

Erlotinib-induced Acute Hepatitis in a Patient With Pancreatic Cancer

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Each year, approximately 32,000 patients are diagnosed with pancreatic cancer in the United States. The incidence has been increasing since the 1930s. The prognosis for pancreatic cancer is extremely poor: approximately 31,000 patients in the United States die from pancreatic carcinoma each year, making it the fourth leading cause of cancer-related death in the country.¹ The overall 5-year survival rate for advanced pancreatic cancer is less than 1%.² Poor prognosis has been attributed to inability to diagnose while the tumor is resectable and its propensity toward early vascular dissemination and spread to regional lymph nodes. Gemcitabine (Gemzar, Eli Lilly) is the only cytotoxic agent currently approved by the US Food and Drug Administration (FDA) for use in inoperable pancreatic cancer, based on the results of a multicenter randomized phase III clinical trial that compared 5-fluorouracil (5-FU) to gemcitabine.² In this study, treatment with gemcitabine resulted in a relative improvement of 36% in median survival (5.7 months with gemcitabine vs 4.2 months with 5-FU). For the past 10 years, many cytotoxic and targeted agents have been pitted against or combined with gemcitabine in randomized phase III trials, with no drug proving superior to single-agent gemcitabine. In the past year, however, two large randomized phase III studies in advanced pancreatic cancer have demonstrated for the first time the superiority of gemcitabine-containing combinations over single-agent gemcitabine: capecitabine (Xeloda, Roche) plus gemcitabine and erlotinib (Tarceva, Genentech/OSI Pharmaceuticals) plus gemcitabine.³⁻⁵ The combination of gemcitabine with the epidermal growth factor receptor (EGFR) inhibitor erlotinib provided a modest 2-week improvement in overall survival compared to gemcitabine alone in a study conducted by the National Cancer Institute of Canada Clinical Trials Group. The study showed a

1-year survival rate of approximately 24% among patients who received both gemcitabine and erlotinib, compared to 17% in the group who received gemcitabine alone.⁵

Erlotinib is a small-molecule inhibitor of EGFR tyrosine kinase that is now FDA-approved for the treatment of metastatic non-small cell lung cancer and advanced pancreatic cancer.^{5,6} Single-agent phase I/II studies and phase III studies with chemotherapy have demonstrated a favorable safety profile for erlotinib.⁷⁻¹⁰ The maximum tolerated dose of 150 mg/day was established from phase I clinical studies based on dose-limiting toxicities, including diarrhea, skin rash, and fatigue. Akin to gefitinib (Iressa, AstraZeneca/Teva), serious liver function test (LFT) abnormalities (including elevated alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin) were uncommonly observed with erlotinib in lung cancer trials.^{11,12} Serum aminotransferase elevations in patients treated for advanced lung cancer, when seen, were transient, with grade 2 toxicity in less than 4% of erlotinib-treated patients (versus 1% of placebo-treated patients) and no reports of grade 3 toxicity.⁶ LFT abnormalities were also observed following the administration of erlotinib (100 mg) plus gemcitabine in patients with pancreatic cancer (Table 1).⁵ In addition, a single case of acute severe hepatitis with erlotinib has been reported recently by other investigators.¹¹

We report a case of locally advanced pancreatic cancer treated with erlotinib plus gemcitabine with elevation in transaminases up to six times baseline values. Upon discontinuation of erlotinib, serum levels of AST, ALT, and alkaline phosphatase (ALP) declined to baseline.

Case Report

A 52-year-old white man was diagnosed with locally advanced pancreatic cancer when he presented with painless jaundice. His total bilirubin was 21 mg/dL (normal: <1.2 mg/dL), and he required endoscopic retrograde cholangiopancreatography with a biliary stent placement on March 8, 2006. A computed tomography (CT) angio-

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Table 1. Liver Function Test Abnormalities (Most Severe NCI-CTC Grade) in Pancreatic Cancer Patients: 100-mg Cohort¹¹

NCI-CTC Grade	Erlotinib + Gemcitabine 1000 mg/m ² IV, % (n=259)			Placebo + Gemcitabine 1000 mg/m ² IV, % (n=256)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
Bilirubin	17	10	<1	11	10	3
ALT	31	13	<1	22	9	0
AST	24	10	<1	19	9	0

ALT=alanine aminotransferase; AST=aspartate aminotransferase; IV=intravenous; NCI-CTC=National Cancer Institute Common Toxicity Criteria.

