by the Food and Drug Administration (FDA) for pancreatic cancer and non small cell lung cancer [3, 4, 5, 6]. Most of the cytotoxic drugs side effect profile is not completely known [7].

Erlotinib is predominantly metabolized in the liver *via* cytochrome P450 system, by the enzyme P450 3A4, and excreted in the bile. Based on the *in vitro* and *in vivo* data suggesting that erlotinib is cleared primarily by the liver, it is possible that erlotinib exposure may be increased in patients with hepatic dysfunction.

Toxicities associated with erlotinib include rash,

diarrhea, fatigue, pneumonitis, AST/ALT elevation, hyperbilirubinemia, [8, 9] renal insufficiency, hemolytic anemia. In less than 1% it causes Steven-Johnson like syndrome, eye lash disorders, hepatic failure, hepatorenal syndrome and gastrointestinal perforation.

Here we present a case of pancreatic cancer patient who developed hepatic and renal failure possibly from erlotinib. Our patient is a 39-year-old Caucasian man who was transferred from outside hospital to our facility for further evaluation of his cancer. He was working as a pharmacist until mid-March 2010 when he developed symptoms of reflux and night sweats. He went to a walk-in clinic where he also noted a right axillary lymph node. A mammogram showed no breast pathology and core biopsy of the right axillary lymph node was performed. Pathology revealed poorly differentiated adenocarcinoma of unknown primary. Immunohistochemistry showed strong positivity for cytokeratin 7, focally positivity for keratin-7 and cytokeratin 20, as well as, negativity for transcription termination factor, RNA polymerase I, alpha-fetoprotein, human chorionic gonadotropin, prostate-specific antigen and ERBB2 (alias Her 2/Neu: v-erb-b2 erythroblastic leukemia viral oncogene homolog 2, neuro/glioblastoma derived oncogene homolog (avian)). It was weakly positive for estrogen receptor. He was seen by local oncologist. Staging computed tomography scans on April 22<sup>nd</sup> showed mediastinal lymphadenopathy, ascites and multiple liver lesions concerning for metastasis. Laboratory data evaluated on the same day showed CA 19-9 to be 42,332 U/mL. Pathology was felt to be unknown primary possibly from pancreas, but less likely breast cancer. His labs prior to starting chemotherapy were shown in Table 1. He was started on chemotherapy with abraxane 100 mg/m<sup>2</sup>, gemcitabine 800 mg/m<sup>2</sup>, on May 3<sup>rd</sup> and erlotinib 100 mg *po* everyday from May 3<sup>rd</sup> to May 5<sup>th</sup>.

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**Key words** erlotinib, Pancreatic Neoplasms

**Abbreviations** FDA: Food and Drug Administration

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On May 5<sup>th</sup> presented to his oncologist with shortness of breath, pruritic rash and leukocytosis. He was found to be febrile, tachycardic, and lethargic along with ascites. Laboratory data were notable for anemia, thrombocytopenia and elevated liver function tests and creatinine. CT chest/abdomen/pelvis showed bilateral pleural effusions, bilateral mediastinal lymphadenopathy, distended esophagus and stomach, ascites, anasarca, extensive liver metastasis with liquefaction necrosis, and an irregular pancreatic tail lesion. He underwent paracentesis which showed malignant cells showing poorly differentiated carcinoma. During the course of the admission he developed worsening hyperbilirubinemia and renal insufficiency. CT scan done on May 11<sup>th</sup> showed diffuse liver metastasis, pancreatic tail lesion, numerous abdominal lymphadenopathy and ascites.

He was transferred to our facility on May 12<sup>th</sup>. He had thoracentesis and paracentesis. His liver function tests continued to worsen (Table 1). He underwent endoscopic ultrasound which showed a 2.5 cm pancreatic tail mass that was biopsied. He underwent fine needle aspiration of the pancreatic lesion which showed poorly differentiated adenocarcinoma consistent with pancreatic origin. The pleural and peritoneal fluid showed poorly differentiated adenocarcinoma of pancreatic origin. His hyperbilirubinemia, serum transaminases and renal function worsened and patient died within 24 hours. Autopsy was not granted.

Erlotinib is being used for non small cell lung cancer and pancreatic cancer and being evaluated for other malignancies and polycythemia vera with Janus kinase 2 (JAK2) mutations. It is important for the oncologists to be aware of the complications of the drug including hepatic failure and hepatorenal syndrome which was seen after 2-7 days of therapy with erlotinib [8, 9, 10]. We suggest routine monitoring of liver transaminases in all patients treated with erlotinib after two weeks of therapy, and monthly thereafter for several months. Dose reduction or discontinuation of erlotinib should be considered if changes in liver function are severe.

This is an uncommon relatively unpublished case. Now with recent FDA warning, such cases should be published to make physicians aware of this rare but real toxicity of erlotinib.

**Table 1.** Serum liver function tests and serum creatinine following start of erlotinib (May 3<sup>rd</sup>, 2010).

Date	Total bilirubin (mg/dL)	AST (U/L)	ALT (U/L)	Creatinine (mg/dL)
Before: April 22 <sup>nd</sup> , 2010	0.67	118	165	0.7
May 6 <sup>th</sup> , 2010	3.96	596	489	1.5
May 8 <sup>th</sup> , 2010	4.02	211	277	1.0
May 12 <sup>th</sup> , 2010	9.27	235	184	1.5
May 14 <sup>th</sup> , 2010	11.8	255	173	1.5
May 16 <sup>th</sup> , 2010	17.2	309	178	2.0
Reference range	0-1	10-37	30-65	0.8-1.3

**Conflict of interest** The authors have no potential conflicts of interest

#### References

1. Saif MW. Hepatic failure and hepatorenal syndrome secondary to erlotinib. Safety reminder. JOP. J Pancreas (Online) 2008; 9:748-52. [PMID 18981559]
2. Raymond E, Faivre S, Armand J. Epidermal growth factor receptor tyrosine kinase as a target for anticancer therapy. *Drugs* 2000; 60(Suppl 1):15-23. [PMID 11129168]
3. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; 353:123-32. [PMID 16014882]
4. Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol* 2004; 22:77-85. [PMID 14701768]
5. Dragovich T, Huberman M, Von Hoff DD, Rowinsky EK, Nadler P, Wood D, et al. Erlotinib plus gemcitabine in patients with unresectable pancreatic cancer and other solid tumors: phase IB trial. *Cancer Chemother Pharmacol* 2007; 60:295-303. [PMID 17149608]
6. Perez-Soler R. Phase II clinical trial data with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib (OSI-774) in non-small-cell lung cancer. *Clin Lung Cancer* 2004; 6:S20-3. [PMID 15638953]
7. Eklund JW, Trifilio S, Mulcahy MF. Chemotherapy dosing in the setting of liver dysfunction. *Oncology (Williston Park)* 2005; 19:1057-63. [PMID 16131047]
8. Ramanarayanan J, Scarpace SL. Acute drug induced hepatitis due to erlotinib. JOP. J Pancreas (Online) 2007; 8:39-43. [PMID 17228132]
9. Saif MW. Erlotinib-induced acute hepatitis in a patient with pancreatic cancer. *Clin Adv Hematol Oncol* 2008; 6:191-9. [PMID 18391918]
10. Huang YS, An SJ, Chen ZH, Wu YL. Three cases of severe hepatic impairment caused by erlotinib. *Br J Clin Pharmacol* 2009; 68:464-7. [PMID 19740406]