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ORIGINAL ARTICLE

Paclitaxel-induced hepatic steatosis in patients with breast cancer

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Summary

Purpose: *Paclitaxel has been associated with serum aminotransferase elevations, however, paclitaxel induced hepatosteatosis has not been evaluated systematically. This study assessed the rate of paclitaxel-related hepatosteatosis.*

Methods: *Forty one early breast cancer (BC) patients were included the study. Hepatic ultrasonograpy, demographic features and biochemical liver function tests before and after 12 weeks of paclitaxel were assessed.*

Results: *New-onset hepatosteatosis was developed in 26.7% of the patients. Baseline triglyceride>200mg/dL (OR, 11.25; p=0.015), LDH at baseline >191.48 IU/L (OR, 4.93; p=0.048), and total bilirubin >0.51 mg/dL after paclitaxel (OR, 6.17; p=0.042) were found as independent prognostic markers for new-onset hepatosteatosis.*

Conclusion: *Paclitaxel may induce hepatosteatosis in patients with BC.*

Key words: *paclitaxel, hepatosteatosis, breast cancer*

Introduction

The effects of chemotherapy on liver steatosis have not been analyzed adequately in the related literature. Hepatic steatosis is characterized by an accumulation of lipids in the liver. Fatty accumulation is possibly considered pathognomonic when the hepatic fat content exceeds 5% of the wet weight of the liver and the severity of steatosis is calculated as a percentage of fatty hepatocytes compared to the total hepatocytes seen [1]. Hepatosteosis may be seen as a common histopathological finding of multiple liver diseases that are unrelated to each other in terms of cause, pathogenesis and clinical course. The incidence of hepatosteatosis increases in the presence of risk factors such as metabolic syndrome, drugs, obesity, diabetes, and hyperlipidemia. Hepatotoxic drugs should be questioned carefully in these patients.

In hepatic steatosis, liver enlargement is commonly radiological finding in the majority of patients. The biochemical findings of liver steatosis are similar to those of other chronic liver diseases. The most common laboratory finding is elevation of transaminases. The increase in transaminases is usually up to 3-fold the normal value. Fatty liver is the main reason for the diagnosis of a patient with elevated asymptomatic transaminases. In gamma-glutamyl transferase (GGT) and alkaline phosphatase (ALP) tests, there is usually a mild increase in less than half of the cases; however total bilirubin levels are normal in most cases. Ultrasonography (USG) is the most commonly used method in the diagnosis of hepatosteatosis because it is cheap, noninvasive and easily accessible and with 82-89% sensitivity and 93% specificity [2]. The

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contribution of the USG is used not only to determine the steatosis but it also allows its grading at the same time, but the clinical significance of this rating is not yet clear [3]. CT and MRI are more sensitive and specific for the diagnosis of liver fat. However, their contribution to this area is less due to their widespread use of USG [4]. The hepatosteatosis can be classified radiologically in four different grades by USG as follows: grade 0 (normal echogenicity), grade 1 (diffuse mildly increased echogenicity, and normal walls of the diaphragm and intrahepatic vessels), grade 2 (moderate echogenicity, mild erosion of the diaphragm and intrahepatic vessel walls), grade 3, marked increase in fine echoes with poor or nonvisualization of the intrahepatic vessel borders, diaphragm and posterior right lobe of the liver [5,6].

Drug-induced hepatic steatosis (DIHS) is a rare form of liver injury. DIHS is generally a chronic but reversible condition and may involve drug accumulation in the liver. Several drugs have been associated with potential DIHS. Drugs which have been determined to induce hepatic steatosis include amiodarone, 5-FU, tamoxifen, irinotecan, and valproic acid, platinum analogues, methotrexate, and some chemotherapeutic and antiretroviral agents. Drug-induced steatosis is largely due to mitochondrial damage. In addition, mitochondrial damage can be induced by the inhibition of fatty acid beta oxidation, oxidative phosphorylation, and mitochondrial respiration [7]. Toxic liver injury can reproduce virtually any known pattern of injury, including necrosis, steatosis, fibrosis, cholestasis, and vascular injury [8]. Several anticancer agents, such as 5-fluorouracil, platinum derivatives, arsenic trioxide, taxanes, and anthracyclines increase the levels of reactive oxygen species (ROS) [9]. Specific forms of liver injury have been associated with various chemotherapeutic regimens, including steatosis and steatohepatitis with prolonged fluorouracil and irinotecan therapy, and sinusoidal injury with oxaliplatin-based regimens [10]. Taxanes are a group of antineoplastic agents with a unique mechanism of action as inhibitors of mitosis [11,12], and they are often used in the treatment of breast cancr (BC) [13,14]. Paclitaxel is the first discovered agent of this group. It is a potent antineoplastic agent and its mechanism of action appears to be mediated by its binding to microtubulin. It is a treatment for many different types of cancer. Adjuvant therapy of node-positive breast cancer; metastatic breast, ovarian, non-small-cell lung, bladder, esophagus, cervical, gastric, and head and neck cancer; AIDS-related Kaposi sarcoma; cancer of unknown origin, myelosuppression, hypersensitivity, nausea and vomiting, alopecia, arthralgia, myalgia, peripheral neuropathy. The available literature does not provide much information about the liver damage caused by taxanes (docetaxel and paclitaxel). Dose reduction is recommended for the patients using

