Tamoxifen treatment reverses the adverse effects of chemotherapy-induced ovarian failure on serum lipids

L Vehmanen¹, T Saarto¹, C Blomqvist¹, M-R Taskinen² and I Elomaa*,¹
¹Department of Oncology, Helsinki University Central Hospital, PO BOX 180, HUCH, FIN-00290, Helsinki, Finland; ²Department of Medicine, Helsinki University Central Hospital, FIN-00290, Helsinki, Finland

In all, 146 premenopausal women with early stage breast cancer were treated with adjuvant chemotherapy. In addition, 5-year tamoxifen treatment was started after chemotherapy to those 112 patients with hormone-receptor-positive tumours while those with hormone-receptor-negative tumours received no further therapy. The serum lipid levels were followed in both groups. The levels of serum total and low-density lipoprotein (LDL) cholesterol increased significantly after chemotherapy only in patients who developed ovarian dysfunction. Total cholesterol increased + 9.5% and LDL cholesterol + 16.6% in patients who developed amenorrhoea (P < 0.00001 and 0.00001, respectively). The cholesterol levels did not change in patients who preserved regular menstruation after chemotherapy. After 6 months of tamoxifen therapy, the total cholesterol decreased − 9.7% and the LDL cholesterol − 16.7% from levels after the chemotherapy, while the cholesterol concentrations remained at increased levels in the control group (P = 0.001 and P < 0.0001, respectively). The high-density lipoprotein cholesterol levels did not change significantly in either tamoxifen or control group. The effects of tamoxifen treatment on serum lipids after chemotherapy have not been studied before. Our current study suggests that adjuvant tamoxifen therapy reverses the adverse effects of chemotherapy-induced ovarian failure on total and LDL cholesterol and even lowers their serum levels below the baseline.

Keywords: breast cancer; chemotherapy; tamoxifen; serum lipids

Adjuvant chemotherapy significantly improves survival of premenopausal and perimenopausal breast cancer patients (Early Breast Cancer Trialists’ Collaborative Group, 1998a). In a majority of these patients, however, adjuvant chemotherapy causes ovarian failure. The incidence of adjuvant chemotherapy induced amenorrhoea varies from 26 to 89% depending on the drug combination used (Del Mastro et al, 1997). Most data are available on regimens based on cyclophosphamide, methotrexate and fluorouracil (CMF) and the average rate of CMF-induced ovarian failure is 68% (Bines et al, 1996). Women most prone to develop ovarian failure are those in their 40s, while women under 40 years of age have better preservation of menstruation after combination chemotherapy (Koyama et al, 1977; Bonadonna et al, 1985; Ludwig Breast Cancer Study Group, 1985; Padmanabhan et al, 1987; Richards et al, 1990; Bianco et al, 1991; Bines et al, 1996). The effects of chemotherapy on serum lipids in premenopausal women with breast cancer have been somewhat conflicting in the few studies available on subject. The levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol decreased and total cholesterol increased only slightly after chemotherapy in one study (Rzymowska, 1999), while in another study HDL cholesterol levels increased and total cholesterol levels decreased (Subramaniam et al, 1991). We have previously shown that the changes in serum lipids after adjuvant chemotherapy correlate to the changes in menstruation: total cholesterol, LDL and HDL cholesterol levels increased significantly only in patients with chemotherapy-induced ovarian dysfunction, while patients who preserved menstruation had no changes in these serum lipid levels (Saarto et al, 1996a). The effects of chemotherapy on serum triglyceride levels have varied across the studies (Subramaniam et al, 1991; Saarto et al, 1996a; Rzymowska, 1999).

