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A prospective, randomized study on hepatotoxicity of anastrozole compared with tamoxifen in women with breast cancer

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Key words

Anastrozole, breast cancer, clinical trial, fatty liver disease, hepatotoxicity, tamoxifen

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Tamoxifen and anastrozole are widely used as adjuvant treatment for early stage breast cancer, but their hepatotoxicity is not fully defined. We aimed to compare hepatotoxicity of anastrozole with tamoxifen in the adjuvant setting in postmenopausal breast cancer patients. Three hundred and fifty-three Chinese postmenopausal women with hormone receptor-positive early breast cancer were randomized to anastrozole or tamoxifen after optimal primary therapy. The primary end-point was fatty liver disease, defined as a liver–spleen ratio <0.9 as determined using a computed tomography scan. The secondary end-points included abnormal liver function and treatment failure during the 3-year follow up. The cumulative incidence of fatty liver disease after 3 years was lower in the anastrozole arm than that of tamoxifen (14.6% *vs* 41.1%, $P < 0.0001$; relative risk, 0.30; 95% CI, 0.21–0.45). However, there was no difference in the cumulative incidence of abnormal liver function (24.6% *vs* 24.7%, $P = 0.61$). Interestingly, a higher treatment failure rate was observed in the tamoxifen arm compared with anastrozole and median times to treatment failure were 15.1 months and 37.1 months, respectively ($P < 0.0001$; HR, 0.27; 95% CI, 0.20–0.37). The most commonly reported adverse events were 'reproductive system disorders' in the tamoxifen group (17.1%), and 'musculoskeletal disorders' in the anastrozole group (14.6%). Postmenopausal women with hormone receptor-positive breast cancer receiving adjuvant anastrozole displayed less fatty liver disease, suggesting that this drug had a more favorable hepatic safety profile than tamoxifen and may be preferred for patients with potential hepatic dysfunction.

Breast cancer is one of the most frequent causes of cancer death in women in both developing and developed countries.(1) According to the Chinese cancer registries, breast cancer incidence rates were ranked sixth in the general population (21.21/100 000) and first among women (42.55/100 000), causing 10.24/100 000 deaths in the Chinese female population in 2009,(2) which has increased from the 9.31/100 000 mortality rate registered in 2007.(3)

The estrogen antagonist tamoxifen is one of the most firmly established drugs used as adjuvant endocrine therapy for breast cancer and is considered a valuable option for hormone receptor (HR)-sensitive early breast cancer in both premenopausal and postmenopausal women.[4] However, anastrozole, a highly selective, non-steroidal aromatase inhibitor (AI), has demonstrated superior efficacy over tamoxifen in treating postmenopausal hormone-sensitive early stage breast cancer in terms of recurrence-free survival and tolerability.[5]

Adjuvant endocrine therapies for breast cancer span at least 5 years, creating long-lasting side-effects, which often results in non-adherence or change of medication. It is widely accepted that tamoxifen and AI possess relatively different safety profiles.[6] Hot flushes, gynecological disorders and thromboembolic events are more common in patients receiving tamoxifen, while joint symptoms, osteopenia or osteoporosis are more frequent in patients receiving AI. In terms of drug-related hepatotoxicity, tamoxifen has been found to be associated with toxic hepatitis,[7] cirrhosis[8] and submassive hepatic necrosis.[9] In addition, fatty liver disease, also known as non-alcoholic fatty liver disease (NAFLD) or non-alcoholic steatohepatitis (NASH), was observed in more than 30% of patients with breast cancer who received tamoxifen as adjuvant therapy.[10,11] The first anastrozole-induced hepatotoxicity case was reported in 2006.[12] A retrospective study demonstrated that fatty liver disease detected using ultrasound was more frequently seen with tamoxifen than with anastrozole (30.4% *vs* 6.25%).[13] To date, there is no prospective, randomized study comparing anastrozole and tamoxifen hepatotoxicity in a comprehensive manner.

