Erlotinib-Induced Hepatitis Complicated by Fatal Lactic Acidosis in an Elderly Man With Lung Cancer

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OBJECTIVE: To report a case of erlotinib-induced hepatitis complicated by fatal lactic acidosis in an elderly patient with lung adenocarcinoma and diabetes mellitus.

CASE SUMMARY: A 77-year-old man with stage IIIB lung adenocarcinoma was treated with erlotinib 100 mg/day, an epidermal growth factor receptor inhibitor, after failure of chemotherapy and radiotherapy. The patient also had type 2 diabetes mellitus; metformin therapy had been initiated 5 years before presentation. Twelve days after the start of erlotinib therapy, he developed drug-related acute hepatitis complicated by renal deterioration (aspartate aminotransferase 1400 U/L, alanine aminotransferase 1299 U/L, creatinine 4.4 mg/dL, urea nitrogen 55 mg/dL). Viral causes of hepatitis were excluded and a recent computed tomography scan had ruled out liver metastases. According to the Roussel-Uclaf causality assessment method, the erlotinib-related hepatitis was classified as probable. The patient's condition was soon complicated by the onset of lactic acidosis, which caused death 2 hours after admission.

DISCUSSION: In this patient, lactic acidosis was promoted by erlotinib-related hepatitis with initial liver failure (decreased lactate clearance), concomitant metformin treatment (increased lactate production), and acute renal deterioration (metformin accumulation). This is the second case of fatal erlotinib-induced liver toxicity in a patient with lung cancer. In the previous case, death occurred after about 11 days and was entirely due to fulminant hepatitis, whereas in our patient, the liver injury only initiated a drug–disease interaction that caused fatal lactic acidosis within a few hours.

CONCLUSIONS: Liver function should be carefully monitored during erlotinib treatment, particularly in elderly and frail patients on multiple medications. Further studies are therefore needed for better testing the safety of erlotinib in such people, commonly encountered in the real world, but often excluded from participation in randomized trials of cancer treatment.

KEY WORDS: acute liver failure, drug-induced hepatitis, erlotinib, metformin.

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Erlotinib is an orally administered potent and reversible epidermal growth factor receptor tyrosine kinase inhibitor.[1-4] Erlotinib was approved by the Food and Drug Administration for the treatment of metastatic non–small-cell lung cancer (NSCLC) and advanced pancreatic cancer. In patients with stage IIIB or IV NSCLC, erlotinib has been proven to prolong survival after failure of first-line or second-line chemotherapy.[1-3] Adverse effects mainly include skin rash, diarrhea, vomiting, kerato-conjunctivitis, and interstitial lung disease, but asymptomatic and mild elevations of serum alanine aminotransferase (ALT) (>2.5–5 times the upper limit of normal) were observed in 4% of erlotinib-treated patients with NSCLC versus less than 1% with placebo.[1-4] Although large trials did not report severe and clinically evident erlotinib-related liver toxicity,[1-4] sporadic cases of hepatic adverse reactions to erlotinib are currently accumulating.[5-8] For instance, erlotinib-induced acute hepatitis has been recently reported in 2 patients affected by stable pancreatic cancer without liver metastases.[5,6] In September 2008, OSI Pharmaceuticals and Genentech reported that, in a pharmacokinetic study of 15 patients with advanced solid tumors complicated by moderate liver impairment, 1 patient died from hepatorenal syndrome and 1 patient died because of progressive liver failure.[7] Both these fatal hepatic complications were potentially attributed to erlotinib use. Finally, a case of fulminant hepatic failure secondary to erlotinib was described in a woman with stage IV NSCLC, but without previous liver disease.[8]

Metformin is an important and widely used antidiabetic drug. Concerns, however, have been raised regarding the possible risk of lactic acidosis in persons taking metformin.[9] This complication is fatal in 50% of cases and occurs mostly in people with predisposing conditions to lactic acidosis, such as advanced age; cardiovascular disease with peripheral hy-

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poxia; respiratory, hepatic, and renal insufficiency; diabetic ketoacidosis; and surgery.[9,10] In addition, lactic acidosis is often misdiagnosed, and many cases may go unrecognized, particularly in elderly individuals affected by chronically symptomatic illnesses. Recent findings, however, suggest that in the absence of predisposing conditions, the risk of lactic acidosis in patients on metformin is not higher than in patients taking other antidiabetic drugs, and therefore presumably is not higher than the risk caused by diabetes per se.[11]

We discuss the case of a man with NSCLC who developed erlotinib-induced acute hepatitis. This drug effect was soon complicated by fatal lactic acidosis, which, in turn, was promoted by the concomitant metformin treatment for diabetes.