Both natural and surgical menopause cause changes in serum lipids that are explained by the deficiency of oestrogens: serum total and LDL cholesterol and triglyceride levels increase and HDL cholesterol levels decrease (Matthews et al, 1989; Newnham 1993; Stevenson et al, 1993; Schaefer et al, 1994; Fukami et al, 1995). These adverse effects of menopause on serum lipids are reversed by hormone replacement therapy (Rijpkema et al, 1990; Nabulsi et al, 1993; Newnham, 1993; Writing Group for the PEPI Trial, 1995; Pripp et al, 1999). A few observational trials suggested a protective effect against coronary heart disease (CHD) among users of oestrogen or combined oestrogen and progestin (Stampfer and Colditz, 1991; Grady et al, 1992). However, two more recent large randomised trials have failed to show any cardioprotection among hormone replacement therapy users (Hulley et al, 1998; Manson et al 2003). The effects of tamoxifen on serum lipids have been extensively studied. Uniformly, the levels of total cholesterol and LDL cholesterol decrease significantly during tamoxifen treatment, but the effects on HDL cholesterol and triglycerides have varied (Love et al, 1990; Grey et al, 1995; Saarto et al, 1996b; Decensi et al, 1998). Two retrospective, randomised trials suggested that tamoxifen might have a cardioprotective effect in
postmenopausal women (McDonald and Stewart, 1991; Rutqvist and Mattsson, 1993). However, a large placebo-controlled randomised study failed to show any effects of tamoxifen on cardiovascular risk (Fisher et al., 1998).

Adjuvant tamoxifen treatment given after chemotherapy extends disease-free and overall survival for oestrogen receptor-positive breast cancer (Early Breast Cancer Trialists’ Collaborative Group, 1992, 1998b). So far no studies are available on the effects of chemotherapy followed by tamoxifen on serum lipid levels. The aim of this study was to investigate whether tamoxifen treatment after chemotherapy could reverse the adverse effects of chemotherapy on serum lipid levels in premenopausal women with breast cancer.

MATERIALS AND METHODS

Patients

The study population consists of 159 premenopausal newly diagnosed breast cancer patients with operable T1-3 N0-2 M0 breast cancer, treated between January 1998 and May 2001 at Helsinki University Hospital, Department of Oncology. Exclusion criteria were the following: (1) Karnofsky performance index <70, (2) hysterectomy or bilateral ovariectomy, (3) pregnancy or lactation, (4) age >55 years, (5) untreated hypothyroidism or hyperthyroidism and (6) other malignancies. Premenopausal status was defined as ongoing menstruation during the last 6 months. Four patients used a levonorgestrel-releasing intrauterine system (LNG IUS) as a contraceptive device at entry and therefore had sparse menstruation; baseline levels of follicle-stimulating hormone (FSH) were within premenopausal range (4.2–18.9 IU/L) also in these patients.

Of the 159 patients at entry, 13 patients were excluded. Four patients developed distant metastases before 1 year of follow-up, four patients discontinued follow-up, three patients had medication affecting lipid metabolism, one patient had missing baseline lipid values and one patient was diagnosed with untreated hypothyroidism. Overall, 146 patients were eligible for analyses.

All patients underwent surgery with axillary evacuation and total mastectomy or breast-conserving resection. Postoperative radiotherapy was given to those treated with breast-conserving surgery and to those diagnosed with axillary lymph node metastases. All patients were treated with adjuvant chemotherapy. The standard adjuvant chemotherapy regimen at Helsinki University Hospital was changed during the study period. Consequently, 73 patients received six cycles of cyclophosphamide (600 mg/m²), methotrexate (40 mg/m²) and 5-fluorouracil (600 mg/m²) intravenously on day 1 with 3 weeks’ intervals and one cycle of cyclophosphamide during the radiotherapy (CMF). In total, 72 patients received six to nine cycles of cyclophosphamide (600 mg/m²), epirubicin (60 mg/m²) and 5-fluorouracil (600 mg/m²) intravenously similarly with 3 weeks’ intervals (CEF) while one patient received four cycles of cyclophosphamide (600 mg/m²) and Adriamycin (60 mg/m²). All patients were treated with a prophylactic antiemetic regimen typically consisting of a serotonin (HT3) receptor antagonist (tropisetron or granisetron), metoclopramide and dexamethasone. After the chemotherapy, adjuvant 5-year tamoxifen was recommended to hormone-receptor-positive patients.

In addition, the first 48 patients were randomly allocated to receive intermittent intravenous clodronate treatment or no further therapy. A measure of 1500 mg of clodronate was given in saline over 3 h before each chemotherapy infusion for seven consecutive cycles. Randomisation was later interrupted due to conflicting results of adjuvant clodronate trials (Diel et al., 1998; Saarto et al., 2001; Powles et al., 2002).