Therefore, we aimed to compare hepatotoxicity of anastrozole with tamoxifen as adjuvant therapy in postmenopausal women with HR-positive breast cancer, especially in drug-induced fatty liver disease. Liver biopsy is probably the most reliable method for fatty liver diagnosis, but this procedure is associated with some morbidity and mortality.[14] Computed tomography (CT) scan is a widely used, less invasive method for fatty liver disease detection.[15–17] Major diagnostic criteria of hepatic steatosis include liver–spleen ratios <0.9 and a hepatic CT attenuation value that is at least 10 HU lower than that of the spleen. In the present study, the primary end-point was the incidence of fatty liver disease defined as a liver–spleen ratio <0.9 on hepatic CT scan. The secondary end-points included abnormal liver function as well as treatment failure during the 3-year follow up. We observed that participants treated with anastrozole displayed less fatty liver disease cases than those in the tamoxifen group, suggesting a more favorable liver safety profile for anastrozole, which should be preferred for patients with potential hepatic dysfunction.

Materials and Methods

Patient eligibility. Postmenopausal women with histologically proven HR-positive invasive breast cancer underwent all optimal treatments for their disease (primary surgery and, in some cases, chemotherapy) before enrollment in the present study. Postmenopausal woman was defined as a woman fulfilling any of the following criteria[4]: (i) age ≥60 years; (ii) prior bilateral oophorectomy; (iii) age <60 years with at least one intact ovary, use of tamoxifen or toremifene, and follicle-stimulating hormone (FSH) and estradiol levels in postmenopausal ranges; (iv) age <60 years with at least one intact ovary and an intact uterus, amenorrhea ≥12 months continuous; or (v) age <60 years with at least one intact ovary and prior history of hysterectomy with FSH and estradiol levels in postmenopausal ranges. Exclusion criterion were: (i) clinical evidence of metastatic disease; (ii) previous adjuvant hormonal therapy for breast cancer; (iii) unwillingness or unsuitability to stop taking any drug affecting hormonal status or with major hepatotoxicity; (iv) previous history of invasive breast cancer at any time or other invasive malignancy within the past 3 years, other than squamous or basal cell carcinoma (skin) or cervix carcinoma *in situ*; (v) hepatic impairment detected using serum chemistry assays (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [AKP], gamma-glutamyl transpeptidase [GGT] or total bilirubin [TB] concentrations more than 1.5 times the upper limit of normal), measured 4 weeks after surgery or 6 weeks after chemotherapy; (vi) fatty liver disease on hepatic CT scan or other major liver disease such as active hepatitis or cirrhosis; or (vii) regular daily alcohol intake >20 g.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and International Conference on Harmonization/Good Clinical Practices. All protocols were approved by all relevant ethics review boards. All patients provided written informed consent before study enrollment.

Study design and treatment. The HEART Hepatotoxicity of ARIMIDEX Compared with Tamoxifen trial is registered with ClinicalTrials.gov, number NCT00537771, and the study was carried out between September 2007 and December 2011. Three hundred and fifty-three patients were randomized in this prospective, multicenter, comparative, open-label study. Patients who met the eligibility criteria were randomized 1:1 to receive anastrozole 1 mg (AstraZeneca, London, UK) or tamoxifen 20 mg (first Shanghai Hualian Pharmaceutical Ltd, then Shanghai Fudan Fuhua Pharmaceutical Ltd, Shanghai, China) orally, once daily.

The primary end-point was incidence of fatty liver disease, defined as a liver–spleen ratio of <0.9 on hepatic CT images. The extent of steatosis was classified according to CT liver–spleen ratios as mild (0.5–0.9), moderate (0–0.5) or severe (<0).[11] The CT scans were performed at baseline and at 48 weeks ± 7 days, 96 weeks ± 7 days and 144 weeks ± 7 days. If a subject was withdrawn, a CT scan was performed if the previous one was performed more than 6 months previously. The CT scan interpretations were performed by a radiologist at each institution and were centrally reviewed by an independent radiologist. Whenever the radiologist from an institution and the central radiologist disagreed on the CT scan results, the central radiologist's view prevailed. Secondary end-points were: (i) incidence of abnormal liver function, defined as AST, ALT, AKP, GGT or TB concentrations more than 1.5 times the upper limit of the reference range; and (ii) time to treatment failure (TTF), defined as the time between randomization and earliest occurrence of fatty liver disease, breast cancer recurrence or withdrawal from study treatment for any reason, including death from any cause. The severity of abnormal liver function was classified into grades 1–4 according to NCI Common Terminology Criteria for Adverse Events (CTCAE) 3.0.[18] The decision criteria bout the adverse events of anastrozole and tamoxifen were the same as those used in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) and the Breast International Group (BIG) 1-98 trials,[19,20] based on the severity grading classified as: mild (awareness of sign or symptom, but easily tolerated); moderate (discomfort sufficient to cause interference with normal activities); or severe (incapacitating, with inability to perform normal activities).