gram done on March 31, 2006, showed an isoattenuating pancreatic head mass involving approximately 50% of the circumference of the superior mesenteric vein. CA 19-9 was elevated at 135 U/mL (reference range: 0–35 U/mL). A follow-up fine-needle aspiration of the pancreas by endoscopic ultrasound confirmed pancreatic adenocarcinoma. The patient received gemcitabine and oxaliplatin (Eloxatin, Sanofi-Aventis) from April 26, 2006, to September 9, 2006, and showed stable disease and no distant metastases. Oxaliplatin resulted in grade 2 neuropathy requiring dose reduction and pregabalin. Therefore, it was decided to administer chemoradiotherapy using capecitabine with concurrent external-beam radiation (September–October). Chemoradiotherapy resulted in a slight reduction in the size of the mass. As he remained unresectable and had oxaliplatin-induced neuropathy, the patient was transitioned to gemcitabine plus erlotinib 100 mg daily. Erlotinib was initiated on November 9, 2006. His baseline LFTs were within normal range. At the beginning of week 7 (December 20, 2006), his liver enzymes started to rise (Table 2). It was decided to continue erlotinib and closely monitor his LFTs with repeat laboratory assessments every week. A CT scan performed January 5, 2007, demonstrated that geographic areas of low attenuation seen in the previous scans within the liver were no longer discretely identified. There were no focal hepatic masses, and the mass in the pancreatic head remained unchanged.

The patient's serum bilirubin levels remained within normal limits but AST, ALT, and ALP levels continued to rise, with AST of 200 U/L, ALT of 119 U/L, and ALP of 444 U/L. Magnetic resonance imaging of the abdomen performed at that time to evaluate the liver dysfunction revealed no significant interval change in the pancreatic mass and no mass lesions in the liver. Therefore it was thought the patient's elevated LFTs were related to erlotinib, which was discontinued February 8, 2007. The patient continued on gemcitabine at the dose

of 1,000 mg/m² weekly every 2 of 3 weeks. A decline of LFT values was observed immediately after discontinuation of erlotinib and came closer to the normal range within 8 weeks.

The patient was not taking other concomitant hepatotoxic medications and did not have any underlying liver dysfunction or metastases. A viral hepatitis panel was obtained and results were negative for hepatitis B and C infections. Serum ferritin level was also within normal limits. The serum levels of transaminases returned to baseline 8 weeks after discontinuation of erlotinib (Figure 1). Serum bilirubin levels remained within normal limits throughout the treatment period. Significant elevation of aminotransferases and ALP levels above normal observed after starting treatment with erlotinib, and the decline of these values after discontinuation of erlotinib, suggests drug-induced hepatitis. The fact that gemcitabine was continued throughout the treatment period and the levels improved further underlines the causation of hepatitis induced by erlotinib in this case.

Discussion

Pancreatic cancer, despite representing only 2–3% of the total cancer incidence, is the fourth leading cause of cancer-related death in the United States.¹³ Pancreatic cancer remains an important cause of cancer mortality, with few long-term survivors. Improvement in the systemic therapy of pancreatic cancer is necessary to treat the frequently encountered metastatic disease. Several new chemotherapeutic agents with modest activity against pancreatic cancer have been identified over the past decade. Gemcitabine is currently the standard treatment for advanced pancreatic cancer. Combination chemotherapy trials incorporating gemcitabine, cisplatin, 5-fluorouracil, oxaliplatin, or irinotecan (Camptosar, Pfizer) generally show improved outcomes in objective

Table 2. Liver Function Tests* and Relation to Erlotinib

Date	Total bilirubin, mg/L	AST, U/L	ALT, U/L	ALP, U/L	GGT, U/L	Timing of erlotinib
04/26/06	0.45	23	39	85	-	
10/02/06	0.28	48	50	92	-	
10/17/06	0.4	44	68	112	-	
10/27/06	0.23	40	42	128	-	
11/09/06	0.5	53	67	176	-	Started
11/28/06	0.3	41	58	168	-	
12/12/06	0.3	41	64	144	-	
12/20/06	0.5	50	76	145	-	
12/26/06	0.4	35	61	127	-	
01/09/07	0.4	42	70	162	-	
01/23/07	0.3	69	131	283	-	
02/01/07	0.7	109	193	376	-	
02/06/07	0.3	119	188	433	-	
02/08/07	0.73	109	193	376	952	Stopped
02/13/07	0.3	101	199	346	554	
02/20/07	0.4	122	288	491	-	
02/27/07	0.2	75	157	444	-	
03/06/07	0.5	61	117	343	-	
03/20/07	0.3	37	85	259		
03/27/07	0.2	52	79	213		
04/10/07	0.4	37	62	176		

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=gamma-glutamyl transferase.