Case Report

A 77-year-old man was diagnosed with stage IIIB adenocarcinoma of the right lung (July 2006), type 2 diabetes mellitus, and hypertension. A serum creatinine level of 1.3 mg/dL was measured in July 2007. Results of baseline liver function tests (LFT) obtained in October 2006 were as follows: aspartate aminotransferase (AST) 18 U/L (reference range 5–40), ALT 22 U/L (7–66), and lactate dehydrogenase (LDH) 606 U/L (313–618). The patient denied alcohol consumption, as well as previous renal and liver disease. A total body computed tomography scan performed on July 13, 2007, had shown normal liver parenchyma and the absence of liver metastases. Daily therapy included metformin 500 mg, glybenclamide 5 mg 3 times per day (0800, 1300, 2000 h), repaglinide 1 mg 3 times per day (0800, 1300, 2000 h), doxazosin 4 mg (2100 h), omeprazole 20 mg (0800 h), prednisone 25 mg (0800 h), and furosemide 25 mg (0800 h). The patient had been taking such drugs for about 5 years, with the exception of prednisone, which was initiated 1 year prior to hospital admission. He had been treated with a chemotherapy regimen of carboplatin (area under the curve 4) and gemcitabine 1 g/m^2 (4 cycles) in 2006, and with radiotherapy plus 6 cycles of docetaxel 75 mg/m^2 in 2007. After this therapy (end of May 2007), the patient did not receive any anticancer drug for 2 months. He was then prescribed erlotinib at a daily dose of 100 mg, started on August 2, 2007, and was asked to continue taking the other drugs. In an outpatient visit on day 9 of erlotinib treatment, a Karnofsky performance status score of 60 (maximum score of 100 indicates normal function) was measured. Of note, this was the same score obtained 1 year before (July 2006) and thus indicated a stable performance status. The Karnofsky performance status scale is a reliable and validated tool for measuring functional impairment in patients with cancer.[12]

At 2300 of day 12 of erlotinib treatment, the patient was admitted to our unit because of tachypnea and delirium. Despite these symptoms, he had completed that day's prescribed therapy before coming to the hospital. He was tachypneic (30 breaths/min) and his blood pressure was 90/70 mm Hg. The results of an electrocardiogram were normal, and the remaining physical examination was unremarkable, except for pallor. Laboratory tests showed: AST 1400 U/L, ALT 1299 U/L, LDH 5990 U/L, creatinine 4.4 mg/dL (0.5–1.5), urea nitrogen 55 mg/dL (7–21), glucose 500 mg/dL (65–110), hemoglobin 13.4 g/dL (12–16), brain natriuretic peptide 62 pg/mL (0–100), troponin I 0.001 ng/mL (0.010–0.040), total bilirubin 1 mg/dL (0.20–1.30) and prothrombin time (international normalized ratio) 1.20. Blood gas analysis showed severe lactic acidosis: pH 7.097 (7.35–7.45), pO_2 80 mm Hg (80–100), pCO_2 11.6 mm Hg (35–45), bicarbonate 6.5 mEq/L (22–26), lactate 30 mEq/L (4–20), anion gap 37.3 mEq/L (12 ± 4). Markers for current viral hepatitis A (virus antibodies, immunoglobulin [Ig] M and IgG), hepatitis B (HB_s antigen), and hepatitis C (virus antibodies) were negative. Despite treatment with intravenous fluids, insulin, and bicarbonates, the patient's clinical status dramatically deteriorated and he died 2 hours after admission. Autopsy was not performed.

Discussion

Available evidence suggests that this fatal cascade started with erlotinib-induced acute hepatitis. The marked elevation of LFT results, compared with the normal values measured at baseline, confirms the diagnosis of acute hepatitis, and several considerations led us to believe that this liver toxicity was secondary to erlotinib. The role of erlotinib is first suggested by the lack of any other possible cause of hepatitis. Liver metastases were excluded by a computed tomography scan performed 1 month prior to the event and viral hepatitis was ruled out by laboratory tests. Indeed, the patient was taking other potentially hepatotoxic medications, such as glybenclamide[13] and repaglinide.[14] Although idiosyncratic (ie, not dose related) drug reactions can theoretically present up to 1 year after the onset of treatment, drug-related causality is suggestive when toxicity occurs between 5 and 90 days after the beginning of therapy.[15,16] Therefore, because these antidiabetic drugs had been started 5 years before this presentation, they were highly unlikely to be responsible for the development of the acute liver reaction. Another factor supporting erlotinib toxicity is its well-recognized potential to cause liver toxicity.[5-8] Even though we could not monitor for any normalization of liver enzyme levels following drug withdrawal (dechallenge), the causative role of erlotinib can be classified as probable according to the Roussel-Uclaf causality assessment method, which is the most reliable scoring system for the evaluation of drug-induced liver toxicity.[16]

