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PANCREAS NEWS

# Hepatic Failure and Hepatorenal Syndrome Secondary to Erlotinib. Safety Reminder

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## Introduction

There have been constant debates regarding the issues of chemotherapy use and dosing in setting of liver insufficiency in patients with solid malignancies. Many chemotherapeutic agents are metabolized by the liver, and it is also relatively common for advanced cancer patients to have liver dysfunction secondary to metastatic disease. Some literature reviews the use of specific cytotoxic drugs in such patients [1] but data are still lacking for most agents. Hence, there are no formal dosing recommendations. Furthermore, most patients with hepatic insufficiency are excluded from clinical trials and case review series, perpetuating the lack of such information. This situation is further complexed when dealing with a patient with pancreatic cancer, where options are extremely limited and liver dysfunction is very common.

## Hepatic Metabolism

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. 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 [2]. 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 [3]. 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 [2]. Among 42 patients with advanced biliary malignancies treated with erlotinib, grade 3 bilirubin toxicity was noted in one patient and one of the 38 patients with hepatocellular carcinoma had developed grade 3 liver enzyme elevation at 150 mg/day dose level [4, 5]. As mentioned earlier, 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. This phase III study 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 (Table 1) [6].

Due to the fact that cytochrome P450 (CYP) system is involved in the elimination of the drug, in patients who are being concomitantly treated with a strong CYP3A4 inhibitor such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin,

**Table 1.** Liver function test abnormalities (most severe NCI-CTC grade) [15] in pancreatic cancer patients: 100 mg cohort.

| | Erlotinib + Gemcitabine 1,000 mg/m$^2$ i.v. (No. 259) | | | Placebo + Gemcitabine 1,000 mg/m$^2$ i.v. (No. 256) | | |
|---|---|---|---|---|---|---|
| **NCI-CTC grade** | **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% |

NCI-CTC: National Cancer Institute Common Terminology Criteria

troleandomycin (TAO), or voriconazole, a dose reduction should be considered should severe adverse reactions occur [7]. Similarly, use of CYP3A4 inducers include, but are not limited to rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort should also be avoided if possible in concomitant use with erlotinib [7].

## Renal Metabolism/Excretion

Less than 9% of a single dose is excreted in the urine [7]. No clinical studies have been conducted in patients with compromised renal function. Cases of hepatorenal syndrome, acute renal failure (including fatalities), and renal insufficiency have been reported as described above. Some were secondary to baseline hepatic impairment while others were associated with severe dehydration due to diarrhea, vomiting, and/or anorexia or concurrent chemotherapy use. In the event of dehydration, particularly in patients with contributing risk factors for renal failure (e.g., pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other predisposing conditions including advanced age), erlotinib therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patient. Periodic monitoring of renal function and serum electrolytes is recommended in patients at risk of dehydration (Table 2).

## Erlotinib in Pancreatic Cancer

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 [8]. Gemcitabine is currently the standard treatment for advanced pancreatic cancer, and offers modest improvement of tumor-related symptoms and marginal advantage of survival [9]. Combination chemotherapy trials incorporating gemcitabine, cisplatin, 5-fluorouracil, oxaliplatin, or irinotecan generally show improved outcomes in objective response rates but with little or no improvement in survival in phase III trials

**Table 2.** General dosage guidelines for erlotinib.

- The dose for non-small-cell lung cancer is 150 mg/day.
- The dose for pancreatic cancer is 100 mg/day.
- All doses of erlotinib should be taken at least one hour before or two hours after food.
- Patients with hepatic impairment (total bilirubin greater than 3 times the upper reference limit or Child Pugh A, B and C) should be closely monitored during therapy with erlotinib.
- Treatment with erlotinib should be used with extra caution in patients with total bilirubin greater than 3 times the upper reference limit.
- Erlotinib dosing should be interrupted or discontinued if total bilirubin is greater than 3 times the upper reference limit and/or transaminases are greater than 5 times the upper reference limit in the setting of normal pretreatment values.
- Interrupt erlotinib in the event of dehydration.
- Monitor renal function and electrolytes in patients at risk of dehydration.
- Reduce in 50 mg decrements, when necessary.

[10]. Despite advances in our understanding of the molecular and genetic basis of pancreatic cancer, the disease remains a clinical challenge. The Food and Drug Administration (FDA) recently approved the combination gemcitabine with erlotinib for first line therapy of advanced pancreatic cancer [6]. 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 conducted by the National Cancer Institute of Canada Clinical Trials Group. Patients were randomized 1:1 to receive erlotinib (100 mg or 150 mg) or placebo once daily on a continuous schedule with intravenous gemcitabine (1,000 mg/m$^2$; cycle 1: days 1, 8, 15, 22, 29, 36 and 43 of an 8-week cycle; cycle 2 and subsequent cycles: days 1, 8 and 15 of a 4-week cycle). Erlotinib or placebo was taken orally once daily until disease progression or unacceptable toxicity. 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 the study. 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.

