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CORRESPONDENCE

Liver Toxicity After Treatment With Gefitinib and Anastrozole: Drug-Drug Interactions Through Cytochrome p450?

TO THE EDITOR: We read with great interest the clinical case reported by Ho et al[1] on hepatitis after treatment with gefitinib. We agree with the authors' conclusions, and we report on a similar case of gefitinib-related liver toxicity in a 63-year-old white female patient with metastatic breast cancer receiving gefitinib plus anastrozole.

Because of the appearance of pleural effusion and metastases in the lymph nodes of the neck, this women was enrolled onto a clinical trial using the tyrosine kinase inhibitor of epidermal growth factor receptor gefitinib (250 mg given orally once per day) plus the aromatase inhibitor anastrozole (1 mg given orally once per day) as a first-line option for metastatic breast cancer. At the immunohistochemical analysis, the pleural biopsies resulted estrogen receptor–positive (90%), progesterone receptor–negative, and human epidermal growth factor receptor 2–positive (score 2+ DAKO HercepTest; Dako, Hamburg, Germany). She had no prior history of liver disease, excess alcohol intake, or hepatitis. Baseline blood tests showed normal cell count, electrolytes, renal function, and liver function. The patient had been taking adjuvant tamoxifen for 4 years. This drug was suspended for 4 weeks before starting gefitinib plus anastrozole.

After 16 weeks of gefitinib plus anastrozole, laboratory investigations showed a significant elevation of her transaminases (AST, 56 U/L; ALT, 77 U/L; range, 0 to 35), which progressively increased after 28 weeks of gefitinib use (AST, 143 U/L; ALT, 213 U/L). Hepatitis work-up was negative. Because it was thought that her liver toxicity was related to gefitinib, she discontinued it, but kept assuming anastrozole. After 7 days, her transaminases levels remained stable (AST, 139 U/L; ALT, 211 U/L). After 2 weeks of gefitinib suspension, her transaminases gradually decreased (AST, 63 U/L; ALT, 102 U/L; Fig 1). At that time, an abdominal ultrasound and computed tomography scan of the abdomen and pelvis demonstrated normal liver and no significant abnormalities. A decision was taken to reintroduce gefitinib (she was assuming anastrozole in the meanwhile) with weekly monitoring of her transaminases. Within 1 week, her enzymes rose rapidly again (AST, 181 U/L; ALT, 283 U/L; Fig 1) and gefitinib was definitively discontinued.

Anastrozole inhibits in decreasing order of magnitude the cytochrome p450 isoenzymes CYP1A2, CYP2C8/9, and CYP3A4.[2] CYP3A4 is believed to be the major CYP450 enzyme involved in the metabolism of gefitinib.[3] Thus, there is potential for drug-drug interactions in our patient. However, the emerging safety profile of gefitinib indicates it is unlikely that the increased exposure seen on coadministration with CYP3A4 inhibitors is clinically relevant.[4] In fact, though exposure to gefitinib is increased by coadministration with CYP3A4 inhibitors, gefitinib is known to have a good tolerability profile, and a dosage reduction is not recommended.[5] In a double-blind, placebo-controlled randomized trial of 56 postmenopausal patients with ER–positive and epidermal growth factor receptor–positive primary breast cancer,[6] 27 women were randomly assigned to gefitinib and anastrozole, while 29 women were assigned to gefitinib and placebo, all given for 4 to 6 weeks before surgery. Treatment was well tolerated in both groups. In particular, these authors[6] reported that (data not shown) pharmacokinetic analyses to investigate interactions between anastrozole and gefitinib showed no effect of anastrozole on gefitinib metabolism, and plasma concentrations of anastrozole and gefitinib were consistent with previous studies.

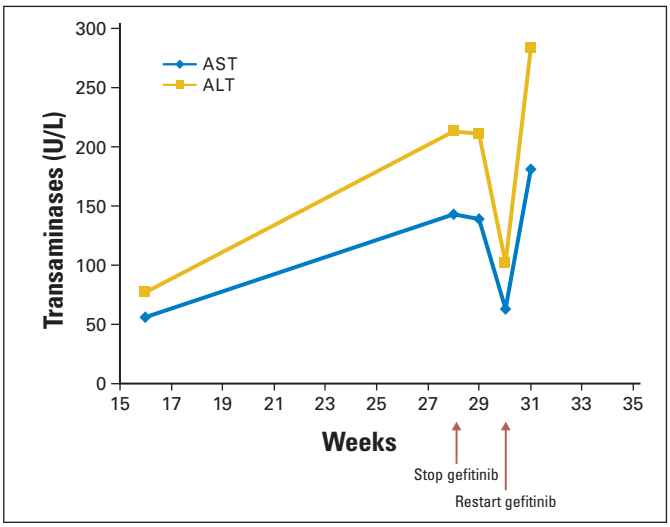

Fig 1. AST and ALT levels during gefitinib treatment. Reintroduction of gefitinib resulted in rapid increases of enzyme levels.

Therefore, based on these data, we agree with Ho et al[1] that, even in this case, gefitinib was implicated in the development of hepatitis, and it is advisable to routinely monitor liver transaminases in all patients treated with this drug. Anastrozole does not seem to be involved in causing or worsening this adverse effect.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.