

CASE REPORT

Acute Drug Induced Hepatitis Due to Erlotinib

Jeyanthi Ramanarayanan¹, Sarah L Scarpace²

¹Division of Hematology and Oncology, Stratton VA Medical Center;

²Albany College of Pharmacy. Albany, NY, USA

ABSTRACT

Context Acute drug induced hepatitis has not been commonly associated with epidermal growth factor receptor (EGFR) inhibitors. Hepatotoxicity seen with erlotinib, a small molecule tyrosine kinase inhibitor to EGFR, is usually transient with mild elevation of transaminases.

Case report We report a case of acute severe hepatitis resulting from erlotinib monotherapy in a patient with locally advanced pancreatic cancer. Hepatotoxicity resolved once erlotinib was discontinued and serum transaminases returned to baseline normal values.

Conclusions Acute severe hepatitis though rare is occasionally observed with EGFR inhibitors gefitinib or erlotinib. As EGFR inhibitors are now incorporated with chemotherapy in advanced pancreatic cancers, clinicians should be aware of this potential complication.

INTRODUCTION

Pancreatic cancer ranks as the fourth leading cause of cancer death in the United States [1]. Due to advanced nature of the disease at presentation, most cases are not surgically resectable. Overall survival rate for advanced pancreatic cancers is poor with less than 1% of patients alive at 5 years [2]. Gemcitabine is the standard of care for patients with locally

advanced or metastatic cancer of the pancreas, based on the results of the multi-centered 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 vs. 4.2 months, gemcitabine vs. 5-FU). While combination chemotherapy with gemcitabine have not shown any significant benefit in terms of overall survival, in recent studies with gemcitabine and capecitabine and with EGFR antagonist, erlotinib have shown some survival benefit [3, 4, 5]. The combination of gemcitabine with the EGFR inhibitor erlotinib provided a modest 2-week improvement in overall survival compared to gemcitabine alone in the study conducted by the National Cancer Institute of Canada Clinical Trials Group. The study showed a 1-year survival rate of about 24% among patients who received both gemcitabine and erlotinib, compared to 17% of the group who received gemcitabine alone [5].

Erlotinib (Tarceva[®]; OSI-774) (OSI Pharmaceuticals, Inc., Melville, NY, USA) is a small molecule inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase which is now Food and Drug Administration (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 good safety profile for erlotinib [7, 8, 9, 10]. Maximum tolerated dose of 150 mg/day was

established from phase I clinical studies, the dose limiting toxicities commonly observed included diarrhea, skin rash and fatigue. Like gefitinib, serious liver function test abnormalities were uncommonly observed with erlotinib in lung cancer trials [11, 12]. Serum aminotransferase elevations when seen, were transient with grade 2 toxicity in less than 4% of erlotinib vs. 1% of placebo treated patients without any reported grade 3 toxicity (5-20 times the upper reference values) in patients treated for advanced lung cancer [6, 13]. We report a case of advanced pancreatic cancer treated with erlotinib with elevation in transaminases up to 12 times baseline values. Upon discontinuation of erlotinib, levels of serum aspartate amino transferase (SGOT) and serum alanine amino transferase (SGPT) declined to baseline.

CASE REPORT

A 70-year-old man was diagnosed with pancreatic cancer when he presented with painless jaundice. An ERCP showed high grade pancreatic duct dilatation, and a 2.5 cm tumor was identified in the head of pancreas in the CT scan. A CA 19-9 was elevated at 1,626 U/mL (reference range: 0-35 U/mL). After undergoing sphincterotomy and biliary stent placement, he underwent laparotomy and Whipple procedure. Final pathology disclosed poorly differentiated adenocarcinoma: 2.8 cm tumor size with one out of 12 peripancreatic nodes positive for tumor. He was started on chemotherapy with gemcitabine at 1,000 mg/m² and after 4 months of treatment his CA 19-9 declined to 67 U/mL. Upon discontinuation of therapy, patient was observed with CA 19-9 which increased to 255 U/mL at 5 months. Imaging studies did not show any evidence of recurrent pancreatic cancer. Patient opted to undergo further treatment due to rising tumor marker levels up to 975 U/mL and was initiated on single agent erlotinib at 100 mg daily dose after its recent approval with gemcitabine for locally advanced pancreatic cancer. Two weeks after starting treatment with erlotinib, SGOT, SGPT and alkaline phosphatase levels increased to 86 U/L, 155

