Fatty liver and transaminase changes with adjuvant tamoxifen therapy

Chien-Liang Liu[a,c], Jon-Kway Huang[b], Shih-Ping Cheng[a], Yuan-Ching Chang[a], Jie-Jen Lee[a,d] and Tsang-Pai Liu[a]

We investigated the time it took to develop fatty liver and changes in serum aspartate aminotransferase and alanine aminotransferase levels in patients with breast cancer treated with adjuvant tamoxifen. Liver sonography to detect fatty liver and measurement of serum aspartate and alanine aminotransferase levels were performed regularly for patients with early breast cancer. The results were compared in groups of patients with and without adjuvant tamoxifen as well as those on chemotherapy. Eighty-two of 156 patients treated with tamoxifen developed fatty liver, compared with eight of 62 patients not taking it. Fatty liver appeared as early as 3 months after beginning tamoxifen and was detected within 2 years in most cases. It persisted for 48 months after discontinuing tamoxifen in 17 of the 82 patients who developed it. The incidence of fatty liver in patients receiving both chemotherapy and tamoxifen was the same as that in patients receiving tamoxifen alone. While 115 patients had elevations of aspartate aminotransferase, alanine aminotransferase or both, the magnitude of the elevation was clinically significant in only 32 patients. Patients on both chemotherapy and tamoxifen had a higher incidence of elevated transaminases than those on tamoxifen alone. Adjuvant tamoxifen increases the incidence of fatty liver, but has only a minimal effect on aspartate aminotransferase and alanine aminotransferase. Fatty liver may appear as early as 3 months after beginning tamoxifen and may persist for more than 4 years after discontinuing it. Therefore, long-term follow-up is warranted. Chemotherapy is not clearly associated with fatty liver, but may cause a greater degree of hepatocellular damage than does tamoxifen. *Anti-Cancer Drugs* 17:709–713 © 2006 Lippincott Williams & Wilkins.

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[a]Department of General Surgery and [b]Department of Radiology, Mackay Memorial Hospital, [c]Mackay Medicine, Nursing and Management College and [d]Graduate Institute of Pharmacology, Taipei Medical University, Taipei, Taiwan.

Correspondence to C.L. Liu, Department of General Surgery, Mackay Memorial Hospital, No. 92, Sec. 2, Chung-San North Road, Taipei, Taiwan.
Tel: +886 2 2543 3535; fax: +886 2 2543 3642;
e-mail: chess.nhcgd@msa.hinet.net

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Introduction

Tamoxifen is a synthetic non-steroidal antiestrogen with both agonist and antagonist properties. It is frequently used as adjuvant systemic therapy in early, hormone-sensitive breast cancer [1,2]. Tamoxifen has very few side-effects serious enough to require withdrawal of treatment [3–6]. While aromatase inhibitors may be replacing tamoxifen in postmenopausal patients, tamoxifen is still the first-line hormonal agent for premenopausal women. Increasing evidence also suggests that tamoxifen is an effective chemopreventive agent to reduce the incidence of breast cancer in healthy women at high risk for the disease [7]. Concern about potential adverse effects is, however, one of the major reasons why women decline to take tamoxifen for chemoprevention [8].

Fatty liver is a well-recognized adverse effect of tamoxifen [9,10] that may result in severe liver dysfunction in some individuals [11,12]. Sequential changes of hepatic transaminases during adjuvant tamoxifen have, however, not yet been studied. It also remains to be investigated how long it takes for fatty liver to develop after beginning tamoxifen and how long before it resolves after withdrawal of the drug.

Adjuvant chemotherapy given for early breast cancer may also be a cause of subclinical hepatic toxicity [13,14]. Concurrent chemotherapy has been reported to increase the adverse effects of tamoxifen [15], but it is unclear whether sequential therapy poses a greater risk of hepatic damage. We designed this study to evaluate the incidence of fatty liver and serial changes in hepatic transaminases in patients on tamoxifen, with or without chemotherapy.

