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Research Article

Tamoxifen-induced hepatic steatosis in premenopausal breast cancer patients

Premenapozal meme kanserli hastalarda tamoksifene bağlı hepatosteatoz

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Abstract
While aromatase inhibitors are replacing tamoxifen in postmenopausal breast cancer patients, tamoxifen continues to be the first-line hormonal therapy in premenopausal patients. Tamoxifen-induced hepatosteatosis may lead to nonalcoholic steatohepatitis (NASH), and NASH may develop into cirrhosis. If the development of hepatosteatosis is predicted, these patients may be treated with fibrates and statins. This study examines the development of hepatosteatosis in our premenopausal breast cancer patients that were taking tamoxifen for adjuvant therapy and were positive for the hormone receptors. Patients histopathologically diagnosed with breast cancer and with immunohistochemically demonstrated estrogen and/or progestron receptor expression were recruited for the study. All patients were assessed with ultrasonography by the same radiologist before tamoxifen therapy, at the sixth month of the follow-up and at the end of the first year. The study results were evaluated in thirty patients. Initial ultrasonography revealed grade 2 hepatosteatosis in four patients (13.3%), no change occurring at the repeat ultrasonography performed at the sixth month of the follow-up. Seven patients (23. 3%) were diagnosed as having grade 1 hepatosteatosis. A total of 12 patients (40%) were found to have hepatosteatosis at the end of the first year. Findings at the outset and those at the end of the first year were significantly different (p=0.021) as determined with the Wilcoxon test and Bonferroni correction performed to ascertain the difference in hepatosteatosis between the outset and the follow-up periods. No difference was obtained between the findings for the sixth month and those obtained at the end of the first year. In conclusion, the rate of hepatosteatosis as assessed with ultrasonography shows an increase with tamoxifen use in premenopausal patients. There was no difference between ultrasonography findings at the end of the first year and those at the sixth month of the follow-up. We think that the sitxh-month ultrasonography bears importance from the viewpoint of hepatosteatosis in these patients.
Keywords: Breast cancer; hepatosteatosis; tamoxifen

Özet
Meme kanserli postmenopozal hastalarda aromataz inhibitörleri tamoksifenin yerini alırken premenopazal hastalarda tamoksifen ilk basamak hormonal tedavi olmaya devam etmektedir. Tamoksifen kullanımına bağlı hepatosteatoz sonrası nonalkolik steatohepatit (NASH) gelişebilmekte ve NASH siroza ilerleyebilmektedir. Hepatosteatoz gelişimi önceden tespit edilirse fibratlar veya statinler ile bu hastalar tedavi edilebilirler. Biz bu çalışmamızda adjuvan tedavisinde tamoksifen kullandığımız hormon reseptörü pozitif premenopozal meme kanseri hastalarımızda hepasteatoz gelişimini araştırdık. Histopatolojik olarak meme kanseri olduğu tespit edilmiş ve östrojen ve/veya progesteron reseptör ekspresyonu immünohistokimyasal olarak gösterilmiş premenopozal hastalar çalışmaya alındı. Bütün hastalara tamoksifen kullanmadan önce, takibinin altıncı ayında ve birinci yılı sonunda aynı radyolog tarafından karaciğer ultrasonografisi yapıldı. Çalışma sonuçları 30 hastada değerlendirildi. Hastalardan dördünde (%13.3) başlangıç ultrasonografisinde grade 2 hepatosteatoz, takibinin altıncı ayında yapılan ultrasonografide bu hastaların hepatosteatozunda değişiklik tespit edilmez iken 7 hastada (%23.3) grade 1 hepatosteatoz, birinci yıl sonunda toplam 12 hastada (%40) hepatosteatoz saptandı. Ultrasonografi takip zamanları arasında hepatosteatoz farkını araştırmak için yapılan Wilcoxon testi ve Bonferroni düzeltmesi ile başlangıç ile altıncı ay bulguları anlamlı farklı idi (p=0.021). Başlangıç bulguları ile birinci yıl bulguları anlamlı farklı bulundu (p=0.003). Altıncı ay bulguları ile birinci yıl bulguları arasında fark tespit edilemedi. Sonuç olarak tamoksifen kullanımı ile ultrasonografik olarak tespit edilen hepatosteatoz oranı premenapozal hastalarda artmaktadır. Birinci yıl sonundaki ultrasonografi bulguları ile altıncı ay ultrasonografi bulguları arasında fark bulunmamaktadır. Bu hastalarda hepatosteatoz açısından altıncı ay ultrasonografisinin önemli olduğunu düşünmekteyiz.
Anahtar kelimeler: Meme kanseri; hepatosteatoz; tamoksifen

Introduction

Tamoxifen is a member of the family of selective estrogen receptor modulators (SERMs). These agents bound to estrogen receptors and exert an antiestrogenic effect in certain tissues. While aromatase inhibitors are replacing tamoxifen in postmenopausal patients with breast cancer, tamoxifen continues to be the first-line hormonal therapy in premenopausal patients (1-2). Side effects associated with tamoxifen use have a rare occurrence. These side effects are hot flashes, endometrial hyperplasia, endometrial tumours and thromboembolic events (3).