U/L and 224 U/L from baseline values of 39 U/L, 70 U/L and 138 U/L, respectively (reference ranges; SGOT: 12-34 U/L; SGPT: 25-65 U/L; alkaline phosphatase: 50-136 U/L). Patient was not taking other concomitant hepatotoxic medications and did not have any underlying liver dysfunction. Therapy with erlotinib was discontinued in two weeks, when liver function tests further worsened. Peak levels were seen at two weeks after discontinuation of erlotinib (SGOT: 425 U/L; SGPT: 580 U/L; alkaline phosphatase: 618 U/L). A viral hepatitis panel was obtained and results were negative for hepatitis B and C infections. A magnetic resonance of the abdomen showed mild intrahepatic ductal dilatation without any mass lesion. Values of transaminases returned to baseline 6 weeks after discontinuation of erlotinib (Figure 1). Serum bilirubin levels remained within normal limits. Significant elevation of aminotransferases and alkaline phosphatase levels above normal observed after starting treatment with erlotinib, and the decline of these values after discontinuation of erlotinib, suggests drug induced hepatitis rather than hepatitis due to progressive tumor. With rising CA 19-9 (9,998 U/mL) and alkaline phosphatase (615 U/L) levels, patient was started on chemotherapy with gemcitabine alone without erlotinib. A CT scan showed intrahepatic biliary dilatation without any tumor. Patient had further reductions in CA 19-9 as well as normalization of alkaline phosphatase after four cycles of chemotherapy with gemcitabine.

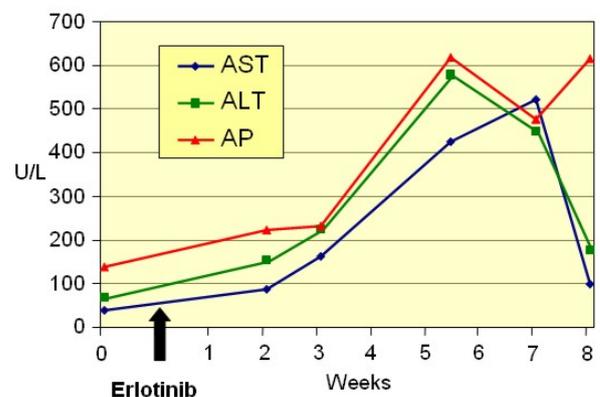


Figure 1. Time course of liver function tests.

DISCUSSION

Pancreatic cancer constitutes up to 2% of newly diagnosed cancers in the United States, but ranks as the fourth-leading cause of cancer deaths [1]. So far, chemotherapy combinations have not provided any significant improvement in overall survival. Thus chemotherapy with gemcitabine remains the standard of care. FDA recently approved the combination gemcitabine with erlotinib for first line therapy of advanced pancreatic cancer based on modest 2-week improvement in overall survival compared to gemcitabine alone.

EGFR is overexpressed in pancreatic cancer and activation of the receptor signaling pathway has been shown to enhance tumor growth, invasion, and metastasis [14, 15]. Additionally, overexpression of EGFR in pancreatic cancer has been correlated with a shorter survival [15]. Inhibition of EGFR-driven autocrine pathway has proved to be a rational target for cancer therapy in pre-clinical as well as clinical studies [16, 17]. Toxicity of these targeted agents have been minimal and acceptable in clinical studies. From phase I pharmacokinetics study in patients with advanced solid tumors, the daily dose 150 mg was considered maximum tolerated dose. The common dose limiting toxicities seen above the maximum tolerated dose were diarrhea, mucositis and skin rash. At varying doses between 50-200 mg/day evaluated in the phase I clinical trial, there were no differences in Cl/F (clearance/bio-availability) values among dosage groups on day 1 and day 24, suggesting a dose-independent pharmacokinetics of the drug [7]. Peak plasma level of erlotinib is achieved about 3 to 4 hours after an oral dose of 150 mg and the elimination half-life is about 36 hours. At 150 mg/day dose level: mean C_{max} (maximum concentration of drug in serum), and AUC_{0-24} (area under curve) values on day 1 were 0.085 ± 0.038 $\mu\text{g/mL}$ and 1.69 ± 1.42 $\mu\text{g/L} \times \text{h}$, respectively [7]. Though no significant correlation could be established in studies between plasma levels and cutaneous toxicity or diarrhea, higher AUC levels were

seen on day 1 of patients experiencing cutaneous toxicity with erlotinib [7]. Our patient did not develop rash or diarrhea with erlotinib.