*Normal reference values: total bilirubin, <1.2 mg/L; AST, 0–35 U/L; ALT, 0–35 U/L; ALP, 30–130 U/L; GGT, 11–51 U/L.

response rates but little or no improvement in survival in phase III trials.^{3,13} Despite advances in our understanding of the molecular and genetic basis of pancreatic cancer, the disease remains a clinical challenge. New approaches, alone and in combination with gemcitabine, are being developed. The FDA recently approved the combination of gemcitabine with erlotinib for first-line therapy of advanced pancreatic cancer based on modest 2-week improvement in overall survival compared to gemcitabine alone.¹⁴

EGFR is overexpressed in many solid tumors, including pancreatic cancer, and activation of the receptor signaling pathway has been shown to enhance tumor growth, invasion, and metastasis.^{15,16} Additionally, overexpression of EGFR in pancreatic cancer has been correlated with a shorter survival.¹⁶ Inhibition of the EGFR-driven autocrine pathway has proven to be a rational target for

cancer therapy in preclinical as well as clinical studies.^{17,18} Toxicity associated with EGFR-targeted agents has been acceptable in the clinical studies. A daily dose 150 mg was considered the maximum tolerated dose in a phase I pharmacokinetic study in patients with advanced solid tumors. The common dose-limiting toxicities observed in this study were diarrhea, mucositis, and skin rash. Pharmacokinetic analyses suggest dose-independent pharmacokinetics.⁷ Peak plasma level of erlotinib is achieved approximately 3–4 hours after an oral dose of 150 mg, and the elimination half-life is about 36 hours. Though no significant correlation could be established in studies between plasma levels and cutaneous toxicity or diarrhea, higher area under the curve (AUC) levels were seen on day 1 in patients experiencing cutaneous toxicity with erlotinib.⁷ Our patient did not develop rash or diarrhea with erlotinib.

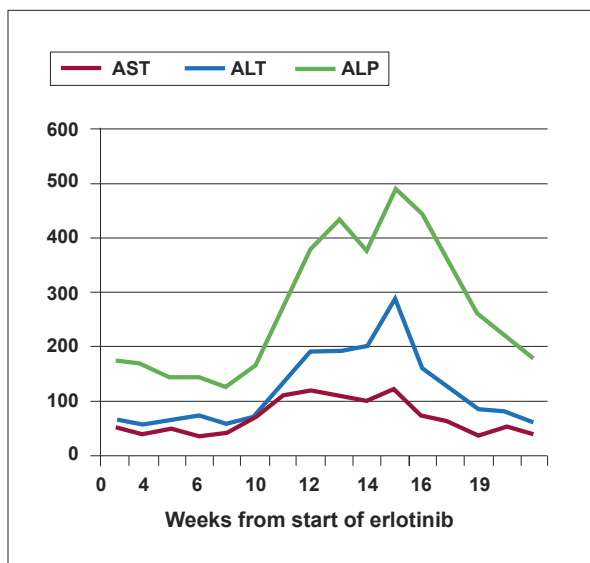


Figure 1. Time course of liver function tests.

ALP=alkaline phosphatase; ALT= alanine aminotransferase; AST=aspartate aminotransferase.

In a Phase Ib study, there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib, nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine. This case further confirms this pharmacologic finding.¹⁹