Patients were followed up for 3 years regardless of whether they discontinued treatment, unless there was evidence of treatment failure, including fatty liver disease detected using

hepatic CT scan (confirmed by two blinded experts) or breast cancer recurrence, or withdrawn consent for any reason. Further treatments were made at the investigators' discretion in the case of discontinued participation in the study. In the event of liver function abnormality, continuation of study medication and/or initiation of specific treatment were at the investigators' discretion as well. However, follow ups were made as planned for patients who remained under study treatment.

Study assessment. At baseline, all patients were assessed by physical examination and appropriate radiological tests. In addition, Eastern Cooperative Oncology Group (ECOG) performance status, hematology, blood chemistry and coagulation profiles were obtained before randomization. All assessments were repeated every 3 months until patients developed disease and all adverse events were recorded.

Statistical analysis. Statistical analyses were conducted according to a pre-defined data analysis plan. The intention to treat (ITT) population was defined as all randomized patients. Primary statistical analyses of the end-points were performed on an ITT basis. The full analysis set population, which excluded patients who were randomized and not treated with study medications, constituted an additional analysis population. All patients who took at least one dose of the study medication were included in the safety population used to analyze drug safety.

It was reported that tamoxifen induced NAFLD in 30–43.2% of patients as detected using imaging.[10,11,13] Power analysis revealed that a Fisher's exact test with a 0.05 two-sided significance level had 80% power to detect a difference between 35% and 20% incidence of fatty liver disease between the tamoxifen and anastrozole groups, respectively, with a sample size of 150 in each group. After adjusting for 10% of non-evaluable patients, 334 patients were randomized using sequentially numbered envelopes in a ratio of 1:1, with 167 in each arm.

Fisher's exact test was performed to assess statistical differences in frequencies such as incidence of fatty liver disease and abnormal liver function test. The Chi-squared test was used to test differences in the proportions of steatosis levels and liver biochemistry grading. The Kaplan–Meier method was used to assess TTF and a log-rank test allowed comparison of the treatment groups. Adverse events were summarized by actual treatment received. The incidence of adverse events was summarized by body system and preferred term for each of the two randomized treatment groups. Physical examination and laboratory data were summarized using descriptive statistics for continuous variables or frequency counts and percentages for categorical variables. Laboratory values outside the normal reference ranges were collected.

SAS (version 9.1.3; SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Results

Patients' characteristics. Between September 2007 and February 2009, 353 estrogen receptor (ER)- and progesterone receptor (PgR)-positive breast cancer patients (175 and 178 patients in the tamoxifen and anastrozole arms, respectively) were randomized in 28 Chinese centers. The last patient completed the last visit on 28 December 2011. Eleven patients in the tamoxifen group did not receive treatment during the study. Therefore, the full analysis set was added as a supportive sensitivity analysis set to the primary analysis to determine the difference between the two groups. The overall study design and detailed disposition of subjects are presented in Figure 1. Patients' demographic and disease characteristics are shown in Table 1. All patient characteristics were similar between the two arms. The median age was 59.6 years.

Anastrozole induces less fatty liver disease than tamoxifen. Our primary end-point data indicated that patients in the anastrozole group developed less fatty liver disease at 48, 96 and 144 weeks of treatment (Fig. 2). The cumulative fatty liver disease incidence in this arm was significantly lower than that in patients treated with tamoxifen (14.6% *vs* 41.1%, $P < 0.0001$) in the ITT population. Patients lost during the 3-year follow up were conservatively considered fatty liver disease cases in the primary analysis. Results of the full analysis set confirmed the results of the primary analysis. The relative risk (RR) for anastrozole to tamoxifen derived from the primary analysis was 0.30 (95% CI, 0.21–0.45). After excluding patients who were lost to follow up, 17 (9.6%) and 57 (32.6%) participants were identified with fatty liver disease in the anastrozole and tamoxifen arms, respectively, in the ITT population ($P < 0.0001$). In this case, the RR for anastrozole to tamoxifen was 0.29 (95% CI, 0.18–0.48).

Fatty liver disease was classified into three severity levels according to the CT liver–spleen ratio. For patients with a confirmed fatty liver disease diagnosis, 47 (26.9%) and 16 (9.0%) patients were found with a mild level ($P < 0.0001$; RR, 0.33; 95% CI, 0.20–0.57), while 10 (5.7%) and 1 (0.6%) participants showed a moderate level ($P = 0.005$; RR, 0.10; 95% CI, 0.01–0.76) in the tamoxifen and anastrozole groups, respectively, during the 3-year study period. No severe case of fatty liver disease was observed.