Table 1. Demographic and laboratory characteristics of all patients

Characteristics	*All patients (N=41)*
Age (years), mean ± SD	56.58 ± 1.46
Sex, n (%)	
Female	41 (100)
Male	0 (0)
ALT (U/L), mean ± SD	
Basal	24.80 ± 1.70
Post CT	26.41 ± 1.96
P	0.51
AST (U/L), mean ± SD	
Basal	21.12 ± 1.02
Post CT	24.85 ± 1.20
P	0.11
GGT (U/L), mean ± SD	
Basal	26.58 ± 3.01
Post CT	30.21 ± 3.41
P	**0.05**
ALP (U/L), mean ± SD	
Basal	77.90 ± 4.11
Post CT	83.51 ± 4.22
P	0.065
LDH (U/L), mean ± SD	
Basal	191.48 ± 8.77
Post CT	238.39 ± 8.41
P	**<0.001**
Total bilirubin (mg/dL), mean ± SD	
Basal	0.51 ± 0.03
Post CT	0.48 ± 0.03
P	0.530
Karnofsky performance score, mean ± SD	
Basal	86 ± 4
Post CT	82 ± 5
P	0.092
BMI (kg/m^2), median (min - max)	
Basal	26.41 (21-38.1)
Post CT	25.88 (20.8-38)
P	0.25
Liver size, mean ± SD	
Basal	131.83 ± 3.51
Post CT	137 ± 4.48
P	**0.028**
Change of liver size, (mm), median, (min-max)	0 (0-70)
Interval (weeks), mean ± SD	12 ± 1.7

ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, BMI: body mass index, SD: standard deviation
Bold numbers denote statistical significance

these drugs with liver dysfunction because of the higher risk for neutropenia, mucositis, and treatment-related death [15]. Paclitaxel-induced hepatic steatosis has not been evaluated systematically [16]. Hepatic metabolism and biliary excretion play pivotal roles in the elimination and distribution of paclitaxel and its metabolites [17]. More trials are needed to evaluate drug interactions, which may influence hepatic metabolism, for example drugs that interfere with the cytochrome P-450 enzyme

Table 2. Comparisons of change on laboratory and demographic characteristics according to before-after chemotherapy and whether or not steatosis

Characteristics	*No hepatic steatosis (n=30)*	*New hepatic steatosis (n=11)*	*p*
Age (years), mean ± SD	56.93 ± 1.87	55.63 ± 1.87	0.91
Sex, n (%)			
Female	30 (100)	11 (27)	
Male	0 (0)	0 (0)	
ALT (U/L), mean ± SD			
Basal	25.30 ± 1.97	23.45 ± 3.47	0.59
Post CT	25.33 ± 2.04	29.36 ± 4.83	0.17
P	0.99	0.27	
AST (U/L), mean ± SD			
Basal	21.46 ± 1.22	20.18 ± 1.91	0.71
Post CT	24.26 ± 1.26	26.45 ± 2.93	0.34
P	**0.05**	0.11	
GGT (U/L), mean ± SD			
Basal	29.06 ± 3.99	19.81 ± 1.44	0.07
Post CT	31.96 ± 4.52	25.45 ± 2.99	0.08
P	0.21	0.07	
ALP (U/L), mean ± SD			
Basal	83.51 ± 4.61	62.63 ± 7.21	0.42
Post CT	87.03 ± 4.53	73.51 ± 9.53	0.61
P	0.32	0.06	
LDH (U/L), mean ± SD			
Basal	200.31 ± 10.21	167.27± 15.20	0.31
Post CT	244.06 ± 10.83	222.90 ± 9.71	0.09
P	**0.006**	**0.005**	
Total bilirubin (mg/dL), mean ± SD			
Basal	0.53 ± 0.04	0.46 ± 0.05	0.62
Post CT	0.47 ± 0.03	0.53 ± 0.07	0.35
P	0.17	0.38	
Karnofsky performance score, mean ± SD			
Basal	86 ± 4	86 ± 10	0.24
Post CT	82± 4	81 ± 6	0.18
P	0.09	0.08	
BMI (kg/m^2), median (range min-max)			
Basal	27.3 (21-37.4)	27.6 (22.03- 38.1)	0.11
Post CT	25.88 (20.7-38)	26.8 (20.7-37.1)	0.13
P	0.21	0.87	
Liver size, mean ± SD			
Basal	133.50 ± 3.91	127.27 ± 4.87	**0.045**
Post CT	139.23 ± 5.76	130.90 ± 5.63	0.24
P	0.73	0.34	
Change of liver size (mm), median (min- max)	0 (0-40)	0 (0-70)	1
Interval (weeks), mean ± SD	13 ± 1	12 ± 1	0.85

