Rhabdomyolysis Resulting from Pharmacologic Interaction Between Erlotinib and Simvastatin

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Abstract

Erlotinib is an epidermal growth factor receptor inhibitor indicated as a second line of therapy for locally advanced and metastatic non–small-cell lung cancer after the failure of 1 previous chemotherpy. Simvastatin belongs to the statin family used to lower blood cholesterol. Drug interaction between erlotinib and statin has not been reported before. Both drugs are major substrates of the CYP3A4 enzyme in the liver. Thus, co-administration of these drugs can increase their serum levels, potentially leading to adverse effects. We report the interaction between erlotinib and simvastatin leading to rhabdomyolysis. Thus, caution is required with increasing usage of both of these drugs.

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Introduction

We report a case of rhabdomyolysis as a result of a drug interaction between erlotinib and simvastatin in a patient with stage IV non–small-cell lung cancer (NSCLC). Non–small-cell lung cancer accounts for approximately 85% of all lung cancers. The majority of patients with NSCLC present with locally advanced inoperable or metastatic disease. Erlotinib is a small-molecule inhibitor of tyrosine kinase (TK) for the human epidermal growth factor receptor (HER1/EGFR). Erlotinib monotherapy is indicated for the treatment of patients with locally advanced or metastatic non–small-cell lung cancer after the failure of ≥ 1 previous chemotherapy regimen.[1] Erlotinib in combination with gemcitabine is indicated in the first-line treatment for locally advanced, unresectable or metastatic pancreatic cancer.[2] Erlotinib has been shown to be effective for relieving symptoms, maintaining stable disease, and improving quality of life in the subset of patients who have experienced chemotherapy failure.[3] Simvastatin is used for pharmacologic management of hypercholesterolemia. Given their not infrequent concurrent use, awareness of this potential interaction is clinically important.

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Case Report

A 75-year-old woman presented to the emergency room with complaints of generalized muscle pain and weakness that had progressed over 4 days. Her medical history was significant for hypertension, hyperlipidemia, and coronary artery disease. She was previously diagnosed with stage IV adenocarcinoma of the lung with diffuse pulmonary involvement and was treated with 6 cycles of carboplatin and paclitaxel. This therapy was completed 9 months before admission with stable radiographic findings and no extra-thoracic disease. She relapsed 7 months after chemotherapy and presented with a left-sided pleural effusion. As a consequence, she underwent a video-assisted thoroscopic surgery procedure with talc pleurodesis 2 months before admission.

She was of Philippine descent and had never used tobacco products. Thus, she initiated second-line therapy with erlotinib 6 weeks before her current presentation. Her additional outpatient medications included acetylsalicylic acid 81 mg once daily, atenolol 50 mg twice daily, amlodipine 5 mg once daily, and ezetimibe/simvastatin 10/80 daily. On examination there was mild bilateral lower extremity weakness (right side 4/5, left side 4/5) which was predominately proximal. Selected laboratory results are shown in Table 1. She had initially developed hyperbilirubinemia when starting erlotinib which spontaneously resolved and had been on simvastatin/ezetimibe for the past 3 years.

Urine evaluation on admission showed large occult blood without red blood cells, indicative of myoglobinuria. These findings were felt to be consistent with rhabdomyolysis as a result of simvastatin and possibly induced by concurrent erlotinib

Table 1 Laboratory Markers During and After Concomitant Treatment with Erlotinib and Simvastatin

Time Course	AST	ALT	ALP	T. Bili	CK	Creatinine
Five Weeks on Erlotinib and Simvastatin	66	54	54	2.0	–	0.8
Six Weeks on Erlotinib and Simvastatin (Day of Admission)	787	473	63	0.9	17978	0.5
One Week off Erlotinib and Simvastatin	197	474	83	0.6	1512	0.5
Six Weeks After Discharge (on Erlotinib)	30	23	85	2.5	78	0.7

Abbreviations: ALP = alkaline phosphatase; ALT = alkaline aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; T. Bili = total bilirubin