Anastrozole and tamoxifen affect liver function at similar levels. The cumulative incidence of abnormal liver function showed no significant difference between the tamoxifen and anastrozole arms (24.6% *vs* 24.7%, $P = 0.619$) after 3 years (Table 2), which is similar to data obtained during other visits (3, 6, 12, 18, 24 and 30 months). These findings indicate that both drugs affected liver function at comparable levels. However, when excluding patients lost to follow up, there was no difference between the tamoxifen and anastrozole groups (16.6% *vs* 20.2%, $P = 0.412$). The severity of abnormal liver function was classified into grades from 1 to 4. No patient was reported with grade 4. There was no significant difference in grades between the two groups (Table 2).

Anastrozole is more efficient in adjuvant treatment of breast cancer than tamoxifen. We observed 128/175 (73.1%) and 58/178 (32.6%) patients with treatment failure in the tamoxifen and anastrozole groups, respectively, in the ITT population. The median TTF was 15.1 months (454 days) for tamoxifen and 37.1 months (1112 days) for anastrozole. Interestingly, Kaplan–Meier analysis confirmed that anastrozole was significantly more efficient in prolonging TTF than tamoxifen (Fig. 3).

In the tamoxifen group, 129 patients had treatment failure: disease recurrence or progression ($n = 8$, 4.6%); fatty liver disease ($n = 60$, 34.3%); patient withdrew informed consent ($n = 23$, 13.1%); safety reasons ($n = 15$, 8.6%); non-compliance to protocol ($n = 2$, 1.1%); incorrect enrolment or randomization ($n = 6$, 3.4%); and lost to follow up ($n = 15$, 8.6%). In the anastrozole group, 60 patients had treatment failure: disease recurrence or progression ($n = 14$, 7.8%); fatty liver disease ($n = 17$, 9.6%); patient withdrew informed consent ($n = 6$, 3.4%); safety reasons ($n = 8$, 4.5%); non-compliance to protocol ($n = 4$, 2.3%); incorrect enrolment or randomization ($n = 2$, 1.1%); and lost to follow up ($n = 9$, 5.1%).

Safety. The most commonly reported adverse events included reproductive system disorders in the tamoxifen group