Non-alcoholic fatty liver disease (NAFLD) is defined as liver biopsy revealing a histopathology similar to that of alcoholic hepatitis in patients with no significant alcohol consumption. Obesity, diabetes, hyperlipidemia, endometrial tumours and metabolic syndrome are other risk factors (4-6). NAFLD covers a wide histologic spectrum ranging from simple hepatic steatosis to the necroinflammatory component of steatohepatitis. Liver enzymes are found to be high in the picture of steatohepatitis. NAFLD diagnosis is established with

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imaging methods such as ultrasonography and computed tomography. Liver biopsy, however, is the method of definitive diagnosis.

Hepatic steatosis, in general, is encountered in breast cancer patients more frequently (7). It is well known to be one of tamoxifen's side effects. Coşkun et al. (8) demonstrated that hepatic steatosis may develop in relation to tamoxifen use. Hepatic steatosis may lead to severe liver dysfunction in some patients (9). Tamoxifen-induced hepatic steatosis may be followed by nonalcoholic steatohepatitis (NASH) development; and NASH may develop into cirrhosis (10). If diagnosed early, patients with hepatic steatosis may be cured with fibrates and statins (11). In the present study, we have examined the development of hepatic steatosis in our premenopausal breast cancer patients who were being given tamoxifen for adjuvant therapy and were positive for the hormone receptors.

Patients and methods

Patients histopathologically diagnosed with breast cancer and with immunohistochemically demonstrated estrogen and/or progestron receptor expression were recruited for the study. Patients with a history of alcoholism, liver or renal insufficiency, diabetes and hypothyroidism were excluded from the study. Patients who were on a drug regimen that might affect their lipid profile were not recruited. All patients were administered adjuvant therapy and radiotherapy when indicated. Following these therapies, as hormonal treatment, gonodotropin-releasing hormone analog (GnRH) and 10 mg tamoxifen twice daily were given. All patients were assessed with ultrasonography by the same radiologist before tamoxifen therapy, at the sixth month of the follow-up and at the end of the first year. Patients with any of these three assessments missing were excluded from the study. Fatty liver findings were divided into four grades and measured ultrasonographically. Patients with normal echogenicity were assessed as normal. A mild, diffuse increase in echogenicity with diaphragm and intrahepatic vessels in normal appearance was assessed as grade 1 hepatic steatosis. Moderate echogenicity increase with slightly impaired diaphragm and intrahepatic vessels visualization was defined as grade 2, and significant echogenicity increase with pronounced impairment in diaphragm, intrahepatic vessels and right lobe posterior visualization was defined as grade 3 hepatic steatosis.

The body mass index of the patients was calculated by dividing their body weight in kilograms by the square of their height in meters.

The statistical analysis was performed using the SPSS 13.0 software. Relationships between the initial, sixth-month and the end of first year ultrasonography findings were examined with Friedman test. Post-hoc analysis was performed using Wilcoxon test with Bonferroni correction.

Results

The study results were evaluated in 30 patients. The numbers of patients in grades 1, 2 and 3 hepatosteatosis were 5 (16.7%), 12 (40%), and 13 (43.3%), respectively. None of the patients recruited for the study had metastatic disease (Table 1). Liver function test results of patients identified an increase by not more than two folds of the normal value in the first sixth month and first year-end follow-up.

Table 1. Patient characteristics

	Mean±SD	Median
Age	41,1±8	43
Height	158,2±5,3	158,5
Weight (kg)	69,1±12,3	65
BMI (kg/m^2)	25,7±5,7	25,3
Triglycerides (mg/dl)	162±90	151,5
BUN (mg/dl)	13±4	12
AST (U/l)	25±6	18
ALT (U/l)	19±8	17,5
LDL (mg/dl)	94,4±21,9	89,5
Total cholesterol (mg/dl)	173,5±24,2	172,5

Initial ultrasonography revealed grade 2 hepatosteatosis in four patients (13.3%). In three of these patients body mass index was over 30 kg/m^2. While no change was found in these patients condition at the ultrasonography performed at the sixth month of the follow-up. 7 patients (23.3%) were diagnosed as having grade 1 hepatosteatosis. Patients who had grade 2 hepatosteastosis initially showed no change in the ultrasonography performed at the end of the first year. No change occurred also in the condition of the patients who were found to have grade 2 hepatosteatosis at the sixth-month ultrasonography. One patient was found to have grade 1 hepatosteatosis. A total of 12 patients (40%) were found to have hepatosteatosis at the end of the first year (Figure 1).