While erlotinib is commonly prescribed at a daily dose of 150 mg in patients with lung cancer,[1] in a previous case report,[8] as well as in our patient, erlotinib-related hepatitis oc-

curred with the lower dose of 100 mg/day. This suggests that erlotinib-related liver toxicity is unpredictable and unrelated to dose, therefore occurring with an idiosyncratic mechanism.[8,15]

In our patient, erlotinib-related hepatitis presumably led to initial acute liver failure, as shown by the sudden deterioration in renal function that often complicates acute liver failure in the context of multiorgan failure.[17] Lactic acidosis, resulting from hypoperfusion and renal failure, is frequent during acute liver failure. In our patient, however, we believe that lactic acidosis was critically worsened by concomitant metformin therapy.[9,10,17] In fact, lactic acid was poorly removed by the damaged liver[17] and simultaneously overproduced by metformin, which accumulated because of renal failure.[9,10] Since even fulminant liver failure is not fatal for several days,[17] the final cause of our patient's death within a few hours was presumably lactic acidosis. Therefore, our case is different from that described by Liu et al.,[8] in which death occurred 11 days after hospital admission and could be fully attributed to fulminant hepatic failure secondary to erlotinib.

To our knowledge, this is the second case of erlotinib-related fatal liver toxicity reported in a patient with NSCLC. Hepatic adverse reactions due to erlotinib are presumably rare in the absence of underlying liver disease, but available observations and our report suggest that liver toxicity is a possibility that oncologists should be aware of while prescribing erlotinib, even in patients without any liver abnormality.[5-8] Thus, it seems highly advisable to screen patients for baseline liver disease before starting erlotinib, as well as to monitor liver function during treatment; dosage reduction or therapy discontinuation should be considered if transaminase levels tend to increase.

Erlotinib was studied in patients with NSCLC (median age 60 y).[1] This drug was also proposed as a first-line treatment in older patients with advanced NSCLC and several comorbid diseases, who are unlikely to tolerate chemotherapy.[18] Indeed, an observational study of 80 chemotherapy-naïve elderly (≥70 y) patients proved that erlotinib may be effective in this clinical setting.[19] Twelve percent of these patients, however, discontinued erlotinib because of adverse effects, mainly acneiform rash (79% of all treated patients) and diarrhea (69%); this was a much higher rate than the 5% of people who stopped taking the drug for toxicity in a younger group studied by Shepherd et al.[1] Also, 15 (18.7%) patients were reported to have elevated liver transaminase levels during treatment[19]; again, that was a higher rate than the 4% reported in younger populations.[3] Importantly, the authors even reported 4 erlotinib-related interstitial lung diseases, with one death.[19] Therefore, elderly patients may have an increased risk of erlotinib-related adverse reactions, including liver toxicity.[20]

The issue of drug safety in older and frail people is further complicated by the potential onset of sudden organ deteriorations, which are unpredictable and common events in the geriatric population. For instance, many elderly persons have normal serum creatinine levels, but decreased glomerular filtration rates.[21] This "concealed" renal insufficiency is often unrecognized and significantly associated with a higher risk of adverse drug reactions to hydrosoluble drugs, including metformin.[21] In such patients, even mild clinical events (eg, diarrhea, a frequent adverse effect in erlotinib-treated elderly patients[19]) can be complicated by unexpected and severe acute renal failure, which in turn leads to accumulation and toxicity of drugs undergoing renal excretion, like metformin.[9,10] In our patient, renal function suddenly worsened as a consequence of acute liver failure and ultimately caused metformin accumulation, with ensuing fatal lactic acidosis. This is a further example of how, in older patients, complex drug–disease interactions may trigger unexpected and life-threatening vicious cycles.[10]

Oral erlotinib does remain an attractive therapeutic option in older persons with NSCLC,[1,2] but there may be safety concerns regarding liver toxicity, particularly in frail elderly patients affected by comorbid diseases and on multiple medications.[10] In such patients, careful monitoring of either LFT results or renal function to prevent the onset of life-threatening liver toxicities may be particularly indicated. In addition, the incidence of erlotinib-related liver toxicity in elderly and complex cancer patients is unclear, since these people are invariably ruled out from randomized controlled trials of cancer therapy.[22] Erlotinib should be tested in this clinical setting, in which the benefit/risk profile of this promising drug may be altered by complex drug–disease interactions.

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Hepatitis Inducida por Erlotinib y Complicada por una Acidosis Láctica Mortal en un Hombre de Mayor Edad

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EXTRACTO

OBJETIVO: Informar un caso de hepatitis inducida por erlotinib la cual se complicó debido a una acidosis láctica mortal en un paciente de mayor edad con adenocarcinoma pulmonar y diabetes mellitus.