Methods

All patients with stage 1 and 2 breast cancer operated on in our hospital from January 1991 to June 1996 were eligible for enrollment in this prospective observational study. Patients gave signed informed consent to receive tamoxifen, which was prescribed if the tumors were positive for estrogen or progesterone receptors, or both. It was given as adjuvant therapy after a definitive surgical procedure, either a modified radical mastectomy or breast conservation therapy. If postoperative adjuvant

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chemotherapy was indicated, tamoxifen was given after completion of the chemotherapy. The chemotherapy used was either CEF [cyclophophamide 500 mg/m^2 body surface area, epirubicin 75 mg/m^2 and 5-fluorouracil (5-FU) 500 mg/m^2 every 3 weeks for six courses] or CMF (cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2 and 5-FU 500 mg/m^2 every 3 weeks for six courses). The choice of regimen was dependent on the judgment of the attending physician and the patient's preference. All patients received adjuvant tamoxifen for 5 years.

We performed liver sonography before beginning tamoxifen, every 3 months while the patients were on it and again 6 months after it was discontinued. For comparison, we also performed liver sonography in patients with stage 1 and 2 breast cancer who were not on tamoxifen. They were examined every 3 months in the first 2 years after surgery and then every 6 months for the next 3 years. Fatty liver was diagnosed in the presence of at least two of the following sonographic features: (i) an increase in liver echogenicity, (ii) loss of echoes from the walls of the portal veins, (iii) exaggeration of the discrepancy between liver and kidney echogenicity, and (iv) ultrasonic attenuation of the liver parenchyma. The operator who performed the liver sonography was not informed as to the treatment the patient was on.

We measured serum aspartate aminotransferase (AST) and alanine transaminase (ALT) levels before, during and after chemotherapy (if it was given); before beginning and every 3 months during tamoxifen therapy; and every 6 months after tamoxifen was discontinued. The normal ranges of AST and ALT in our laboratory are 5–35 and 5–30 U/l, respectively. The median follow-up was 66 (49–119) months after discontinuation of tamoxifen. For patients who did not take tamoxifen, the median follow-up was 62 (60–64) months after surgery.

The patient's height was measured at the time of enrollment, and the weight taken at enrollment and every 3 months thereafter. From these values, we calculated the body mass index (BMI). Fasting blood sugar, serum total cholesterol and triglyceride levels were checked before enrollment and every 3 months thereafter. Any history of medication and alcohol use were recorded.

Patients were excluded if they had (i) preexisting fatty liver, (ii) a history of hepatitis B or C, (iii) a history of hyperlipidemia or diabetes mellitus, (iv) elevated serum AST, ALT, triglycerides, total cholesterol or blood sugar levels before treatment, (v) alcohol abuse (more than 140 g per week), or (vi) use of hepatotoxic medications other than the chemotherapeutic agents mentioned above. Patients were excluded from analysis if they developed significant hypertriglyceridemia on tamoxifen that warranted medical intervention, had a cancer recurrence, discontinued tamoxifen before 5 years or were lost to follow-up (17 patients).

Categorical variables were analyzed with a χ^2-test and continuous variables with a paired two-tailed Student's *t*-test. The level of statistical significance was set at 0.05.

A power analysis was not performed before enrollment of patients. The accrued sample size, however, was examined retrospectively using Altman's nomogram, demonstrating that the power to detect a 0.4 standardized difference between patients treated with or without tamoxifen at a 0.05 significance level would be about 0.8. The power to detect a 0.3 standardized difference would be 0.6.

Results

The demographic characteristics of patients who did or did not take tamoxifen were similar. The only exception was the higher percentage of patients with hormone receptor-positive disease in the tamoxifen group (Table 1). Tamoxifen was used in 156 patients, of whom 82 (52.6%) developed fatty liver, compared with only eight of 62 (12.9%) not on tamoxifen ($P < 0.001$). Chemotherapy did not influence the development of fatty liver (Table 2). Patients with chemotherapy developed fatty liver in 59 out of 141 and those without chemotherapy developed fatty liver in 31 out of 77 ($P = 0.82$). Patients with a higher BMI at enrollment were more liable to develop fatty liver than those with a lower BMI, but the difference was not statistically significant (Table 3).