Erlotinib is predominantly metabolized in the liver via the cytochrome P450 (CYP) system by CYP3A4 and excreted in the bile.¹¹ 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. The

mean peak level of the principal metabolite of erlotinib, OSI-420 (an O-demethylated derivative), was 0.09 µg/L on day 1 of administration of 150 mg once daily, and accumulation of the metabolite was not seen after subsequent dosing in clinical trial patients.⁷ No significant LFT abnormalities were noted at the dose level of 150 mg/day with chemotherapy in advanced non-small cell lung cancer in the TRIBUTE study.¹⁰ In the phase I study by Hidalgo and colleagues, grade 1 hyperbilirubinemia occurred in patients with advanced solid tumors that was not associated with elevated hepatic transaminases.⁷ Among 42 patients with advanced biliary malignancies treated with erlotinib, grade 3 toxicity was noted in 1 patient (0.2%), and 1 of the 38 patients with hepatocellular carcinoma developed grade 3 liver enzyme elevation at the 150 mg/day dose level.^{14,17,20} The efficacy and safety of erlotinib in combination with gemcitabine as a first-line treatment was assessed in a randomized, double-blind, placebo-controlled trial in 569 patients with locally advanced unresectable or metastatic pancreatic cancer. Patients were randomized 1:1 to receive erlotinib (100 or 150 mg) or placebo once daily on a continuous schedule with intravenous gemcitabine. Erlotinib or placebo was taken orally once daily until disease progression or unacceptable toxicity. This phase III study showed no statistically significant elevation in grade 3 liver toxicity with the addition of erlotinib, although grade 3 elevations of aminotransferases were reported in 10% of patients in both groups (Table 1).⁵ Therefore, it is recommended that liver functions should be closely monitored in those with hepatic impairment.

Because the CYP system is involved in the elimination of erlotinib, a dose reduction should be considered if severe adverse reactions occur in patients who are being

Table 3. Summary of Time Course of Liver Function Tests

Lead Author	Age, y	Sex	Diagnosis	Dose of EGFR TKI	Concomitant drug	Time to elevation of LFTs	Time to improvement of LFTs	Comment
Ramanarayanan ¹²	70	M	Pancreas Cancer	Erlotinib 100 mg	—	2 weeks	3.5 weeks	—
Ho ²²	57	F	NSCLC	Gefitinib 250 mg	—	8 weeks	8 weeks	No benefit of prednisone
Carlini ²³	63	F	Breast cancer	Gefitinib 250 mg	Anastrozole	16 weeks	2 weeks	Rechallenge caused LFTs to rise again
Current case	52	M	Pancreas cancer	Erlotinib 100 mg	Gemcitabine	7 weeks	8 weeks	Gemcitabine was continued

EGFR=epidermal growth factor receptor; LFTs=liver function tests; NSCLC=non-small cell lung cancer; TKI=tyrosine kinase inhibitor.

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concomitantly treated with a strong CYP3A4 inhibitor (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin, or voriconazole).¹¹ On the other hand, pretreatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by approximately two thirds. Alternate treatments lacking CYP3A4-inducing activity should be considered. If an alternative treatment is unavailable, an erlotinib dose greater than 150 mg should be considered. If the erlotinib dose is adjusted upward, the dose will need to be reduced upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include, but are not limited to, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital, and St. John's wort. These too should be avoided if possible.¹¹ Our patient was not on any other drugs that could increase the risk of hepatotoxicity of erlotinib.

This case also becomes more interesting, as gemcitabine was continued during and off the erlotinib treatment. This decision was made based on the results of a phase I pharmacokinetic trial of gemcitabine in patients with hepatic dysfunction (Cancer and Leukemia Group B 9565).²¹ Among 40 patients in this study, transient transaminase elevations were widely observed but were not dose-limiting. Patients with AST elevations tolerated gemcitabine without increased toxicity, but patients with elevated bilirubin levels had significant deterioration in liver function after gemcitabine therapy. Therefore, it was concluded that if gemcitabine is used for patients with elevations in AST level, no dose reduction is necessary. Patients with elevated bilirubin levels have an increased risk of hepatic toxicity, and a dose reduction is recommended. The patient in this case had normal bilirubin during the entire treatment period.

Grade 3 and 4 elevations in transaminases are also uncommon following gefitinib therapy (Table 3). There have been two published case reports in the literature of gefitinib-induced acute hepatotoxicity, one in a patient treated for lung cancer and another in a patient with metastatic breast cancer receiving gefitinib plus anastrozole.^{22,23}

In conclusion, the second case of acute drug-induced hepatotoxicity secondary to erlotinib in a patient with pancreatic cancer who was on concomitant gemcitabine is reported. Acute hepatotoxicity may be more commonly seen in patients receiving therapy for hepatobiliary malignancies with EGFR inhibitors. As erlotinib is now commonly incorporated into treatment of advanced pancreatic cancer, it is important that clinicians be aware of this potential complication in practice. Based on this experience, routine monitoring of liver transaminases is suggested in all patients treated with erlotinib after 2 weeks of therapy, and monthly thereafter for several months. Dose reduction or interruption of erlotinib should be considered if changes in liver function are severe.