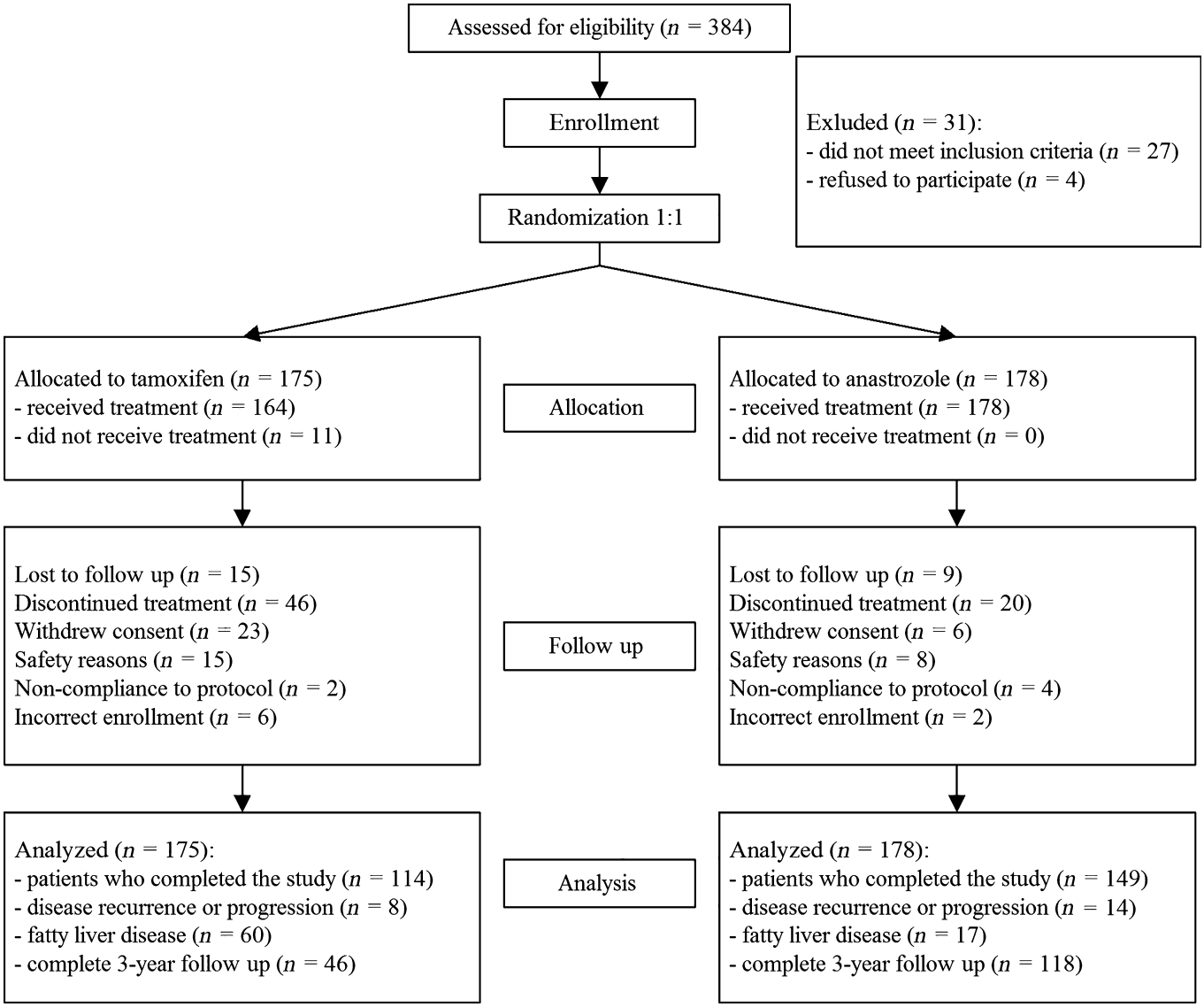

Fig. 1. Study design and patient flowchart.

(17.1%) and musculoskeletal and connective tissue disorders in the anastrozole group (14.6%). However, gastrointestinal complaints were the most frequently reported adverse events in both treatment groups. Table 3 summarizes the most common adverse events (>2%) observed in the present study.

Our data showed that 32 (19.5%) and 23 (12.9%) patients presented at least one drug-related adverse event in the tamoxifen and anastrozole groups, respectively. Of note, most drugs-related adverse events were mild or moderate in both groups. Eight (2.3%) patients experienced a total of 10 non-fatal but serious adverse events during the treatment period, none of which was related to the study medication. Overall, 25 (7.3%) patients discontinued study treatment due to adverse events, with 16 (9.8%) and 9 (5.1%) in the tamoxifen and anastrozole groups, respectively. Fewer patients experienced arthralgia, musculoskeletal pain and bone pain in the tamoxifen group, while fewer reported vaginal discharge, vaginal hemorrhage and endometrial hypertrophy in the anastrozole group. Only two severe bone pain events were reported in the anastrozole group. Other adverse events reported showed similar frequency in both study arms. Overall, both drugs were well tolerated.

No death due to disease progression was reported. However, two patients died from serious adverse events (cor pulmonale for one and acute myocardial infarction for the other) during the present study. Both were in the anastrozole group.

Discussion

Tamoxifen has been used for many years as the standard adjuvant endocrine therapy in patients with HR-positive early breast cancer. However, third-generation AI, including anastrozole, letrozole (non-steroidal) and exemestane (steroidal), have shown superior efficacy to tamoxifen, either as initial monotherapy or as adjuvant endocrine therapy after 2–3 years treatment with tamoxifen in postmenopausal patients with HR-positive early breast cancer.[20–22] However, considering that endocrine therapy is a long-term treatment, drug toxicity is a very important factor to consider besides efficacy. Indeed,