Fatty liver appeared as early as 3 months after beginning tamoxifen in some patients, but the incidence increased with time. Most cases (72 of 82, 87.8%) were detected

Table 1 Demographic characteristics of patients with early-stage breast cancer

	Treated with tamoxifen ($N=156$)	Not treated with tamoxifen ($N=62$)	*P*-value
Age (year)	48.8 (47.1–50.5)[a]	47.4 (45.0–49.7)[a]	0.34
Premenopausal	77	35	0.34
Postmenopausal	79	27	
BMI (kg/m^2)	24.9 (24.6–25.3)[a]	25.5 (24.9–26.1)[a]	0.08
Size of tumor (cm)	2.5 (2.4–2.7)[a]	2.3 (1.9–2.6)[a]	0.11
Node-positive	49	20	0.90
Node-negative	107	42	
Stage 1	54	24	0.85
Stage 2A	69	26	
Stage 2B	33	12	
With chemotherapy	97	44	0.22
Without chemotherapy	59	18	
ER (+), PR (+)	126	10	<0.001
ER (+), PR (−)	26	2	
ER (−), PR (+)	4	1	
ER (−), PR (−)	0	49	

BMI, body mass index; ER, estrogen receptor; PR, progesterone receptor.
[a]95% confidence interval.

Table 2 Proportion of patients with fatty liver stratified by treatment

	Number of patients	Patients with fatty liver (%)	*P*-value
Tamoxifen	156	82 (52.6)	<0.001
No tamoxifen	62	8 (12.9)	
Chemotherapy	141	59 (41.8)	0.82
No chemotherapy	77	31 (40.3)	
Both TAM and CT	97[a]	52 (53.6)	
Tamoxifen alone	59[b]	30 (50.8)	0.74[c]
Chemotherapy alone	44[d]	7 (15.9)	<0.001[c]
Neither TAM nor CT	18[e]	1 (5.6)	

TAM, tamoxifen; CT, chemotherapy.
[a]Median follow-up 64 (49–114) months after discontinuation of tamoxifen.
[b]Median follow-up 67 (53–119) months after discontinuation of tamoxifen.
[c]Compared with patients received both tamoxifen and chemotherapy.
[d]Median follow-up 62 (60–64) months after surgery.
[e]Median follow-up 61 (60–64) months after surgery.

Table 3 Proportion of patients on tamoxifen with fatty liver, stratified by body mass index

BMI value	Number of patients	Number with fatty liver (%)	*P*-value[a]
≤ 25	93	47 (51)	0.79
25–28	37	20 (54)	
>28	26	15 (58)	

BMI, body mass index.
[a]*P* value = 0.54 when comparing only two subsets (BMI ≤ 25 and BMI > 25).

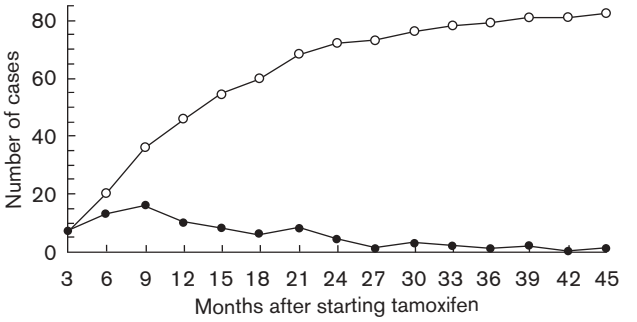
within 2 years after starting therapy (Fig. 1). In 17 (20.7%) cases, it persisted for at least 48 months after discontinuing tamoxifen (Fig. 2). None of these 17 patients had other factors during the follow-up period that might induce fatty liver, such as weight gain, hyperglycemia, hyperlipidemia, alcohol abuse, corticosteroids or other toxic agents.

