The effect of exemestane on serum lipid profile in postmenopausal women with metastatic breast cancer: a companion study to EORTC Trial 10951, ‘Randomized phase II study in first line hormonal treatment for metastatic breast cancer with exemestane or tamoxifen in postmenopausal patients’

G. Atalay1, L. Dirix2, L. Biganzoli1, L. Beex3, M. Nooij4, D. Cameron5, C. Lohrisch6, T. Cufer7, J. P. Lobelle8, M. R. Mattiacci9, M. Piccart1 & R. Paridaens10*

1Jules Bordet Institute, Brussels; 2Algemeen Ziekenhuis Sint-Camillius/Sint-Augustinus, Wirlrijk; 3Pharmacia, Diegem; 4EORTC Data Center, Brussels; 5Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium; 6University Medical Center St Radboud, Nijmegen; 7Leids Universitair Medisch Centrum, Afdeling Klinische Oncologie, Leiden, The Netherlands; 8Western General Hospital, Edinburgh, UK; 9EORTC Data Center, Brussels; 10Institute of Oncology, Ljubljana, Slovenia

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Background: The impact of aromatase inhibitors (AIs) on non-cancer-related outcomes, which are known to be affected by oestrogens, has become increasingly important in postmenopausal women with hormone-dependent breast cancer. So far, data related to the effect of AIs on lipid profile in postmenopausal women is scarce. This study, as a companion substudy of an EORTC phase II trial (10951), evaluated the impact of exemestane, a steroidal aromatase inactivator, on the lipid profile of postmenopausal metastatic breast cancer (MBC) patients.

Patients and methods: The EORTC trial 10951 randomised 122 postmenopausal breast cancer patients to exemestane (E) 25 mg (n = 62) or tamoxifen (T) 20 mg (n = 60) once daily as a first-line treatment in the metastatic setting. Exemestane showed promising results in all the primary efficacy end points of the trial (response rate, clinical benefit rate and response duration), and it was well tolerated with low incidence of serious toxicity. As a secondary end point of this phase II trial, serum triglycerides (TRG), high-density lipoprotein cholesterol (HDL), total cholesterol (TC), lipoprotein a (Lip a), and apolipoproteins (Apo) B and A1 were measured at baseline and while on therapy (at 8, 24 and 48 weeks) to assess the impact of exemestane and tamoxifen on serum lipid profiles. Of the 122 randomised patients, those who had baseline and at least one other lipid assessment are included in the present analysis. The patients who received concomitant drugs that could affect lipid profile are included only if these drugs were administered throughout the study treatment. Increase or decrease in lipid parameters within 20% of baseline were considered as non-significant and thus unchanged.

Results: Seventy-two patients (36 in both arms) were included in the statistical analysis. The majority of patients had abnormal TC and normal TRG, HDL, Apo A1, Apo B and Lip a levels at baseline. Neither exemestane nor tamoxifen had adverse effects on TC, HDL, Apo A1, Apo B or Lip a levels at 8, 24 and 48 weeks of treatment. Exemestane and tamoxifen had opposite effects on TRG levels: exemestane lowered while tamoxifen increased TRG levels over time. There were too few patients with normal baseline TC and abnormal TRG, HDL, Apo A1, Apo B and Lip a levels to allow for assessment of E’s impact on these subsets. The atherogenic risk determined by Apo A1:Apo B and TC:HDL ratios remained unchanged throughout the treatment period in both the E and T arms.

Conclusions: Overall, exemestane has no detrimental effect on cholesterol levels and the atherogenic indices, which are well-known risk factors for coronary artery disease. In addition, it has a beneficial effect on TRG levels. These data, coupled with E’s excellent efficacy and tolerability, support further exploration of its potential in the metastatic, adjuvant and chemopreventive setting.