Methods

Informed consent was obtained from all participants. The study was approved by the Local Ethical Committee, at the Department of Oncology, at the Helsinki University Hospital. Staging investigations for breast cancer included clinical investigation, liver ultrasound and bone scintigraphy. Basic laboratory tests before randomisation included a complete blood count and sedimentation rate, liver enzymes (transaminase, alkaline phosphatase, 5-nucleotidase), serum creatinine, albumin, calcium and kalium. Patients were interviewed regarding menopausal status, medications and other diseases before randomisation and at 6 and 12 months. Permanent amenorrhoea was defined as absent menstruation for at least 6 months. At 12 months, the patients were divided into three groups with respect to menstrual function after chemotherapy (regular menstruation, irregular menstruation and amenorrhoea). The following measurements were analysed from the fasting blood samples before the initiation of therapy and at 3, 6, 9 and 12 months: serum concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, serum FSH, luteinizing hormone (LH) and oestriol.

The serum cholesterol level was determined with an enzymatic colorimetric CHOD-PAP method and the triglyceride level with an enzymatic colorimetric GPO-PAP method (Roche Diagnostics). The concentration of HDL cholesterol was measured by an enzymatic HDL-C plus second-generation method (Roche Diagnostics). The equipment used to measure serum cholesterol, HDL-cholesterol and triglyceride levels was Hitachi 917 or Modular analyser (Hitachi Ltd, Tokyo, Japan). LDL cholesterol was calculated according to Friedewald equation (LDL cholesterol = cholesterol – HDL cholesterol – Trigly/2.2) (Friedewald et al., 1972).

Statistical methods

The Wilcoxon matched pair test was used to compare lipid and hormonal changes from baseline to 6 months within each menstrual group (regular menses, irregular menses and amenorrhoea). The Wilcoxon matched pair test was also used to test lipid changes from 6 to 9 months and from 6 to 12 months within the tamoxifen and control groups. The differences between the menstrual groups were tested by a repeated measures ANOVA model using the programs Statistical Package for the Social Science (SPSS) for Macintosh. Similarly, the effects of tamoxifen and clodronate treatment on changes in serum lipids were tested by repeated measures ANOVA. The correlations between the changes in serum lipids and weight were assessed by Spearman’s rank-order correlation coefficient. Other comparisons were made using the Mann–Whitney test. Owing to multiple comparisons, the significance level was set at 0.01.

RESULTS

Responses of serum lipids to chemotherapy-induced ovarian dysfunction (from baseline to 6 months)

Chemotherapy caused amenorrhoea in the majority of the patients. During 1 year follow-up, 78 patients of 146 (53%) had developed permanent amenorrhoea (absence of menstruation for at least 6 months) and 47 (32%) had irregular menstruation, while only 21 patients (14%) had regular menstruation. The mean age of the patients at the start of the chemotherapy was 47 years for those who developed amenorrhoea, 41 years for those with irregular menstruation and 36 years for those who preserved regular menstruation, respectively.

The gonadotropin FSH and LH changes during the chemotherapy period correlated with the changes observed in menstrual cycle. In patients who developed amenorrhoea, the median value of
FSH rose from 5.45 to 71.10 IU l\(^{-1}\) \((P<0.00001)\). The median FSH value rose from 5.30 to 47.90 IU l\(^{-1}\) \((P<0.00001)\) in patients with irregular menstruation and from 5.10 to 19.60 IU l\(^{-1}\) \((P=0.0001)\) in those who preserved regular menstruation. Similarly, the median LH values rose significantly during the chemotherapy in each menstrual group (Table 1).

Changes in total and LDL cholesterol during the chemotherapy correlated significantly with menstrual function. Only those patients who developed either amenorrhoea or irregular menstruation had marked elevations in serum total and LDL cholesterol, while no significant changes occurred in those who preserved regular menstruation.

In patients who developed amenorrhoea, the total cholesterol increased by +9.5% and the LDL cholesterol by +16.6% \((P<0.00001\) and 0.0001\), respectively. The LDL/HDL ratio increased by 21.7% \((P<0.00001)\) and the total cholesterol/HDL ratio by +13.3% \((P<0.00001)\).

