CASE REPORT

Acute Drug Induced Hepatitis Due to Erlotinib

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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 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 adeno-
carcinoma: 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 preclinical 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 CI/F (clearance/bioavailability) 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 $C_{\text{max}}$ (maximum concentration of drug in serum), and $\text{AUC}_{0-24}$ (area under curve) values on day 1 were $0.085\pm0.038$ µg/mL and $1.69\pm1.42$ µg/L x·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 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 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.

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