For abbreviations see footnote of Table 2. Bold numbers denote statistical significance

system [18]. Identification of paclitaxel metabolites and their potential role in toxicity or activity in several malignancies should be investigated. Paclitaxel has been associated with serum aminotransferase elevations in 7-26% of patients [19]. Similar rates of alkaline phosphatase elevations and occasional mild bilirubin elevations also occur in patients with biochemical evidence of cholestatic liver impairment [20]. The abnormalities are usually asymptomatic, mild and self-limited, rarely requiring dose modification or discontinuation. The mild liver injury that arises during therapy is probably due to a direct effect of paclitaxel in inhibiting microtubular function [21]. Hepatic toxicity is not dose-dependent and prolonged exposure to taxanes is not associated with cumulative hepatic toxicity [22].

Methods

In this retrospective study, patients who received weekly 80 mg/m^2 paclitaxel treatment as adjuvant chemotherapy of breast cancer were evaluated. Patients were included if they underwent regular USG examinations, and liver dimensions were measured by USG before and after completion of paclitaxel therapy. Hepatosteatosis was classified as grade 0, grade 1, grade 2 and grade 3. Grade 0 (normal echogenicity); Grade 1: slight diffuse increase in fine echoes in liver parenchyma with normal visualization of diaphragm and intrahepatic borders; Grade 2: moderate diffuse increase in fine echoes with slightly impaired visualization of intrahepatic vessels and diaphragm; Grade 3: marked increase in fine echoes with poor or no visualization of the intrahepatic vessel borders, diaphragm and posterior right lobe of the liver [5,6].

Exclusion criteria were determined as follows; alcohol use, diabetes mellitus, acute or chronic liver and kidney diseases, liver metastases, hypothyroidism, male cases and HER2(+) on immunohistochemical staining. Age, body mass index (BMI), triglyceride (TG) levels before and after treatment, changes in liver function and cholestasis test of the liver were compared.

Statistics

All statistical analyses were performed using SPSS (version 22.0, SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test and the Shapiro-Wilk test were used to determine whether the data were normally distributed. Mean and standard deviation were used for normally distributed data and median and min-max values were used for non-normally distributed data. Student t-test was used for comparison of normally distributed and Mann-Whitney U test was used for non-normally distributed data. Categorical variables were analyzed using the Chi-square or Fisher exact test. Continuous variables were reported as median (range) and analyzed using non-parametric Mann-Whitney U tests. Multivariate binary-logistic regression analysis was used for the analysis of independent predictive factors of hepatosteatosis. P value <0.05 was considered as statistically significant.

Results

All the patients participating in the study were female. The patient demographic characteristics are shown in Table 1. When baseline values of all patients were analyzed there was a statistically significant difference between LDH (p=0.05) and GGT (p<0.001) levels before and after paclitaxel treatment. There was an average increase of 5.61 mg/dL in ALP values, however this increase did not reach statistical significance (p=0.065). No statistically significant differences were found in AST, ALT, and total bilirubin levels. There was a statistically significant increase in liver size of 5.17 cm (p=0.028).