Key words: breast cancer, exemestane, lipid profile

Introduction

As the most frequently diagnosed cancer and the second cause of cancer mortality following lung cancer, breast cancer continues to
be a major health problem for women in the Western world [1]. One third of all breast cancers are oestrogen dependent and regress on endocrine therapy (ET), which aims to minimize the exposure of breast cancer cells to oestrogen, either by inhibiting its synthesis or its receptor-mediated activity [2, 3]. The anti-oestrogen tamoxifen has been the cornerstone of endocrine therapy for >25 years in breast cancer. More recently, the potent and selective inhibitors of aromatase, the enzyme that converts androgens to estrogens, have emerged as alternative agents to tamoxifen for postmenopausal women with hormone-dependent breast cancer. Following their wide acceptance as standard second-line therapy after tamoxifen failure in the metastatic setting, the two non-steroidal aromatase inhibitors (AIs) letrozole and anastrozole have recently been approved for first-line treatment of postmenopausal metastatic breast cancer (MBC) patients based on favourable efficacy and safety results from several randomised clinical trials [4–7]. Exemestane, a steroidal, irreversible aromatase inactivator, has also been shown to be a safe and highly active agent in first-line treatment of MBC in a randomised phase II study [8]. Following these promising results, the study was extended into a multicentre randomised comparison of exemestane (E) and tamoxifen (T), and has recently completed its accrual.

Apart from their effects on target organs, including skin, urogenital tract, endometrium and breast, oestrogens are known to have important actions on bone and lipid metabolism, and cardiovascular, cognitive and sexual functions [9]. On the basis of their mechanism of action, one might expect that AIs may have certain adverse effects on multiple oestrogen-dependent metabolic functions such as bone and lipid metabolism when compared with tamoxifen, which is a selective oestrogen receptor modulator. The potentially harmful effects of oestrogen deprivation induced by the AIs may not be problematic in the non-curative setting of metastatic disease, with the patients being treated for a short period of time. However, in the adjuvant treatment and chemoprevention settings, such effects could represent a major problem. We all know that the target population of AIs in breast cancer, postmenopausal women, are relatively older and therefore more prone to multiple non-cancer-related morbidities. Of note, breast cancer survivors are known to be at increased risk for developing not only secondary cancers but also cardiovascular disease, osteoporosis and diabetes [10]. Therefore, it is essential to know all the consequences of removing oestrogen from a postmenopausal patient’s body, since the woman’s health as a whole is of paramount importance and a precise assessment of risk to benefit ratio is mandatory for optimal treatment.

Heart disease is the leading cause of death in both sexes, and more than half of coronary heart disease (CHD) is attributed to the dyslipidemias [11, 12]. While oestrogens have long been known to lower serum lipid levels [13], a recent publication has shown that hormone replacement therapy with combined estrogen and progesterone had no positive effect on reducing coronary events in postmenopausal healthy women [14]. The selective oestrogen-receptor modulator tamoxifen also exerts protective effects on the lipid profile as a result of its agonist activity. A reduction in serum low density lipoprotein (LDL) cholesterol, total serum cholesterol (TC) and lipoprotein a (Lip a) levels, and an increase in apolipo-
remove LDL and very-low-density lipoprotein (VLDL). Apo A1 and Apo B in serum are quantitated by nephelometry. Lip a levels were determined quantitatively using a ‘sandwich’ enzyme-linked immunosorbent assay (ELISA), Apo-Tek Lp(a)™. Sample concentrations are interpolated from the standard curve generated by the calibrators. The normal levels were as follows: TG <1.87 g/l, HDL >0.89 mmol/l, TC <5.15 mmol/l, Apo A1 = 1.01 g/l, Apo B = 0.57 g/l, and Lip a = 0.57–1.38 g/l. Lip a values up to 30 mg/dl were accepted as normal.

Statistical analysis

The baseline patient characteristics, including age, prior adjuvant chemotherapy and endocrine therapy, are summarized for the population examined for lipid alterations, as described in Patients and methods. Descriptive statistics of TRG, HDL, TC, Apo A1, Apo B and Lip a are presented per week and per treatment arm, as well as overall and separately for patients with normal or abnormal baseline values. For patients with normal or abnormal baseline values, the frequencies of those who experienced an increase or decrease of >20%, or no change in lipid parameters are calculated for each lipid parameter and treatment arm, at weeks 8, 24 and 48, both overall and separately.