RESUMEN DE UN CASO: Un hombre de 77 años con adenocarcinoma pulmonar en etapa IIIB recibió tratamiento con 100 mg diarios de erlotinib, un inhibidor del receptor del factor de crecimiento epidérmico, luego de que la quimio y la radioterapia fracasaran. El paciente también sufría de diabetes mellitus tipo 2 y desde hacía cinco años recibía tratamiento con metformín. Doce días después de comenzada la terapia con el erlotinib, desarrolló una hepatitis aguda relacionada al uso de medicamentos que se complicó con un deterioro renal (aspartato aminotransferasa 1400 U/L, alanina aminotransferasa 1299 U/L, creatinina 4.4 mg/dL, urea nitrogenada 55 mg/dL). Se excluyeron las causas virales de la hepatitis y una tomografía computadorizada había descartado la metástasis hepática. Según el método de evaluación de causalidad de Roussel-Uclaf, la hepatitis relacionada al uso del erlotinib fue clasificada como "probable". La situación del paciente pronto se complicó con el inicio de una acidosis láctica, la cual le causó la muerte dos horas después de la admisión.

DISCUSION: La acidosis láctica fue promovida por la hepatitis inducida por el erlotinib con una insuficiencia hepática inicial (disminución en la eliminación de lactato), el tratamiento concomitante con metformín (aumento en la producción de lactato) y el deterioro renal agudo (acumulación de metformín). Este es el segundo caso de toxicidad hepática mortal inducida por el erlotinib en cáncer pulmonar. En el caso anterior, la muerte ocurrió después de 10 días y fue totalmente debida a una hepatitis fulminante, mientras que en nuestro paciente la lesión hepática sólo inició una interacción entre el medicamento y la enfermedad que causó una acidosis láctica mortal en pocas horas.

CONCLUSIONES: Es preciso monitorizar las pruebas de función hepática durante el tratamiento con el erlotinib, particularmente en los pacientes frágiles de mayor edad que reciben múltiples medicamentos. Por lo tanto, se requieren más estudios para probar la seguridad del erlotinib en estos pacientes que comúnmente se encuentran en el "mundo real", pero a menudo excluidos en los estudios aleatorios de cáncer.

Traducido por Rafaela Mena

Une Hépatite Induite par l'Erlotinib et Compliquée d'une Acidose Lactique Fatale chez un Homme Âgé

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RÉSUMÉ

OBJECTIF: Signaler un cas d'hépatite induite par l'erlotinib et compliquée d'une acidose lactique fatale chez un homme âgé souffrant d'un adénocarcinome du poumon et de diabète sucré.

PRÉSENTATION SOMMAIRE DU CAS: Chez un homme âgé de 77 ans et souffrant d'un adénocarcinome du poumon de stade IIIB, un traitement à base de 100 mg par jour d'erlotinib, un inhibiteur du récepteur du facteur de croissance épidermique, est initié après un échec de la chimiothérapie et de la radiothérapie. Le patient souffre aussi d'un diabète de type 2 traité depuis 5 ans avec de la metformine. Douze jours après le début de l'erlotinib, le patient développe une hépatite aigue compliquée d'une détérioration rénale (AST 1400 U/L, ALT 1299 U/L, créatinine 4.4 mg/dL, BUN 55 mg/dL). Les causes virales d'hépatite sont exclues et une tomographie axiale récente permet d'éliminer des métastases hépatiques. Selon la méthode d'évaluation da la causalité Roussel-Uclaf, il existe un lien probable entre l'hépatite présentée par le patient et l'erlotinib. La condition du patient s'est compliquée d'une acidose lactique qui a causé la mort du patient 2 heures après son admission.

DISCUSSION: L'acidose lactique a été favorisée par l'insuffisance hépatique associée à l'hépatite induite par l'erlotinib (diminution de la clairance des lactates), par la prise concomitante de metformine (augmentation de la production des lactates) et par l'insuffisance rénale aigue (accumulation de la metformine). Il s'agit du second cas de toxicité hépatique fatale induite par l'erlotinib lorsqu'utilisé dans le traitement du cancer du poumon. Dans le cas antérieur, la mort était survenue après environ 10 jours et était entièrement due à une hépatite fulminante alors que dans le présent cas, la toxicité hépatique a initié une interaction médicament-maladie qui a résulté en une acidose lactique fatale en quelques heures.

CONCLUSIONS: Un suivi minutieux des tests de la fonction hépatique devrait être fait lors d'un traitement avec l'erlotinib spécialement chez les patients âgés et frêles recevant plusieurs médications. Des études supplémentaires sont donc nécessaires pour mieux tester la sécurité de l'erlotinib chez de telles personnes fréquemment rencontrées dans la réalité mais souvent exclues des essais cliniques sur le cancer.

Traduit par Marie Larouche