The total cholesterol increased by +7.3% and LDL cholesterol by +11.8% in patients with irregular menstruation \((P=0.003\) and 0.017, respectively). The LDL/HDL ratio increased by +14.7% \((P=0.02)\) and the cholesterol/HDL ratio +9.4% \((P=0.005)\).

In patients who preserved regular menstruation, the total cholesterol increased only +2.4% and the LDL cholesterol +3.0% \((P=0.52\) and 0.57, respectively). Accordingly, LDL/HDL cholesterol and cholesterol/HDL cholesterol ratios remained unchanged (Table 1).

The differences in the changes of serum total and LDL cholesterol were insignificant between patients with amenorrhoea and irregular menstruation \((P=0.61\) and 0.22, respectively), but the differences in the changes of serum total and LDL cholesterol between patients with regular menses and irregular or absent menstruation (amenorrhoea) were more marked \((P=0.04\) and 0.008). Similarly, the differences in the changes of LDL/HDL ratios and total cholesterol/HDL ratios were insignificant between patients with amenorrhoea and irregular menstruation \((P=0.50\) and 0.84), but the changes in the differences of LDL/HDL ratios were significant \((P=0.006)\) and of total cholesterol/HDL ratios nearly significant \((P=0.02)\) between patients with regular menses and irregular or absent menstruation (amenorrhoea). Serum triglyceride levels increased and HDL cholesterol levels slightly decreased regardless of menstrual function and the differences between the groups were statistically insignificant (Table 1).

The mean weight gain during the chemotherapy was 2.5 kg for those who preserved regular menstruation, 2.0 kg for those with irregular menstruation and 1.2 kg for those with amenorrhoea. No correlation was found between the changes in weight and serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides).

**Effect of adjuvant chemotherapy followed by tamoxifen on serum lipids (from 6 to 12 months)**

After the chemotherapy period at 6 months, adjuvant 5-year tamoxifen was started to those 112 patients with hormone-receptor-positive tumours (tamoxifen group). In all, 34 patients with hormone-receptor-negative tumours received no further medication (control group). The patient characteristics (age, weight, body mass index, serum FSH, LH and oestradiol) were well balanced in the tamoxifen and control groups as well as the baseline values of the serum lipids (Table 2). All differences in these pretreatment characteristics between the treatment groups were statistically nonsignificant. Overall, 67% of the women who continued to menstruate regularly after the chemotherapy, 77% of the women who developed irregular menstruation and 79% of the women who became amenorrhoeic went on to tamoxifen. The differences in the relative proportions of the women starting tamoxifen were insignificant between the three menstrual groups \((P=0.29)\). In the control group, the changes seen in the serum lipids (total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides) were insignificant between those with regular menses and irregular or absent menstruation (amenorrhoea). Serum triglyceride levels increased and HDL cholesterol levels slightly decreased regardless of menstrual function and the differences between the groups were statistically insignificant (Table 1).
FSH, LH, oestradiol and lipid values from 6 to 12 months did not differ between the three menstrual groups (regular menstruation, irregular menstruation and amenorrhoea).

The total and LDL cholesterol and triglyceride levels increased during the chemotherapy in all patients. After 3 and 6 months of tamoxifen treatment, the total cholesterol decreased by −9.6% and −9.7% from the levels after chemotherapy, while total cholesterol remained unchanged in the control group (P = 0.001 and 0.001, respectively). The LDL cholesterol decreased by −16.0% and −16.7% after 3 and 6 months of tamoxifen treatment while in the control group the LDL cholesterol did not change (P < 0.0001 and 0.001, respectively). The changes in HDL cholesterol levels after 3 and 6 months of tamoxifen therapy were insignificant both in the tamoxifen group and in the control group (P = 0.78 and 0.94, respectively). The serum triglyceride remained at an increased level in both groups (Table 2).

After 3 and 6 months of tamoxifen treatment, the LDL/HDL ratio decreased −14.7% and −15.0% from the levels after the chemotherapy, while the LDL/HDL ratio remained at an increased level in the control group (P = 0.006 and 0.003, respectively). A similar trend was observed for the total cholesterol/HDL ratio which decreased by −8.4% and −8.6% after 3 and 6 months of tamoxifen treatment, while the changes were marginal in the control patients (P = 0.02 and 0.02, respectively) (Table 2).