The changes in lipid assessments over time were analysed with a repeated analysis of variance is:

Where, Yijk = lipid assessment, μ = overall constant, \( \theta_i \) = fixed effect of the \( i \)th week, \( \alpha_{ijk} \) = random effect of the \( j \)th patient within the \( k \)th hospital, \( \epsilon_{ijk} \) = residual. \( i = 1, 2, \ldots, \) number of hospitals; \( j = 1, 2, \ldots, \) number of patients in each hospital; and \( k = 1, 2, \ldots, \) number of weeks.

The Fisher’s least significant difference procedure (a protected F-test) was used to test the time (i.e. week) effect, and the pair-wise comparison of the least square means ‘week 8 versus baseline’ and ‘week 24 versus baseline’ [30].

Results

Seventy-two patients are included in this study, 36 treated with exemestane and 36 treated with tamoxifen. Baseline patient characteristics are shown in Table 1. The median body mass index (BMI) prior to treatment was 24.3 (range = 17.0–37.8) in the E group (n = 32) and 26.8 (range = 19.0–42.3) in the T (n = 24) group. The number of available samples decreased over time, mainly because of disease progression; thus only a few patients had lipid assessments at week 48. The total number of patients with baseline, and 8, 24 and 48 week samples for each lipid parameter in the lipid substudy group is shown in Table 2. Since some patients did not have all lipid parameters assessed, the number of patients for the different lipid parameters are not the same. At baseline most patients had normal TRG, HDL, Apo A1, Apo B, apolipoprotein B; Lip a, Lipoprotein a; Abn, abnormal; Nrl, normal.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exemestane</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (range)</td>
<td>64 (37–78)</td>
<td>62 (46–80)</td>
</tr>
<tr>
<td>Prior adjuvant ET (%)</td>
<td>5 (13.9)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>Prior adjuvant CT (%)</td>
<td>8 (22.2)</td>
<td>7 (19.5)</td>
</tr>
<tr>
<td>Median BMI before treatment* (range)</td>
<td>24.3 (17.0–31.8)</td>
<td>26.8 (19–42.3)</td>
</tr>
</tbody>
</table>

*The body weights and heights of 32 patients in the exemestane group and 24 patients in the tamoxifen group were available to calculate BMI before study treatment.

ET, endocrine therapy; CT, chemotherapy; BMI, body mass index.

Table 2. The number of patients with lipid assessments at baseline, and weeks 8, 24 and 48 (lipid substudy group)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exemestane</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC</td>
<td>34 (9/25)</td>
<td>36 (11/25)</td>
</tr>
<tr>
<td>HDL</td>
<td>32 (31/1)</td>
<td>36 (34/2)</td>
</tr>
<tr>
<td>TRG</td>
<td>34 (30/4)</td>
<td>36 (31/5)</td>
</tr>
<tr>
<td>Apo A1</td>
<td>35 (32/3)</td>
<td>36 (31/5)</td>
</tr>
<tr>
<td>Apo B</td>
<td>35 (22/13)</td>
<td>36 (23/13)</td>
</tr>
<tr>
<td>Lip a</td>
<td>32 (26/6)</td>
<td>31 (26/5)</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Exemestane</th>
<th>Tamoxifen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total n (Nrl/Abn)</td>
<td>36 (11/25)</td>
<td>36 (11/25)</td>
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<tr>
<td>Total n (Nrl/Abn)</td>
<td>36 (11/25)</td>
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<td>Total n (Nrl/Abn)</td>
<td>36 (11/25)</td>
<td>36 (11/25)</td>
</tr>
</tbody>
</table>