Among the 156 patients treated with tamoxifen, 115 had elevations of AST, ALT or both at least once while on tamoxifen, but the magnitude of the elevation was clinically insignificant in most cases. Only 32 patients had enzyme elevations more than 2 times above the upper limit of normal (Table 4). The incidence of transaminase elevation did not differ between patients with and without fatty liver. Those on both chemotherapy and tamoxifen had a higher incidence of transaminase elevations than those on tamoxifen alone. At 2 years after discontinuing tamoxifen, the AST and ALT levels had returned to the normal range in almost all patients who had not received chemotherapy. The levels remained higher than normal in about 10% of patients on chemotherapy (Fig. 3).

Discussion

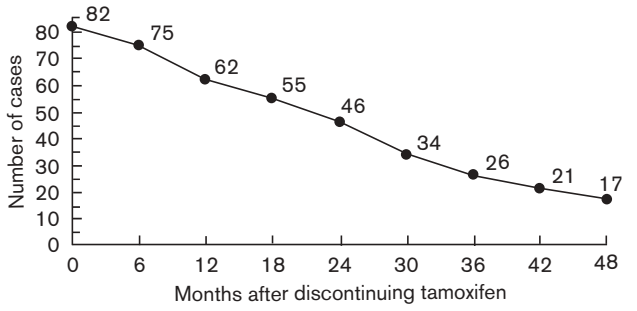
Our study showed that the incidence of fatty liver increased in women with breast cancer who were receiving adjuvant tamoxifen. Sonographic evidence of steatosis appeared as early as 3 months after beginning

Fig. 1



Cumulative incidence of fatty liver diagnosed over time after starting tamoxifen. Open circles: number of patients diagnosed with fatty liver for the first time. Solid circles: cumulative number of patients diagnosed with fatty liver.

Fig. 2



Number of patients with persistent fatty liver over time after discontinuing tamoxifen.

tamoxifen. The use of tamoxifen alone, however, was not associated with clinically significant or persistent elevations of liver transaminases. Significant elevations of these enzymes were more likely to occur in women who had also received adjuvant chemotherapy.

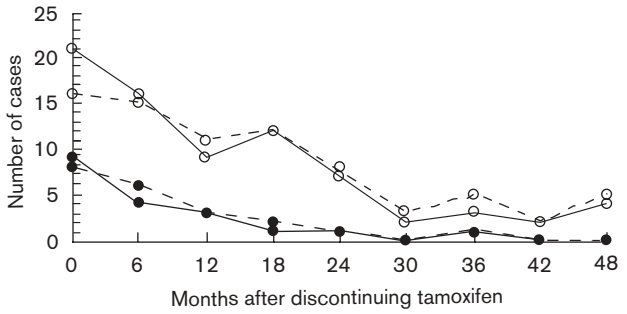
Fatty liver is associated with obesity, diabetes mellitus, hyperlipidemia, alcohol abuse, corticosteroids and other toxic agents [16,17], and the disorder has been reported to occur more frequently in patients taking tamoxifen than in controls [9]. Chu *et al.* [18] reported a higher incidence of fatty liver in breast cancer patients than in controls. In their study, tamoxifen was associated with a higher but nonstatistically significant incidence. They, however, included patients with chronic liver disease, diabetes mellitus and hyperlipidemia, potentially confounding the role of tamoxifen. We excluded patients with these possible causes of fatty liver in order to clarify the effect of tamoxifen alone on the liver in patients with breast cancer.

Table 4 Patients with transaminase[a] elevations on tamoxifen

	Total number of patients	At least one episode of transaminase elevation [*N* (%)]	*P*-value	Transaminase over twice the normal upper limit [*N* (%)]	*P*-value
With TAM	156	115 (73.7)	0.11	32 (20.5)	0.85
No TAM	62	39 (62.9)		12 (19.4)	
TAM with FL	82	63 (76.8)	0.35	18 (22.0)	0.64
Without FL	74	52 (70.3)		14 (18.9)	
TAM with CT	97	80 (82.5)	0.001	26 (26.8)	0.013
Without CT	59	35 (59.3)		6 (10.2)	

TAM, tamoxifen; FL, fatty liver; CT, chemotherapy.
[a]Aspartate aminotransferase or alanine aminotransferase or both.