References

- Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2006. *CA Cancer J Clin*. 2006;56:106-130.
- Burris HA 3rd, Moore MJ, Andersen J, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreatic cancer: a randomized trial. *J Clin Oncol*. 1997;15:2403-2413.
- Saif MW. Pancreatic cancer: highlights from the 42nd annual meeting of the American Society of Clinical Oncology, 2006. *JOP*. 2006;7:337-348.
- Herrmann R, Bodoky G, Ruhstaller T, Glimelius B, Saletti P, Bajetta E, et al. Gemcitabine (G) plus Capecitabine (C) versus G alone in locally advanced or metastatic pancreatic cancer. A randomized phase III study of the Swiss Group for Clinical Cancer Research (SAKK) and the Central European Cooperative Oncology Group (CECOG). *J Clin Oncol*. 2005;23(16S):LBA4010.
- Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol*. 2007;25:1960-1966.
- Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005; 353:123-132.
- Hidalgo M, Siu LL, Nemunitis J, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol*. 2001;19:3267-3279.
- 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.
- Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multi-center 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.
- Herbst RS, Prager D, Hermann R, Fehrenbacher L, Johnson BE, Sandler A, et al. 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;23:5892-5899.
- Tarceva package insert. Available online: <http://www.gene.com/gene/products/information/oncology/tarceva/insert.jsp>. Accessed April 19, 2007.
- Ramanarayanan J, Scarpace SL. Acute drug induced hepatitis due to erlotinib. *JOP*. 2007;8:39-43.
- Saif MW. Pancreatic cancer: are we moving forward yet? Highlights from the Gastrointestinal Cancers Symposium. Orlando, FL, USA. January 20th, 2007. *JOP*. 2007;8:166-176.
- Cohen MH, Johnson JR, Chen YF, Sridhara R, Pazdur R. FDA drug approval summary: erlotinib (Tarceva) tablets. *Oncologist*. 2005;10:461-466.
- Korc M, Chandrasekar B, Yamanaka Y, Friess H, Buchler M, Beger HG. Overexpression of the epidermal growth factor receptor in human pancreatic cancer is associated with concomitant increases in the levels of epidermal growth factor and transforming growth factor alpha. *J Clin Invest*. 1992;90:1352-1360.
- Yamanaka Y, Friess H, Koblitz MS, Buchler M, Beger HG, Korc M. Coexpression of epidermal growth factor receptor and ligands in human pancreatic cancer is associated with enhanced tumor aggressiveness. *Anticancer Res*. 1993;13:565-569.
- Philip PA, Mahoney MR, Allmer C, et al. Phase II study of erlotinib (OSI-774) in patients with advanced hepatocellular cancer. *J Clin Oncol*. 2005; 23: 6657-6663.
- Durkin AJ, Bloomston PM, Rosemurgy AS, et al. Defining the role of the epidermal growth factor receptor in pancreatic cancer grown in vitro. *Am J Surg*. 2003;186:431-436.
- Dragovich T, Huberman M, Von Hoff DD, et al. Erlotinib plus gemcitabine in patients with unresectable pancreatic cancer and other solid tumors: phase IB trial. *Cancer Chemother Pharmacol*. 2006;60:295-303.
- Philip PA, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, et al. Phase II study of erlotinib in patients with advanced biliary cancer. *J Clin Oncol*. 2006; 24:3069-3074.
- Venook AP, Egorin MJ, Rosner GL, et al. Phase I and pharmacokinetic trial of gemcitabine in patients with hepatic or renal dysfunction: Cancer and Leukemia Group B 9565. *J Clin Oncol*. 2000;18:2780-2787.
- Ho C, Davis J, Anderson F, Bebb G, Murray N. Side effects related to cancer treatment: CASE 1. Hepatitis following treatment with gefitinib. *J Clin Oncol*. 2005;23:8531-8533.
- Carlini P, Papaldo P, Fabi A, et al. Liver toxicity after treatment with gefitinib and anastrozole: drug-drug interactions through cytochrome p450? *J Clin Oncol*. 2006;24:e60-61.