Table 1. Patients, tumors and primary treatment characteristics at baseline

Characteristic	Tamoxifen (n = 175)	Anastrozole (n = 178)	Total (n = 353)
Demographics			
Age (years)	59.4 ± 8.84	59.7 ± 7.77	59.6 ± 8.31
Body mass index (kg/m^2)	24.1 ± 3.42	23.8 ± 3.08	23.9 ± 3.25
Pathological type, n (%)			
Invasive ductal carcinoma	158 (90.3)	154 (86.5)	312 (88.4)
Invasive lobular carcinoma	5 (2.9)	6 (3.4)	11 (3.1)
Medullary carcinoma	1 (0.6)	1 (0.6)	2 (0.6)
Paget's disease	1 (0.6)	0	1 (0.3)
Other	10 (5.7)	17 (9.6)	27 (7.6)
Tumor size, n (%)			
T1	73 (41.7)	69 (38.8)	142 (40.2)
T2	87 (49.7)	98 (55.1)	185 (52.4)
T3	4 (2.3)	6 (3.4)	10 (2.8)
T4	4 (2.3)	2 (1.1)	6 (1.7)
Tis	0	2 (1.1)	2 (0.6)
Tx	7 (4.0)	1 (0.6)	8 (2.3)
Nodal status, n (%)			
N0	110 (62.9)	114 (64.0)	224 (63.5)
N1	47 (26.9)	40 (22.5)	87 (24.6)
N2	14 (8.0)	18 (10.1)	32 (9.1)
N3	4 (2.3)	6 (3.4)	10 (2.8)
Primary therapy, n (%)			
Chemotherapy			
No	36 (20.6)	38 (21.3)	74 (21.0)
Yes	139 (79.4)	140 (78.7)	279 (79.0)
Anthracycline based, n (%)	140 (80.0)	137 (77.0)	277 (78.5)
Taxol based, n (%)	98 (56.0)	90 (50.6)	188 (53.3)
Radiotherapy			
No	157 (89.7)	158 (88.7)	315 (89.2)
Yes	18 (10.3)	19 (10.7)	37 (10.5)
Missing	0	1 (0.6)	1 (0.3)

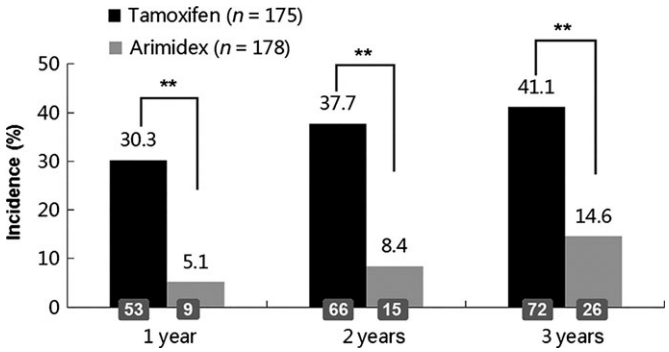

Fig. 2. Incidence of fatty liver disease in the intention to treat population. Patients lost to follow up were conservatively considered as having fatty liver disease. $^{**}P < 0.01$

it was reported that more than 30% of patients using tamoxifen as adjuvant treatment for breast cancer would develop hepatic steatosis.[10,11] No prospective study investigated whether AI are better for liver safety than tamoxifen, although several large randomized trials have reported that tamoxifen and AI had distinct toxicity profiles.[23] In the present prospective, randomized, multicenter, open-label study we compared anastrozole and tamoxifen hepatotoxicity in the adjuvant setting. Incidence of fatty liver disease and TTF values demonstrated that anastrozole was associated with less hepatotoxicity compared with tamoxifen. In addition, there were more patients who had TTF due to patient withdrawal in the tamoxifen group, mostly due to adverse effects. Our TTF rate was similar to previous studies.[10,11,23]

Ultrasound is widely used in fatty liver disease diagnosis, but this method is operator dependent and less reproducible. In the present study, CT scan was used for detection of fatty liver disease cases. We observed a lower incidence of fatty liver disease in anastrozole-treated patients compared with the tamoxifen group (14.6% *vs* 41.1%). When disease severity was evaluated, all cases were graded as mild, without severe event.

Estrogen positively affects lipid metabolism and tamoxifen increases the hepatic fat content by blocking estrogen function in hepatic lipid homeostasis, but the exact mechanisms are unknown.[24,25] Tamoxifen acts as a competitive antagonist of the ER in tissues, while anastrozole directly decreases the circulating plasma estrogen levels. Therefore, further investigation is needed to understand the important difference in fatty liver disease induction after treatment with anastrozole and tamoxifen. Interestingly, we noticed that the incidence of NAFLD and NASH due to tamoxifen was approximately 20–30%, most of which were reported by authors from Asia. No specific data on hepatic steatosis were reported in previous trials, including the ATAC, BIG 1-98, Tamoxifen Exemestane Adjuvant Multinational (TEAM) and The Intergroup Exemestane Study (IES) trials.[5,20–22,26] This may be due to the low incidence of hepatotoxicity and to the lack of data about variations of tamoxifen and AI efficacy and toxicity between races.

