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Original article

Clinical significance of fatty liver disease induced by tamoxifen and toremifene in breast cancer patients

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ABSTRACT

Background and Aim: The aim of this study was to identify the effect of selective estrogen receptor modulator (SERM) on non-alcoholic fatty liver disease (NAFLD) in Asian women.
Methods: We retrospectively evaluated fatty liver development and/or serum alanine aminotransferase (ALT) elevation during SERM treatment in 1061 women who were diagnosed and treated with breast cancer in 2005 at Asan Medical Center.
Results: 45 of 618 SERM-treated patients with normal ALT at baseline experienced ALT elevation during SERM treatment. Among the 112 SERM-treated patients who underwent liver imaging test, fatty liver was observed in 47 and both fatty liver and ALT elevation developed in 16 of 102 SERM-treated patients with normal baseline ALT. The cumulative rates of ALT elevation (10.7 vs. 4.3%; $P = 0.002$), fatty liver (48.5 vs. 20.9%; $P < 0.001$), and both fatty liver and ALT elevation (17.7 vs. 7.1%; $P = 0.02$) at 60 months were significantly higher in the SERM group than non-SERM group. By multivariate analysis, SERM treatment increased the risk of ALT elevation (hazard ratio [HR], 2.20; $P = 0.01$), fatty liver development (HR, 3.59; $P < 0.001$), and both fatty liver and ALT elevation (HR, 4.98; $P = 0.01$). After discontinuation of SERM, elevated serum ALT normalized in 39 (92.9%) and there were no instances of liver-related death or progression to liver cirrhosis in patients who experienced fatty liver or ALT elevation.
Conclusions: Although SERM treatment is significantly associated with NAFLD in Asian women, considering the tolerability and reversibility of NAFLD induced by SERM, it can be continued with liver function monitoring in relevant patients.

Introduction

Selective estrogen receptor modulators (SERMs), including tamoxifen and toremifene, are well-established adjuvant endocrine therapies for estrogen receptor-positive breast cancer patients that improve disease-free and overall survival and reduce local recurrence [1–3]. However, tamoxifen also induces several adverse events such as endometrial cancer, deep vein thrombosis, pulmonary embolism, and non-alcoholic fatty liver disease (NAFLD).

Tamoxifen is thought to cause NAFLD by not only increasing serum triglycerides and inhibiting mitochondrial β-oxidation of fatty acids, but also suppressing estrogen synthesis [4–6] though the exact mechanism is unknown. Several previous studies have shown that hepatic fatty changes develop in 30–50% of patients treated with tamoxifen, and 2–3% of these patients develop nonalcoholic steatohepatitis (NASH), especially those with obesity, hypercholesterolemia, or glucose intolerance [7,8]. However, the investigations that have been reported so far were performed in Western women—the majority of whom were overweight or obese—and it is remain unclear whether liver enzyme elevation during tamoxifen treatment is solely influenced by tamoxifen or not [9]. In addition, while toremifene—which has a different structure from

List of abbreviations: ALT, alanine aminotransferase; BMI, body mass index; CT, computed tomography; DM, diabetes mellitus; HTN, hypertension; NAFLD, nonalcoholic fatty liver disease; NASH, nonalcoholic steatohepatitis; PS, propensity score; SERM, selective estrogen receptor modulator; USG, ultrasonography.

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tamoxifen because of the replacement of a hydrogen atom on the ethyl side chain with chlorine—results in fewer thromboembolic disease and endometrial cancer and provides more beneficial effects in lipid profile in comparison with tamoxifen, little is known about the effects of toremifene on NAFLD [10–15].

Accordingly, the present study was performed to identify the effects of the two SERMs on fatty liver development and serum alanine aminotransferase (ALT) elevation, especially in Asian women. Furthermore, we evaluated the changes in fatty liver and ALT elevation induced by SERM following treatment cessation to provide baseline data for SERM treatment guideline.

Patients and methods

Study patients

We retrospectively reviewed data from 1185 women who were first diagnosed and treated with breast cancer in 2005 at Asan Medical Center (Fig. 1). We excluded 124 patients who had anti-hepatitis C virus antibodies or hepatitis B surface antigen (n = 72), significant alcohol consumption (140 g/week, n = 12), a diagnosis of stage IV breast cancer (n = 14), or SERM treatment duration was less than 12 months (n = 26); the remaining 1061 patients were analyzed in this study. Among 1061 patients, 537 were treated with 20 mg/day tamoxifen and 105 received 40 mg/day toremifene for more than 12 months. 419 patients were not treated with any kind of SERM. We collected the patient characteristics, including age, body mass index (BMI), history of diabetes mellitus (DM), hypertension (HTN), breast cancer stage, and the presence of fatty liver at baseline. If patients received systemic chemotherapy for breast cancer, we identified the regimen and treatment duration. We prescribed SERMs every 3–6 months with laboratory test at each regular visit and the data from the patients who were treated with SERM were collected by the end of SERM treatment. 503 (78.3%) patients have completed a 4–5 year course of SERM treatment, whereas 139 (21.7%) patients discontinued SERM treatment due to the change of treatment regimen (n = 79), adverse effect of SERM treatment such as hot flush and insomnia (n = 30), and lost to follow-up (n = 30) and the mean follow-up duration of these 139 patients was 32.5 months. The data from the patients who were not treated with SERM were collected by December 2013. The patients who developed fatty liver and/or elevated ALT during SERM treatment were additionally investigated after the end of SERM treatment in order to evaluate the changes in NAFLD. The results of abdominal ultrasonography (USG) or computed tomography (CT) were also included, if they were performed.