Review

Hepatotoxicity and EGFR Inhibition

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Saif reports an interesting case of acute hepatitis induced by erlotinib in a patient with pancreatic cancer.¹ Prompt discontinuation of erlotinib resulted in complete resolution of hepatotoxicity, providing indirect evidence for drug-induced hepatitis secondary to erlotinib. With the expanding role of epidermal growth factor receptor (EGFR) inhibitors among various tumor types for palliation or cure, this report is of clinical relevance, as it highlights the potential for EGFR inhibitors to cause significant hepatotoxicity among patients with baseline normal liver function.

EGFR inhibition is a promising strategy, specifically targeting tumors that overexpress EGFR. The two major classes of EGFR inhibitors available today are the monoclonal antibodies and small-molecule tyrosine kinase inhibitors (TKIs). Clinical applications for EGFR inhibitors have broadened with reports from phase III trials showing survival benefits in head and neck, lung, and gastrointestinal malignancies.²⁻⁴ Erlotinib, an EGFR TKI, is the most advanced drug of its class in clinical studies. Compared to conventional chemotherapeutic drugs, erlotinib is more tumor-specific, with a good safety and tolerability profile at 100–150 mg/day administered orally.⁵

Although frequently encountered toxicities with EGFR TKIs include diarrhea and skin rash, hepatotoxicity with significant elevation in transaminases has not been reported at the above dose levels from phase II or III studies.^{3,6,7} Among patients with pancreatic cancers

treated with erlotinib-gemcitabine/capecitabine combinations, no increase in liver toxicity was observed with the addition of erlotinib.^{4,8} Thus, acute hepatitis from erlotinib is apparently uncommon. The case report by Saif cautions physicians of this rare complication.

Drug-induced acute hepatocellular liver injury is defined biochemically as an increase in transaminases more than 2-fold that of upper limit of normal values or an increase in alanine aminotransferase/alkaline phosphatase ratio greater than or equal to 5 after exposure to certain medications.⁹ During preclinical and clinical testing, dose-related toxic acute hepatitis is one of the common toxicities encountered with chemotherapeutic agents. With EGFR TKIs, earlier clinical studies have shown a greater incidence of transaminase elevations at higher dose levels of gefitinib, suggesting that hepatotoxicity among EGFR TKIs could be a dose-related phenomenon.

However, some of the chemotherapeutic or targeted agents have the potential for causing dose-unrelated or idiosyncratic hepatotoxicity, with transaminase elevations several times over the upper limits of normal.^{10,11} Idiosyncratic hepatitis, whether metabolic or immunologic, is a rare phenomenon that becomes evident during subsequent clinical use of a therapeutic agent in a broader patient population. Metabolic idiosyncrasy is seen in 0.1–2.0% of patients who metabolize the drug differently than most people, with toxic metabolites predisposing to liver injury. On the other hand, the incidence of immunologic idiosyncrasy is a relatively rare event in the general population. In this type of idiosyncratic hepatotoxicity, the immune system is activated via byproducts of drug metabolism, causing liver damage.⁹ With erlotinib, hepatic metabolism to an active O-demethylated derivative (major metabolite) occurs through the cytochrome P450 (CYP) pathway, primarily via CYP3A4.⁵ At a fixed dose level, variations in hepatic function and toxicity could probably reflect individual variation in metabolism and clearance of the drug. To this extent, wide interindividual differences in activity of CYP3A4 have been described.^{12,13} Variations in the metabolism of erlotinib caused by genetic polymorphisms or concomitant enzyme inducers/inhibitors could explain occasional rare cases of hepatitis, such as those described by Saif. Further research is needed to identify determinants of idiosyncrasy in erlotinib-induced hepatitis.

In an attempt to continue EGFR inhibition and overcome sustained worsening of liver function, Seki and colleagues have suggested an intermittent treatment schedule as opposed to daily treatment with gefitinib.¹⁴ The efficacy of such a regimen is not known as treatment interruptions can be associated with the emergence of tumor resistance at the molecular level and need to be

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further explored. Rechallenges, with or without corticosteroids, are not successful and have been studied by Carlini and associates and Ho and colleagues with gefitinib in breast and lung cancer, respectively.^{15,16}

Finally, among the cases reported in the literature, treatment with erlotinib was discontinued and therapy was switched to alternative agents in most patients.¹⁵⁻¹⁷ Thus, prior to rechallenging with EGFR inhibition, any anticipated beneficial effects need to be weighed against the recurrence of hepatitis, fulminant hepatic failure, treatment costs, and the availability of safer alternative therapies. The case reported by Saif underscores the importance of close monitoring of liver-function tests during treatment course with erlotinib.