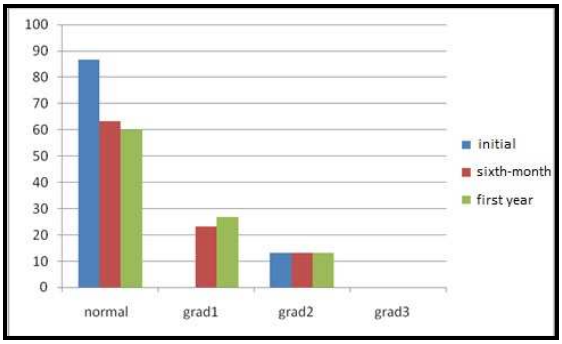

Figure 1. Change in the grade of hepatosteatosis during the follow-up.

Findings at the outset and those at the end of the first year were significantly different (p=0.021) as determined with the Wilcoxon test and Bonferroni correction performed to ascertain the difference in hepatosteatosis between the outset and the follow-up periods. No difference was obtained between the findings for the sixth month and those at the end of the first year.

Discussion

At the end of one-year follow-up, 12 patients (40%) were diagnosed as having hepatosteatosis. The diagnosis was established prior to tamoxifen use in four patients and after tamoxifen use in eight patients. The majority of the patients with newly developing hepatic steatosis were diagnosed with ultrasonography performed at the sixth month. None of our patients developed transaminase elevation during the follow-up.

Hepatic steatosis is one of the tamoxifen-induced side effects. As it is asymptomatic, it is generally overlooked. Findings are reversed with the withdrawal of the drug (12). The mechanism by which tamoxifen induces hepatosteatosis is not fully known. It has been proposed that the reason may be the changes in the lipid profile (13-15). Tamoxifen *in vitro* has been shown to lead to mitochondrial β-oxidation dysfunction (16,17). It is suggested that the gene expression profile in rats exposed to tamoxifen is changed and that this may lead to hepatosteatosis (18). Ohnishi et al. (19) argued that CYP17 polymorphism may be determinant of the probability of fatty liver development in patients using tamoxifen. Glucose intolerance in tamoxifen using patients may lead to hepatosteatosis (20).

The risk of hepatosteatosis development is higher with tamoxifen use in obese patients (21). The majority of the patients who had hepatosteatosis prior to tamoxifen use in our study were obese patients. Those with newly-developing hepatosteatosis were not obese. The patients had previously received chemotherapy. It has been shown that chemotherapy did not have a role in hepatosteatosis development in these patients (22,23). Coşkun et al. found the rate of hepatosteatosis as 43% in the sixth-month follow-up of the patients using premenopausal and post-menopausal adjuvant tamoxifen. In our study, the rate was smaller. The reason may be the inclusion of postmenopausal patients in the study mentioned (8).

Saphner et al. (24) found steatohepatitis at the rate of 2.2% in patients using tamoxifen. In our study, the one-year follow-up period yielded no findings pertaining to steatohepatitis. We think that this may be due to our follow-up period's being shorter in comparison to the Saphner's study.

In detecting fatty liver, ultrasonography, computed tomography or magnetic resonance imaging are the methods of choice. Magnetic resonance imaging is more effective in showing hepatic steatosis. However, it is not used as a routine test on account of its being costly and difficult to access. Ultrasonography is a reliable and reasonably priced method. Its prime disadvantage, however, is its being operator dependent. In detecting fatty liver, the sensitivity of ultrasonography is 89% and its specificity is 93% (25,26).

Nishino et al. (27) found hepatic steatosis at the rate of 43.2% for tamoxifen use in their two-year follow-up. We also found a similar rate for hepatosteatosis in our one-year follow-up period. Ashraf et al. (28) found the mean interval between tamoxifen use and the development of fatty liver as seven months. In our study, this period was six months.

In conclusion, the percentage of hepatosteatosis as assessed with ultrasonography shows an increase with tamoxifen use in premenopausal patients. There is no difference found between ultrasonography findings at the end of the first year and those at the sixth month of the follow-up. We recommend that an ultrasonographic examination should be performed at the sixth month of the follow-up with a view to detect hepatosteatosis in this patient group.

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