TC, total cholesterol; HDL, high-density lipoprotein; TRG, triglyceride; Apo A1, apolipoprotein A1; Apo B, apolipoprotein B; Lip a, Lipoprotein a; Abn, abnormal; Nrl, normal.
The majority of the normal HDL, Apo A1 and Apo B levels remained unchanged in both the E and T arms at weeks 8, 24 and 48. No patient in the E arm had abnormal TRG levels at weeks 8, 24 and 48. In the T arm, the predominant direction of change was opposite: among those patients whose TRG levels changed over time, most experienced an increase of >20% over time. According to the available number of samples at weeks 8, 24 and 48, most patients with normal baseline values experienced a change of >20% (increase or decrease) in Lip a levels during treatment with exemestane and tamoxifen, and the direction of change was not consistent in either arm. The majority of the patients with abnormal baseline TC levels remained unchanged at weeks 8 and 24 of treatment with exemestane and tamoxifen. At baseline, there were too few patients with normal TC levels and abnormal TRG, HDL, Apo A, Apo B and Lip a levels to allow an accurate assessment of the impact of exemestane or tamoxifen on these starting lipid parameters.

Table 3 shows the evolution of the lipid profile per arm at weeks 8 and 24, as well as the results of pairwise comparisons between baseline and week-8 or -24 lipid assessments. The analysis demonstrates that exemestane has a consistently favourable effect on TRG over time, leading to a reduction that is statistically significant ($P = 0.002$) at week 24 compared with the baseline level. Although both Apo A1 and HDL levels seem to decrease in the E arm, these changes are not statistically significant. Overall, no significant changes are observed in TC, Apo B and Lip a levels at weeks 8 and 24 of treatment with exemestane. There is a non-significant trend for the TRG levels to increase in the T arm ($P = 0.07$ at the 8th week and $P = 0.08$ at the 24th week of treatment). Tamoxifen increases Apo A1 levels significantly at weeks 8 and 24 of treatment compared with baseline values ($P = 0.005$ and 0.02, respectively) and has no detrimental effect on the rest of the lipid parameters analysed.

The number of patients who had lipid measurements at all pre-determined time points (at baseline and weeks 8, 24 and 48) are very few in both treatment arms: TC ($n = 9$), HDL ($n = 9$), TRG ($n = 10$), Apo A1 ($n = 10$), Apo B ($n = 10$), Lip a ($n = 7$) in the E arm; and TC ($n = 5$), HDL ($n = 5$), TRG ($n = 5$), Apo A1 ($n = 3$), Apo B ($n = 3$), Lip a ($n = 4$) in the T arm. Therefore no valid comparisons are allowed between baseline and later lipid assessments under treatment.

The ApoA1:ApoB and TC:HDL ratios did not change significantly, indicating that the atherogenic risk basically remains unchanged at weeks 8 and 24 of study treatment in both arms (Table 4).

**Discussion**

The present analysis demonstrates that exemestane has significant beneficial effects on TRG levels, without detrimental effects on other lipid parameters over a 1-year treatment period. The reasons why exemestane had significant beneficial effects only on TRG but not on other lipid parameters might be explained by the relatively high variability in lipid measurements, which could have prevented detection of small but significant changes between the different weeks of exemestane treatment, and the fact that 50%
of the patients had non-fasting lipid samples that could affect the precision of the lipid measurements.

Not all of the previously established effects of tamoxifen on lipid parameters were observed. The only significant change observed in our patients was an increase in Apo A1 values compared with baseline and a non-significant trend for the TRG levels to increase, most probably due to the high variability and the small number of samples, especially at week 24. Nevertheless, we confirmed the well-documented effect of tamoxifen on Apo A1 and TRG levels, and also showed that exemestane has no detrimental effect on serum cholesterol levels (TC and HDL fraction) or on atherogenic risk. Knowing that TRG levels are more strongly associated with CAD in women compared with men, the significant beneficial effects of exemestane on TRG levels are of particular interest [31]. It is noteworthy that exemestane and tamoxifen seem to have opposite actions on TRG and Apo A1 levels over time, and although the changes in HDL and in Apo A1 values are in the same direction, the changes in HDL values recorded in either treatment arm are not statistically significant.