Fig. 3



Number of patients with persistent hepatic enzyme elevation after discontinuing tamoxifen. Open circles: patients on chemotherapy. Solid circles: patients not on chemotherapy. Solids lines: patients with elevated serum aspartate aminotransferase. Dashed lines: patients with elevated serum alanine aminotransferase.

Methotrexate is a well-recognized cause of fatty liver [19]. Our results, however, indicate that chemotherapy did not significantly increase the incidence of fatty liver, perhaps because only 19 of our patients received methotrexate as part of the chemotherapy regimen (CMF regimen). Moreover, methotrexate-associated fatty liver usually develops after long-term treatment with a total cumulative dose of more than 600 mg [20,21]. Our patients received lower cumulative doses of 360–420 mg.

Overweight and obesity may lead to non-alcoholic fatty liver and steatohepatitis [16,18,22]. Although our patients with a higher BMI were somewhat more likely to develop fatty liver on tamoxifen, the difference was not statistically significant. This might be due to a relatively small sample size. We also, however, excluded patients with preexisting fatty liver. This may indicate that tamoxifen induces fatty liver by a mechanism independent of that occurring secondary to obesity.

Imaging diagnosis of fatty liver may be accomplished using sonography, computed tomography or magnetic resonance imaging [23–26]. Magnetic resonance imaging is generally considered too expensive as a routine test for this disease. The diagnostic criteria for a computed tomographic diagnosis are more objective [12] than those for sonography, which is more operator-dependent. Sonography is, however, the cheapest, safest, most readily available test and is easiest for the patient [27]. One recent study on sonography [28] gives a sensitivity of 89% and a specificity of 93% for the diagnosis of fatty liver.

Nishino *et al.* [10] performed hepatic computed tomography for breast cancer patients receiving tamoxifen and reported a 43.2% incidence of fatty liver within the first 2 years of treatment. Murata *et al.* [12] reported that 40 of 105 patients on tamoxifen developed fatty liver, 35 of them within the first 2 years of therapy. Our results were similar and we documented that the steatosis may appear as early as 3 months after beginning tamoxifen. Nishino's group [10] reported that the mean recovery of fatty liver after discontinuing tamoxifen was 1.2 years. We found that it had resolved by 2 years after discontinuing tamoxifen in 59.8% (49 of 82), but persisted for more than 4 years in one-fifth of the patients. Although tamoxifen is associated with fatty liver, it has only rarely been reported in association with non-alcoholic steatohepatitis [11,12,29], the diagnosis of which requires liver biopsy [29]. It is, however, impractical to perform liver biopsy routinely, and serum AST and ALT are reasonable surrogates for detecting hepatocellular damage [19,30,31]. In our series, 73.7% of patients on tamoxifen had increases in one or both enzymes, but the magnitude of the increase was clinically significant (i.e. greater than 2 times the upper limit of normal) in only 20.5%. Elevated transaminases did not correlate with the presence of fatty liver. Larroquette *et al.* [13] reported abnormal liver function tests in 77% of patients receiving adjuvant chemotherapy for breast cancer. Our study also showed that patients who received both adjuvant chemotherapy and tamoxifen were more likely to have increases in transaminases than those treated with tamoxifen alone (82.5 versus 59.3%), suggesting that chemotherapy is more likely to cause significant hepatocellular damage than tamoxifen. Further support for this assertion is the fact that in most of the patients with elevated transaminases on tamoxifen alone, the values returned to baseline within 1 year after completing therapy.

Conclusion

It would therefore appear that, while tamoxifen is associated with fatty liver in a significant proportion of women receiving it as adjuvant therapy for breast cancer, the risk of serious hepatocellular damage is low. Chemotherapy does not increase the risk for fatty liver, but it does appear to cause more hepatic damage than does tamoxifen. Long-term sonographic follow-up after discontinuing tamoxifen may be necessary to assure that the steatosis resolves, but long-term monitoring of transaminases is even more important, especially for patients who have received chemotherapy.

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