Abnormal liver function is often observed in drug-related hepatotoxicity. Our data showed no difference in abnormal liver function between patients treated with anastrozole or tamoxifen. These findings, together with higher fatty liver disease incidence in the tamoxifen group, suggest that there is no direct relationship between hepatic steatosis and abnormal liver function. However, more patients with abnormal AKP and TB were detected in the anastrozole group. Interestingly, anastrozole treatment was found to be associated with AKP increase in the ATAC trial.[19] This phenomenon is not well understood and more studies are needed to fill the knowledge gap. In addition, we evaluated five parameters of liver function (ALT, AST, AKP, GGT and TB) and observed 29 (16.6%) and 36 (20.2%) patients with abnormal liver function in the tamoxifen and anastrozole groups, respectively (excluding patients lost to follow up). These results contrast with the results from the National Cancer Institute of Cancada (NCIC) nnnMA.27, in which only 3% of patients presented liver function abnormalities as indicated by ALT, AST or bilirubin levels.[27] An Italian tamoxifen chemoprevention trial showed that 78 (3.1%) tamoxifen-treated women had a single elevation of ALT compared with 92 (3.6%) placebo-treated women, while 42 (1.7%) had multiple elevations of ALT compared with 22 (0.9%). Of these 64 women with multiple elevations of ALT, 12 tested positive for hepatitis C virus.[28]

The TTF, a parameter that depends on many factors, was significantly longer in the anastrozole group compared with tamoxifen-treated patients, mainly due to the lower incidence of fatty liver disease observed in the anastrozole arm. The safety and tolerability parameters were comparable in both groups. Adverse events detected in the present study were mild and moderate, consistent with previous reports, including the

Table 2. Incidence of abnormal liver function in the intention to treat population

Parameter	Tamoxifen (n = 175)	Anastrozole (n = 178)	Total (n = 353)	P-value	RR	95% CI for RR
144-week cumulative abnormal liver function, n (%)†				0.6186	0.91	(0.63, 1.30)
Yes	43 (24.6)	44 (24.7)	87 (24.6)			
No	113 (64.6)	132 (74.2)	245 (69.4)			
Missing	19 (10.9)	2 (1.1)	21 (5.9)			
Abnormal liver function, n (%)‡	29 (16.6)	36 (20.2)	65 (18.4)	0.412	1.22	(0.78, 1.90)
Grade 1	21 (12.0)	22 (12.4)	43 (12.2)	0.918	1.03	(0.59, 1.80)
Grade 2	7 (4.0)	12 (6.7)	19 (5.4)	0.254	1.69	(0.68, 4.18)
Grade 3	1 (0.6)	2 (1.1)	3 (0.8)	0.572	1.97	(0.18, 21.49)
Grade 4	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA	NA

†Patients lost to follow up were conservatively considered as having abnormal liver function. ‡Patients with abnormal liver function excluding those lost to follow up. CI, confidence interval; RR, relative risk.

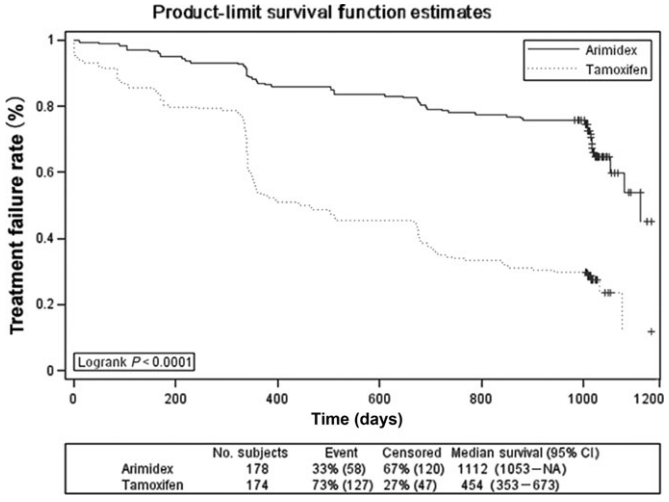

Fig. 3. Time to treatment failure using the Kaplan–Meier method in the intention to treat population.

ATAC trial. Adverse events caused by endocrine therapies can negatively affect the quality of life, considering the long treatment duration. Indeed, treatment-related symptoms can result in poor adherence to therapy or early treatment discontinuation, and therefore worst breast cancer outcomes.