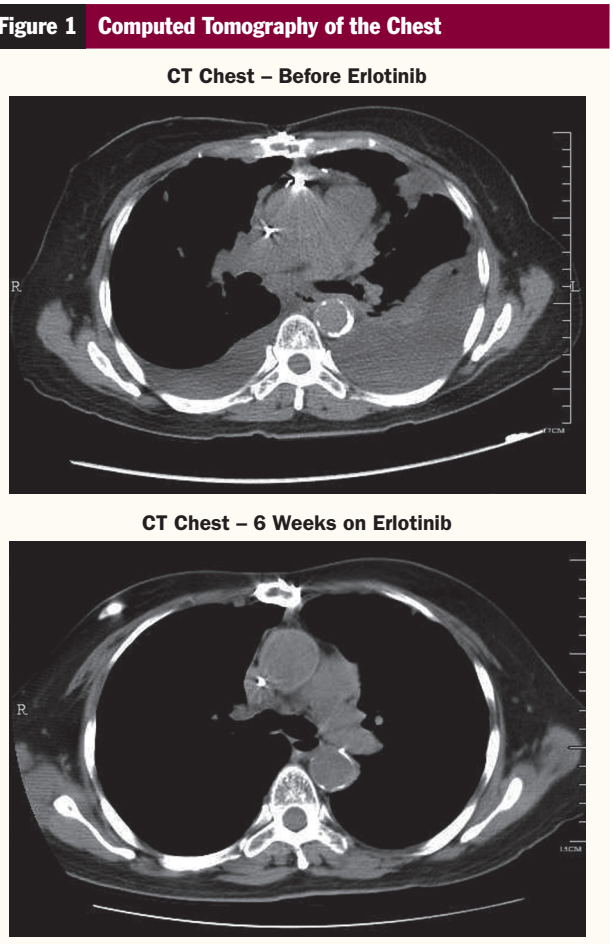
use. She was treated with hydration and discontinuation of erlotinib and simvastatin/ezetimibe. With her improving laboratory parameters and slowly improving weakness, she was discharged to a rehab ilitation facility. Because of her excellent initial response (Figure 1), the patient was started back on erlotinib when her laboratory markers for rhabdomyolysis had normalized, and simvastatin treatment was permanently held.

Discussion

Myositis or rhabdomyolysis secondary to simvastatin can occur at any point in time; however, the majority of cases tend to occur during the first few weeks to months after initiation of statin therapy. These serious adverse events are dose and plasma concentration related.[4]

Approximately 80% of erlotinib metabolism occurs by means of CYP3A4 and, to a lesser extent, by CYP1A2 enzyme activity.[5] Non-smokers have a higher plasma trough level of erlotinib compared with smokers, presumably because of induction of CYP1A1 in lung and CYP1A2 in liver. Simvastatin is uniquely metabolized by CYP 3A4 in the liver and is well tolerated; thus, it is commonly recommended as a model drug for testing drug interactions involving CYP3A4 substrates. It is an inhibitor of HMG-CoA reductase and lowers low-intensity lipoprotein synthesis.[6] Thus, the concurrent use of 2 major substrates of the CYP3A4 can have a competitive effect, resulting in elevated drug levels. Product inserts for HMG CoA reductase inhibitors suggest caution regarding the potential of drug interactions with substrates, inhibitors, and inducers of CYP3A4 compounds. The elevations of liver enzymes observed a week before hospital admission could be a grade I liver function abnormality that can occur with erlotinib. In a phase I study by Hidalgo et al, the grade I hyperbilirubinemia that was observed with treatment of solid tumors with erlonitib was not associated with elevated hepatic transaminases.[7] In the TRIBUTE study, no significant liver function abnormalities were noted at dose levels of 150 mg per day for treatment of NSCLC.[8] Therfore, the grade 3 (> 5.0-20.0 upper limit of normal) alanine transaminase observed in our patient was attributed to hepatotoxicity from simvastatin. Because our patient was a nonsmoker and because of her excellent clinical response (Figure 1), she was started back on erlonitib after her liver function tests normalized. Pao et al studied that adenocarcinomas from "never-smokers" (< 100 cigarettes over lifetime) comprise a distinct subset of lung cancers, frequently containing mutations within the TK domain of the EGFR gene have erlotinib sensitivity.[9]

Figure 1 Computed Tomography of the Chest



Notably, the lingular mode shrunk from 24 mm × 18 mm to 8 mm × 5 mm.
Abbreviation: CT = computed tomography

Conclusion

The potential for pharmacokinetic drug interaction and adverse effects could be minimized by the use of pravastatin, which is excreted by the kidney and does not undergo significant metabolism via the cytochrome P450 system.[10] However, all the other statins are major substrates of the CYP3A4 enzyme. Given the widespread use of cholesterol management medications, the concurrent use of these agents in an oncologic practice is not uncommon. Caution and awareness of potential interaction is therefore required when co-administering these agents.

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