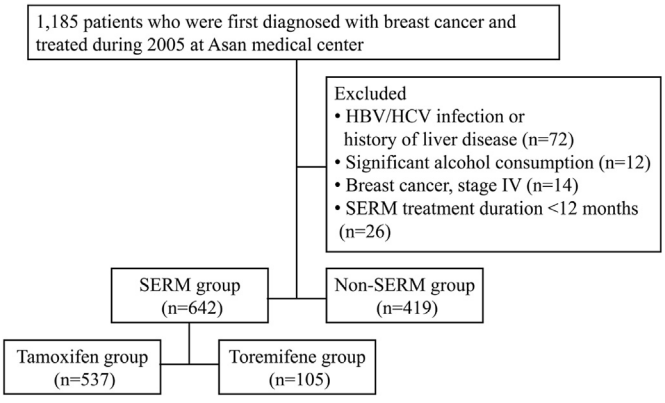

Fig. 1. Patients selection algorithm.

Study endpoints

The primary endpoints of this study were the development of fatty liver, ALT elevation, and both fatty liver development and ALT elevation. The development of fatty liver was defined as new identification of fatty liver or aggravation of fatty liver that had been observed before breast cancer treatment. Serum ALT elevation was defined as at least two elevations in ALT level above the 1.5 times of upper normal limit (40 IU/L) without significant alcohol consumption and hepatotoxic medication other than chemotherapeutic drugs in patients with normal ALT level at baseline. Both fatty liver development and ALT elevation was evaluated as a surrogate marker of NASH and defined as the simultaneous detection of fatty liver and ALT elevation. In addition, we also evaluated any liver-related death and the development of liver cirrhosis in patients who experienced fatty liver or ALT elevation.

Statistical analysis

We compared the differences in the baseline characteristics of the study patients using the chi-square test and t-test for categorical and continuous variables, respectively. We evaluated the cumulative probabilities for the time-dependent primary outcomes based on Kaplan–Meier method and used univariate and multivariate Cox proportional-hazards regression model to identify independent factors associated with the outcome variables. In addition, we performed propensity score (PS) matching in order to evaluate the effects of SERM treatment on serum ALT elevation and correct for differences in the baseline characteristics between the SERM and non-SERM groups and between the tamoxifen and toremifene groups. The absolute standardized differences were used to diagnose the balance after matching, and all absolute standardized differences after matching were less than 0.25. SPSS software (version 20) was used for the data analysis. In this study, $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The baseline characteristics of the study patients are presented in Table 1. The mean ages, the baseline total cholesterol, fasting glucose levels, and serum ALT levels did not differ between the SERM and non-SERM groups. The prevalence of DM (4.5 vs. 1.9%) and HTN (18.6 vs. 8.9%), and BMI (23.9 vs. 23.1 kg/m^2) were significantly greater in the non-SERM group than SERM group (Ps < 0.05). The breast cancer stage at diagnosis was mainly stage 1 or 2 in both groups. However, the non-SERM group included more patients with advanced stage cancer than the SERM group ($P < 0.001$) and more patients in non-SERM group received systemic chemotherapy (80.7 vs. 51.4%; $P < 0.001$). The mean follow-up period was significantly longer in the non-SERM group (79.0 vs. 53.5 months; $P < 0.001$). When we compared the baseline characteristics of the 642 SERM-treated patients according to the SERM regimen, the toremifene-treated patients were older (65.9 vs. 46.0 years), and had higher BMI (25.0 vs. 22.8 kg/m^2), the baseline total cholesterol (205.8 vs. 177.8 mg/dl), and serum ALT levels (20.4 vs. 16.4 IU/L) than the tamoxifen-treated patients (Ps < 0.05). The prevalence of DM and baseline fasting glucose level were comparable between the tamoxifen and toremifene groups, whereas the prevalence of HTN (5.0 vs. 28.6%) was significantly higher in the toremifene group ($P = 0.001$). The proportions of patients with advanced stage cancer and patients who received systemic chemotherapy (56.8 vs. 23.8%), and the