Notably, already after 3 months of tamoxifen therapy both total and LDL cholesterol levels had decreased even below the baseline levels measured before the chemotherapy: total cholesterol had decreased −8.4% and LDL cholesterol −8.3% below the baseline levels (P < 0.0001 and 0.0001, respectively) (Figure 1).

**Effect of clodronate on lipid levels**

Totally, 19 patients were treated with intravenous clodronate in addition to adjuvant chemotherapy. Clodronate did not have significant effects on serum lipids (data not shown).

**DISCUSSION**

In line with previous findings, adjuvant chemotherapy caused ovarian dysfunction (amenorrhoea or irregular menstruation) in the majority of patients in the present study. The risk of amenorrhoea was age-related, the older the women the higher was the risk of premature menopause after chemotherapy. As we have reported previously (Saarto et al, 1996a), the changes in serum total and LDL cholesterol correlated significantly with menstrual function after chemotherapy. The total and LDL cholesterol levels increased significantly only in patients who developed ovarian dysfunction while no changes were seen in patients who preserved regular menstruation. In the present study, HDL cholesterol remained unchanged in the patients with ovarian dysfunction while it even increased in our previous study.
In the present study, adjuvant tamoxifen therapy initiated after chemotherapy decreased the increased concentrations of total and LDL cholesterol. Already after 3 months of tamoxifen therapy, the total and the LDL cholesterol levels had decreased by 4.6% and 8.3% below the baseline levels before chemotherapy, while total and LDL cholesterol remained at increased levels in the control group. The HDL cholesterol levels did not change in either tamoxifen or control group.

Tamoxifen treatment is associated with decreases in serum total and LDL cholesterol. This has been true especially in postmenopausal women (Love et al, 1990; Gray et al, 1995; Saarto et al, 1996b) but also to some extent in pre- and perimenopausal women (Caleffi et al, 1988; Powles et al, 1994). The effects of tamoxifen therapy on HDL cholesterol have varied across previous studies and have mostly been marginal. Retrospective studies have suggested a reduction of cardiac morbidity among tamoxifen users (McDonald and Stewart, 1991; Rutqvist and Mattsson, 1993), which has been related to the cholesterol-lowering effect of antioestrogens. However, a large double-blind, randomised, placebo-controlled NSABP Breast Cancer Prevention Trial (BCPT) reported that prophylactic tamoxifen did not influence cardiovascular risk in 13 388 women (Fisher et al, 1998). When the study population was further divided to those with high or low risk for cardiovascular events, tamoxifen was not associated with beneficial or adverse cardiovascular effects in either group (Reis et al, 2001).

Dyslipidaemia is an independent risk factor of CHD in both men and women. Low-serum HDL cholesterol levels seem to be even a stronger predictor of cardiovascular mortality than elevated LDL cholesterol levels in postmenopausal women (Bass et al, 1993). Cholesterol-lowering therapy with statins reduces cardiovascular events (Scandinavian Simvastatin Survival Study Group, 1994; Sacks et al, 1996; Long-term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group, 1998) and mortality rates (Scandinavian Simvastatin Survival Study Group, 1994).

Hormone replacement therapy lowers total and LDL cholesterol and increases HDL cholesterol concentrations. Observational studies have found lower rates of CHD in postmenopausal women who use oestrogen as compared to nonusers (Stampfer and Colditz, 1991; Grady et al, 1992). However, two large intervention trials (HERS and WHI) found no benefit of oestrogen–progesterin treatment on the risk of cardiovascular events (Hulley et al, 1998; Manson et al, 2003). The HERS trial did not inhibit disease progression among women with established CHD and in fact an early increase in the risk of CHD events was noted in the HERS trial (Hulley et al, 1998). In the WHI trial, oestrogen plus progesterin did not confer cardiac protection and actually increased the risk of CHD among generally healthy postmenopausal women, especially during the first year after the initiation of hormone use (Manson et al, 2003).

We conclude that adjuvant tamoxifen therapy reverses the adverse effects of chemotherapy on total and LDL cholesterol and lowers their serum levels even below the baseline. The serum HDL cholesterol levels, however, remained unchanged after chemother-apy followed by tamoxifen. The clinical implications of these findings still need to be studied as many factors other than serum cholesterol levels affect the risk of cardiovascular disease.

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