The selection of patients for treatment with EGFR TKIs, either as monotherapy or in combination with other therapies, remains a challenge. Yet, due to convenient oral dosing and the limited availability of alternate therapeutic agents, treatment with erlotinib is often incorporated for pancreatic cancer with marginal benefit. As suggested by the author, these patients should be monitored with liver function tests at 2 weeks and then periodically at regular intervals. Patients already on EGFR inhibitors who develop a rise in serum transaminases should be monitored more closely. Mild transaminase elevations could be transient, but with persistent or moderate increases in liver functions, therapy should be interrupted. A thorough evaluation of alternate etiologies such as infection, drug interactions with chemotherapy or concurrent hepatotoxic medications, or tumor progression in the liver need to be ruled out after appropriate investigation. Because patients with liver dysfunction were excluded from the clinical studies that led to the approval of the drug, the pharmacokinetics of erlotinib at decreased dose levels were tested in patients with hepatic dysfunction by Cancer and Leukemia Group B in a phase I study that was reported recently.¹⁸ Longer half-life of erlotinib, decreased clearance, and inability of patients to complete their daily dosing regimen were noted among patients with hepatic dysfunction compared to those without liver function abnormalities. It is

thus recommended to initiate treatment with erlotinib at a decreased dosage for those patients with liver dysfunction and adjust, as tolerated.

References

1. Saif MW. Erlotinib-induced acute hepatitis in a patient with pancreatic cancer. *Clin Adv Hematol Oncol*. 2008;6:191-194,199-201.
2. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med*. 2006;354:567-578.
3. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005; 353:123-132.
4. Moore MJ, Goldstein D, Hamm J, Figer A, Hecht J, Gallingeret S, et al. Erlotinib plus gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG). *J Clin Oncol*. 2005;23(16S):1.
5. Hidalgo M, Siu LL, Nemunaitis J, et al. Phase I and pharmacologic study of OSI-774, an epidermal growth factor receptor tyrosine kinase inhibitor, in patients with advanced solid malignancies. *J Clin Oncol*. 2001;19:3267-3279.
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.
7. Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multi-center 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.
8. Kulke MH, Blaszkowsky LS, Ryan DP, et al. Capecitabine plus erlotinib in gemcitabine-refractory advanced pancreatic cancer. *J Clin Oncol*. 2007;25:4787-4792.
9. Navarro VJ, Senior JR. Drug related hepatotoxicity. *N Engl J Med*. 2006; 354:731-739.
10. Benichou C. Criteria for drug induced liver disorders. Report of an international consensus meeting. *J Hepatol*. 1990;11:272-276.
11. Lee WM. Drug-induced hepatotoxicity. *N Engl J Med*. 2003;349:474-485.
12. Wolff T, Strecker M. Endogenous and exogenous factors modifying the activity of human liver cytochrome P-450 enzymes. *Exp Toxicol Pathol*. 1992;44:263-271.
13. Thummel KE, Wilkinson GR. In vitro and in vivo drug interactions involving human CYP3A. *Annu Rev Pharmacol Toxicol*. 1998;38:389-430.
14. Seki N, Uematsu K, Shibakuki R, et al. Promising new treatment schedule for gefitinib responders after severe hepatotoxicity with daily administration. *J Clin Oncol*. 2006;24:3213-3214.
15. Carlini P, Papaldo P, Fabi A, et al. Liver toxicity after treatment with gefitinib and anastrozole: drug-drug interactions through cytochrome p450? *J Clin Oncol*. 2006;24(35):e60-1.
16. Ho C, Davis J, Anderson F, et al. Side effects related to cancer treatment: CASE 1. Hepatitis following treatment with gefitinib. *J Clin Oncol*. 2005;23:8531-8533.
17. Ramanarayanan J, Scarpace SL. Acute drug induced hepatitis due to erlotinib. *JOP*. 2007;8:39-43.
18. Miller AA, Murry DJ, Owzar K, et al. Phase I and pharmacokinetic study of erlotinib for solid tumors in patients with hepatic or renal dysfunction: CALGB 60101. *J Clin Oncol*. 2007;25:3055-3060.