The present study has some limitations that need to be addressed. First, we acknowledge the possibility that open-label trials might influence the reporting of adverse events. However, we were unable to obtain placebo pills for anastrozole. Second, the follow-up time used in the present study, 3 years, may appear to be short. Nishino *et al.*[11] have demonstrated that 43.2% of patients developed hepatic steatosis within the first 2 years of treatment, with no apparent correlation between duration of medication and disease development. Hepatic steatosis rapidly reversed after completion of tamoxifen therapy, with a mean recovery time of 1.2 years.[11] In addition, Murata *et al.*[10] reported that 40/105 patients developed hepatic steatosis while receiving adjuvant tamoxifen therapy, with 35 developing the disease within the first 2 years of treatment. Based on these findings, the duration of follow up was selected as 3 years in the present study. In contrast, although steatosis is non-progressive, patients with NASH/advanced stage fibrosis are at risk of developing liver complications within 7 years.[29] Fibrosis progression, largely associated with cirrhosis, may be affected by amounts of liver fat, degree of steatohepatitis and a variety of other sensitizing factors.[30] Nevertheless, it is not yet clear how this happened in patients with hepatic steatosis in the HEART study. Third, we performed a CT scan at baseline only to determine if the patients already suffered from hepatic fatty disease, but we did not record the liver–spleen ratio, preventing us from making adjustments based on the baseline value. Fourth, we did not assess further treatments for discontinued participation that can potentially cause fatty liver disease. Indeed, after withdrawal, treatment was at each physician's discretion and no follow-up data are available for these patients. Fifth, we did not record the HER2 status. Indeed, as in the ATAC and BIG 1-98 tri-

Table 3. Treatment-induced adverse events in the safety population

System organ class/preferred term	Tamoxifen (n = 164)				Arimidex (n = 178)				P-value
	Mild	Moderate	Severe	Total	Mild	Moderate	Severe	Total	
Subjects with at least one drug-related adverse event, n (%)	25 (15.2)	7 (4.3)	0	32	17 (9.6)	4 (2.2)	2 (1.1)	23	0.107
Reproductive system and breast disorders, n (%)									
Endometrial hypertrophy	9 (5.5)	0	0	9	0	0	0	0	0.001
Vaginal discharge	5 (3.0)	3 (1.8)	0	8	1 (0.6)	0	0	1	0.016
Vaginal hemorrhage	2 (1.2)	3 (1.8)	0	5	1 (0.6)	0	0	1	0.108
Musculoskeletal and connective tissue disorders, n (%)									
Arthralgia	0	1 (0.6)	0	1	5 (2.8)	0	0	5	0.217
Bone pain	0	0	0	0	3 (1.7)	1 (0.6)	2 (1.1)	6	0.031

Percentages were calculated as a proportion of the number of randomized subjects who took at least one dose of the study drug.

als,[19,20] we assumed that patients received all optimal primary treatments for their cancer. Last, one-third of the world's individuals infected with hepatitis B virus (HBV) reside in China, with 130 million carriers and 30 million chronically infected.[31] It is unfortunate that HBV infection history was not collected in the present study, rendering it impossible to determine whether high frequency of hepatic steatosis or abnormal liver function was associated with HBV. Except for obesity, no other risk factors for NASH (such as diabetes and hyperlipidemia) were taken into account. The three AI differentially affect lipid metabolism. Some studies have shown that anastrozole and exemestane do not negatively affect the lipid profile, although evidence suggests that letrozole does.[23] Hypercholesterolemia is a well-known risk factor for the development of cardiovascular diseases. In the ATAC trial, although lipid levels were not assessed, hypercholesterolemia incidence was higher in patients treated with anastrozole than those in the tamoxifen group; no difference was observed in the occurrence of ischemic cardiovascular events and death, while there were more cerebrovascular events and deaths in the tamoxifen group compared with the anastrozole arm.[19,32]

In summary, our results suggest that anastrozole treatment results in less fatty liver disease incidence than tamoxifen. No difference was found in liver function parameters between the anastrozole and tamoxifen groups. In contrast, TTF of anastrozole was significantly longer compared with that of tamoxifen. Although tamoxifen and anastrozole showed distinct safety profiles, both drugs were well tolerated. Future studies are needed to confirm these findings, especially in different ethnicities.

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Disclosure Statement

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