Table 3. Adjusted multivariate logistic regression analysis (backward LR selection) of clinical factors and odds ratio (OR) of new onset hepatosteatosis after paclitaxel therapy

Factors	*OR*	*95% confidence interval*	*p#*
Basal triglycerides >200 mg/dL	11.25	1.58 to 79.79	**0.015**
ALT+	0.80	0.34 to 18.40	0.85
AST+	2.11	0.35 to 12.5	0.40
Post-CT bilirubin+	6.17	1.09 to 37.47	**0.042**
ALP+	2.45	0.33 to 17.97	0.37
GGT+	1.22	0.15 to 9.81	0.84
Pre-CT LDH+	4.93	1.011 to 24.04	**0.048**
Increased liver size	0.21	2.10 to 6.62	0.41
Obesity	0.29	0.02 to 3.83	0.35
Age >60	2.00	0.25 to 15.81	0.50

+More than basal mean value. #Calculated by binary-logistic regression analysis. ALT: alanine aminotransferase, AST: aspartate aminotransferase, CT: chemotherapy, ALP: alkaline phosphatase, GGT: gamma-glutamyl transferase, LDH: lactate dehydrogenase, OR: odds ratio. Bold numbers denote statistical significance

New hepatic steatosis was seen in 11 (26.7%) of 41 patients after chemotherapy. There was a statistically significant increase compared to basic levels in the LDH of cholestasis enzymes in both steatosis group (p=0.005) and non-steatosis group (p=0.006). Also, GGT (p=0.07) and ALP (p=0.06) tests were close to statistical significance, however, there were no statistically significant differences found in other liver function tests after chemotherapy. Additionaly, there was no statistically significant difference in increase of liver size in all patient groups and new steatosis group (Table 2). A statistically significant difference was found between the groups in basic liver measurements (p=0.045), but no differenc was found to be important in regression analysis. When multivariate regression analysis was performed in the new steatosis group, the risk of developing steatosis in patients with a baseline triglyceride level higher than 200 mg/dL was 11.25-fold higher (p=0.015). The risk of developing new hepatosteatosis was 6.17-fold higher (p=0.048) in patients whose bilirubin level was higher than the mean bilirubin level of all patients after therapy. Patients whose pre-chemotherapy LDH levels were higher than the mean LDH levels of all patients had a 4.93-fold increased risk of developing new hepatosteatosis (p=0.048). No statistically significant difference was found in terms of risk of new steatosis in the other parameters on the multivariate analysis table (Table 3).

Discussion

This study showed that paclitaxel chemotherapy induced hepatic steatosis in some patients with BC within three months of the drug administration. It was observed that liver function tests primarily changed the cholestatic tests in all patients included in the study. Recognition of steatosis in patients receiving chemotherapy is important. In this study, new hepatic steatosis was present in 11 (26.7%) of 41 patients after treatment. Our findings are not strong enough to conclude that the liver damage and the degree of steatosis are related. Steatosis and liver damage may be underdiagnosed because the laboratory abnormalities are slight. Further investigations are needed to assess the relationship between liver damage and the degree of steatosis in patients receiving paclitaxel. We did not find any publication investigating the effects of paclitaxel use on hepatosteatosis when the literature was searched. We have reached a limited number of data on the effects of paclitaxel on liver functions [20,21]. In 2015, a case of sclerosing cholangitis associated with the use of docetaxel, which paclitaxel semisynthetic derivative has been reported [11]. In addition, a case of sclerosing cholangitis with the use of nab-paclitaxel in 2015 has been published [22].

Our study has some limitations. None of our patients was histologically evaluated by liver biopsy because all had mild liver damage. Patients could have used non-contrast abdominal computed tomography to give better information than ultrasound for liver steatosis, but our patients had only regular ultrasonography as imaging method.

Our patients could be more. We did not include patients with factors that could increase steatosis in the liver, so our patient count was low. Four cycles of adriamycin and cyclophosphamide combination were administered before paclitaxel therapy. We cannot discern how much this combination influences hepatosteatosis by paclitaxel. More accurate information can be obtained if patients treated with paclitaxel alone are included in subsequent studies. However, our study can be valuable in that respect. We were able to observe the paclitaxel effect more than other studies because we excluded other causes that might affect hepatosteatosis and liver function tests. For example, alcohol-using patients, diabetic patients, patients with liver metastases, and hypothyroidism patients were not included in the study.

In conclusion, this study found that hepatic steatosis was developed in 26.7% of patients with BC who were treated with paclitaxel. The change of liver function was seen mostly on cholestatic liver tests after paclitaxel therapy in all patients. Moreover, we found a statistically significant increase in liver cholestatic enzymes in the patient group who developed new steatosis. Consequently, patients treated with paclitaxel should be closely monitored with liver function tests and ultrasonography. Undoubtly, there is need for more randomized prospective trial in this topic.

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Conflict of interests

The authors declare no conflict of interests.

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