Our findings are in line with the results of other preclinical and clinical studies showing that exemestane has no detrimental effect on the lipid profile. So far, preclinical data have suggested that exemestane significantly reduces serum cholesterol and LDL levels in animal models [26, 27]. It has been concluded that exemestane and its principal metabolite, probably due to their androgenic structure, exert beneficial effects on lipid profiles in these experimental studies. Engan et al. evaluated the impact of tamoxifen, exemestane and dexamethasone on lipid profile in cancer patients [28]. Exemestane was given at escalating doses from 5 to 200 mg/day to 12 postmenopausal MBC patients who had prior endocrine therapy and/or chemotherapy, and six out of nine breast cancer patients in the tamoxifen group received tamoxifen (20–30 mg/day) as an adjuvant treatment. Significant reductions were observed in TC, TRG, HDL and Apo A1 levels and the Apo A1:Apo B ratio following 12 weeks of therapy with exemestane. TC was significantly increased, while the Apo A1 levels and Apo A1:Apo B ratio were significantly reduced after 9 weeks of treatment with tamoxifen. Lipid assessments were done by classical biochemical methods and also by nuclear magnetic resonance spectroscopy; both methods of lipid assessment yielded similar results. It should be noted that this study is rather focused on a comparison between different lipid measurement methods with small numbers of patients.

Since tamoxifen exerts beneficial effects on lipid profile due to its agonist oestrogenic activity, it is assumed that the potent oestrogen deprivation caused by the AIs may cause deterioration of lipid profile and bone metabolism. Therefore, several small-scale clinical studies attempted to investigate the impact of different non-steroidal AIs on lipid profile. A randomised phase III study comparing the efficacy and safety of letrozole (2.5 mg and 0.5 mg/day) with aminoglutethemide (AG) (250 mg twice daily) as second-line endocrine treatment in postmenopausal metastatic breast cancer patients reported that 3.8% of patients in the letrozole arm developed hypercholesterolemia [32]. Then, Elisaf et al. evaluated prospectively the impact of letrozole (2.5 mg/day) on lipid parameters (TC, TRG, LDL, HDL, Apo A1, Apo B, Apo E and Lip a) in 20 postmenopausal MBC patients [23]. Patients with comitant diseases that could lead to dyslipidaemia and those who were receiving concomitant drugs that could affect lipid metabolism were not enrolled in the study. Lipid assessments at baseline, and at weeks 8 and 16 of treatment showed that letrozole significantly increased serum TC, LDL cholesterol and ApoB levels, and the atherogenic risk ratio TC:HDL as well. However, Harper et al. evaluated the impact of letrozole on breast cell proliferation, lipid and bone indices in 32 postmenopausal healthy women (those women who were not on hormone replacement therapy, but had been previously treated for benign breast disease, ductal or lobular carcinoma in situ, or those who were referred from a breast cancer screening unit) and they reported that letrozole had no negative effects on lipid metabolism after 3 months of treatment [25].

Wajtacki et al. studied the effects of both anastrozole (n = 27) and letrozole (n = 3) on lipid parameters (TC, TRG, LDL and HDL in 30 postmenopausal MBC patients treated for a median duration of 32 weeks [22]. Patients received both agents as second-line endocrine therapy. Lipid parameters were shown to remain stable without significant changes throughout the treatment with the two non-steroidal AIs; however, body mass index (BMI) was significantly increased. The impact of anastrozole versus tamoxifen on lipid profile was monitored in two randomised trials with identical designs that evaluated the role of these agents as first-line therapy in MBC patients [4–6]. The lipid assessments (TC, TRG, HDL, LDL, Apo A, Apo B, Lip a) were done at baseline, and at weeks 84 and 108 of treatment [21]. Preliminary results showed that anastrozole had no detrimental effect on all lipid end points, and the impact of tamoxifen on lipid profile was similar to that reported previously. In addition, no major differences were noticed between the effects of tamoxifen and anastrozole.