## Phase I–III Data on Erlotinib and Safety

Erlotinib (Tarceva®; OSI-774, OSI Pharmaceuticals, Inc., Melville, NY, USA) is a small molecule inhibitor of EGFR tyrosine kinase. Single agent phase I-II studies and, phase III studies with chemotherapy have demonstrated a favorable safety profile for erlotinib [2, 11, 12, 13]. Maximum tolerated dose of 150 mg/day was established from phase I clinical studies based on the dose limiting toxicities, including diarrhea, skin rash and fatigue. Akin to gefitinib, serious liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) were uncommonly observed with erlotinib in lung cancer trials [3, 14].

## Hepatic Abnormalities with Erlotinib

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. Liver function test abnormalities have also been observed following the administration of erlotinib (100 mg) plus gemcitabine in patients with pancreatic cancer Table 1 displays the most severe National Cancer Institute Common Terminology Criteria (NCI-CTC) grade [15] of liver function abnormalities that developed in this study [6]. A single case of acute severe hepatitis with erlotinib was earlier reported by other investigators [16]. We published the second such case of locally advanced pancreatic cancer patients treated with erlotinib plus gemcitabine who was complicated with elevation in transaminases up to 6 times baseline values [17].

## Is This a Class Effect?

These findings are similar to other agents belonging to the EGFR family, such as gefitinib. Grade 3 and 4 elevations in transaminases are also uncommon following gefitinib. There has been two published case reports in the literature of gefitinib induced acute hepatotoxicity in a patient treated for lung cancer by Ho *et al*. [18] and another patient with metastatic breast cancer receiving gefitinib plus anastrozole by Carlini *et al*. [19].

## Hepatic Failure and Hepatorenal Syndrome: New Findings

In September 2008, OSI Pharmaceuticals, Inc. and Genentech, Inc. (South San Francisco, CA, USA) notified that cases of hepatic failure and hepatorenal syndrome, including fatalities, have been reported during use of erlotinib, particularly in patients with baseline hepatic impairment [7, 20].

## Pharmacokinetic Study

In a pharmacokinetic study in patients with moderate hepatic impairment (Child-Pugh B)

associated with significant liver tumor burden, 10 out of 15 patients died on treatment or within 30 days of the last erlotinib dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six out of the 10 patients who died had baseline total bilirubin greater than 3 times the upper reference limit suggesting severe hepatic impairment [7, 20]. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh B), patients with hepatic impairment (total bilirubin greater than 3 times the upper reference limit or Child-Pugh A, B and C) should be closely monitored during therapy with erlotinib (Table 2). Treatment with erlotinib should be used with extra caution in patients with total bilirubin greater than 3 times the upper reference limit. Erlotinib dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside the reference range. In the setting of worsening liver function tests, before they become severe, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. Erlotinib dosing should be interrupted or discontinued if total bilirubin is greater than 3 times the upper reference limit and/or transaminases are greater than 5 times the upper reference limit in the setting of normal pretreatment values.

## New Information Updated

New information from a pharmacokinetic study in patients with moderate hepatic impairment associated with significant liver tumor burden has been provided in the revised prescribing information, and other recommendations are included in the "Warnings" and "Dosage and Administration" sections [7]:

- The previous "Precaution" section, entitled "Hepatotoxicity", has been updated and this section has been moved to the "Warnings" section. The section indicates that "Erlotinib dosing should be interrupted or discontinued if total bilirubin is greater than 3 times the upper reference limit and/or transaminases are greater than 5 times the upper reference limit in the setting of normal pretreatment values".
- The previous "Precaution" section, entitled "Renal Failure", has been updated to include the term "hepatorenal syndrome" and this section was moved to the "Warnings" section.

## Conclusions

As erlotinib is now commonly incorporated into treatment of advanced pancreatic cancer [21], it is important that clinicians are aware of this potential complication in practice. 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 interruption of erlotinib should be considered if changes in liver function are severe as outlined in the drug insert.

**Keywords** Bilirubin; gemcitabine; erlotinib; Hepatitis; Hepatorenal Syndrome; Kidney Failure; Pancreatic Neoplasms

**Abbreviations** CYP: cytochrome P450

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