Erlotinib is predominantly metabolized in the liver *via* cytochrome P450 system, by the enzyme P450 3A4, and excreted in the bile. The mean peak level of the principal metabolite of erlotinib, OSI-420 (O-demethylated derivative), was 0.09 $\mu\text{g/L}$ 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 liver function test abnormalities were noted at 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 *et al.*, grade 1 hyperbilirubinemia occurred in patients with advanced solid tumors which was not associated with elevated hepatic transaminases [7]. Among 42 patients with advanced biliary malignancies treated with erlotinib, grade 3 toxicity was noted in one patient (0.2%) and one of the 38 patients with hepatocellular carcinoma had developed grade 3 liver enzyme elevation at 150 mg/day dose level [13, 16, 18]. Recent phase III study of gemcitabine with erlotinib (100 mg/day) or placebo in patients with advanced pancreatic malignancies, showed no statistically significant elevation in grade 3 liver toxicity with addition of erlotinib, although 10% grade 3 elevation of aminotransferases were reported in both the groups [5].

It is however 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. 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. In conclusion, we report a case of acute drug-induced hepatotoxicity secondary to erlotinib. Grade 3 and 4 elevations in transaminases are uncommon after single agent gefitinib and erlotinib. There has been one published case

report in the literature of gefitinib induced acute hepatotoxicity in a patient treated for lung cancer by Ho *et al.* [11]. 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 are aware of this potential complication in practice.

Received October 4th, 2006 - Accepted November 7th, 2006

Keywords erlotinib; Hepatitis; Pancreatic Neoplasms; Receptor, Epidermal Growth Factor

Correspondence

Jeyanthi Ramanarayanan
Stratton VA Medical Center

113, Holland Avenue
Albany, NY 12208

USA

Phone: +1-518.626.6380

Fax: +1-518.626.5777

E-mail: jeyanthi.ramanarayanan2@med.va.gov

Document URL: <http://www.joplink.net/prev/200701/06.html>

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C, Thun MJ. Cancer statistics, 2006. *CA Cancer J Clin* 2006; 56:106-30. [PMID 16514137]
2. Burris HA 3rd, Moore MJ, Andersen J, Green MR, Rothenberg ML, Modiano MR, et al. Improvements in survival and clinical benefit with gemcitabine as first-line therapy for patients with advanced pancreas cancer: a randomized trial. *J Clin Oncol* 1997; 15:2403-13. [PMID 9196156]
3. Hochster HS, Haller DG, de Gramont A, Berlin JD, Philip PA, Moore MJ, Ajani JA. Consensus report of the international society of gastrointestinal oncology on therapeutic progress in advanced pancreatic cancer. *Cancer* 2006; 107:676-85. [PMID 16847885]
4. 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.
5. 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.
6. 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]
7. Hidalgo M, Siu LL, Nemunitis J, Rizzo J, Hammond LA, Takimoto C, 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; 19:3267-79. [PMID 11432895]
8. 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]
9. 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]
10. 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; 23:5892-9. [PMID 16043829]
11. 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; 23:8531-3. [PMID 16293881]
12. Fukuoka M, Yano S, Giaccone G, Tamura T, Nakagawa K, Douillard JY, et al. Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small-cell lung cancer (The IDEAL 1 Trial). *J Clin Oncol* 2003; 21:2237-46. [PMID 12748244]
13. Cohen MH, Johnson JR, Chen YF, Sridhara R, Pazdur R. FDA drug approval summary: erlotinib (Tarceva) tablets. *Oncologist* 2005; 10:461-6. [PMID 16079312]
14. Korc M, Chandrasekar B, Yamanaka Y, Friess H, Buchier 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; 90:1352-60. [PMID 1401070]

15. Yamanaka Y, Friess H, Kobrin 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; 13:565-9. [PMID 8317885]

16. Philip PA, Mahoney MR, Allmer C, Thomas J, Pitot HC, Kim G, et al. Phase II study of Erlotinib (OSI-774) in patients with advanced hepatocellular

cancer. *J Clin Oncol* 2005; 23:6657-63. [PMID 16170173]

17. Durkin AJ, Bloomston PM, Rosemurgy AS, Giarelli N, Cojita D, Yeatman TJ, Zervos EE. Defining the role of the epidermal growth factor receptor in pancreatic cancer grown in vitro. *Am J Surg* 2003; 186:431-6. [PMID 14599602]

18. 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; 24:3069-74. [PMID 16809731]