A neoadjuvant endocrine therapy trial that compared the systemic and intratumoural effects of tamoxifen with vorozole, another third generation non-steroidal AI, randomised postmenopausal patients with primary breast cancer to receive either tamoxifen

| Table 4. The evolution of atherogenic ratios in both treatment arms |
|----------------------|----------------------|----------------------|
|                     | Exemestane           | Tamoxifen            |
|                     | Week 0 | Week 8 | Week 24 | Week 0 | Week 8 | Week 24 |
| TC:HDL (median)     | 3.77   | 4.03   | 3.78    | 3.83   | 3.49   | 3.88    |
| ApoA1:ApoB (median) | 1.12   | 1.08   | 1.09    | 1.13   | 1.26   | 1.19    |

TC:HD, total cholesterol:high-density lipoprotein; Apo A1:Apo B, apolipoprotein A1:apolipoprotein B.
20 mg/day \((n = 27)\) or vorozole 2.5 mg/day \((n = 26)\) orally for 12 weeks [19]. Non-fasting blood samples were collected at baseline, and at weeks 4, 8 and 12 of treatment for lipid assessments. Vorozole did not cause any significant change in TC, LDL and HDL levels, while tamoxifen reduced both LDL and TC levels significantly in this study.

Among the second generation non-steroidal aromatase inhibitors, fadrozole (1.8–4 mg/day) showed no significant effect on lipid profile (TC, TRG, LDL, HDL or VLDL) in 21 postmenopausal MBC patients in a clinical study. Blood samples were taken at baseline and every 3 months, and the patients were treated with fadrozole up to 24 months [18].

The data regarding the effects of exemestane on lipid and bone metabolism suggest that despite their similarly potent oestрадiol lowering activities, non-steroidal and steroidal AIs have distinct features, in particular with respect to some of their effects on multiple oestрадiol-dependent physiologic events. The favourable profile of exemestane may indeed provide interesting opportunities to improve several expected consequences of oestрадiol deprivation such as vasomotor symptoms, dyslipidemia and osteoporosis, which not only reduce quality of life but may also cause substantial morbidity and mortality in breast cancer patients. Exemestane is an irreversible aromatase inactivator, which in contrast to non-steroidal AIs does not compete with the aromatase enzyme. It permanently inactivates the aromatase so that de novo enzyme synthesis is required for further oestрадiol synthesis. Furthermore, both exemestane and its main metabolites are androgenic; they mimic the natural substrate androstenedione and are able to reduce serum hormone binding globulin in a dose-dependent way in women [33]. Through this mechanism, it is possible that exemestane may exert protective effects on bone and lipid metabolism. Indeed there are already some hints of clinical evidence highlighting its different safety profile, such as the occurrence of fewer grade 3–4 hot flushes in exemestane-treated breast cancer patients compared with those treated with the non-steroidal aromatase inhibitors and tamoxifen [8]. It has also been shown that exemestane has neutral effects on bone metabolism and, when one considers the results of the present study and others, exemestane has beneficial effects on lipid profile.

To our knowledge, this is the first study that prospectively evaluated the impact of exemestane on lipid profile in MBC patients. It should be noted that it is difficult to conduct long-term analyses on lipids in MBC trials since most patients eventually progress and go off protocol treatment. Nevertheless, our study provides prospective clinical evidence that exemestane has no detrimental effect on lipid profile in postmenopausal MBC patients. Aromatase inhibitors (AIs) are now being investigated in adjuvant breast cancer trials and the preliminary findings from the ATAC trial underscore their potential also in the preventive setting [34]. Since endocrine therapy is administered for long periods of time, particularly in the adjuvant and preventive settings, the eventual application of AIs in these clinical situations will require long-term follow-up in order to assess their effects on several oestрадiol-dependent physiologic/metabolic functions, including lipid metabolism. Exemestane, with its unique chemical structure, may prove to be useful in these settings, not only with its demonstrated efficacy and safety, but also with its multiple beneficial effects on several non-cancer-related outcomes. Adjuvant studies with exemestane are also exploring its impact on lipid metabolism.

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References


