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Short-term effects of anastrozole therapy on serum lipid profile in patients with breast cancer, previously treated with tamoxifen. Preliminary report*

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Background. Estrogens play a crucial part in the regulation of lipid metabolism – they decrease the serum concentrations of total- and low-density lipoprotein (LDL) cholesterol and elevate the concentrations of high-density lipoprotein (HDL) cholesterol. Endocrine therapy of breast cancer patients is aimed at inhibiting estrogen-dependent proliferation of cancer cells. Tamoxifen, an antiestrogen used in breast cancer hormonotherapy, exerts beneficial influence on the lipid profile, arising from its estrogen-like properties. The value of new-generation aromatase inhibitors used sequentially with the initial adjuvant – tamoxifen is currently being investigated in a number of clinical trials. There are concerns, however, that the deprivation of estrogens by aromatase inhibitors may reverse the beneficial effects of tamoxifen on the serum lipid profile, and thus increase the risk of coronary heart disease.

Aim of the study. To assess the effects of a short-term therapy with anastrozole, a third generation aromatase inhibitor, on the basic lipid profile in women with breast cancer, who have progressed on tamoxifen.

Material and methods. The analysis included 44 postmenopausal patients (median age: 64.5 years, range: 47-75), who were assigned to receive anastrozole. All the patients were previously treated with tamoxifen in adjuvant therapy (n=31) or for advanced disease (N=13). Anastrozole 1mg was given orally once a day. Concentrations of basic blood lipids and body mass index values (weight in kilograms divided by squared height in meters) were measured before anastrozole administration and after 12-32 weeks (median: 13, average: 16.2) of therapy.

Results. There were no statistically significant differences in lipid parameters during anastrozole treatment, namely, the total cholesterol (p=0.50), LDL-cholesterol (p=0.51), HDL-cholesterol (p=0.69), triglycerides (p=0.95) and the number of hypercholesterolemic patients (total cholesterol > 5.7 mmol/l; p=0.85). We did not observe any influence of anastrozole administration on the body mass index mean values, either (p=0.94).

Conclusion. Our preliminary results indicate that anastrozole does not compromise lipid metabolism during short-term treatment. The study will be continued to assess long-term effects of anastrozole on the lipid and lipoprotein profile.

Wpływ krótkotrwałej terapii anastrozolem na profil lipidowy chorych na raka piersi, uprzednio leczonych tamoksyfenem. Doniesienie wstępne

Wprowadzenie. Estrogeny odgrywają kluczową rolą w regulacji metabolizmu lipidów – powodują obniżenie stężeń cholesterolu całkowitego i zawartego we frakcji lipoprotein o niskiej gęstości (LDL), podwyższają poziom cholesterolu, należącego do frakcji lipoprotein o wysokiej gęstości (HDL). Celem leczenia hormonalnego chorych na raka piersi jest zniesienie działania estradiolu na komórki nowotworowe. Tamoksyfen, antyestrogen stosowany w hormonoterapii raka piersi, wpływa ko-

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rzystnie na profil lipidowy dzięki właściwościom estrogenopodobnym. W aktualnie prowadzonych badaniach klinicznych ocenia się wartość sekwencyjnej hormonoterapii uzupełniającej, gdzie po leczeniu tamoksyfenem planowo stosuje się leki hamujące syntezę estrogenów z grupy inhibitorów aromatazy. Istnieje obawa, że obniżenie stężeń krążących estrogenów może spowodować zniesienie korzystnego wpływu tamoksyfenu na metabolizm lipidów i ryzyko wystąpienia choroby niedokrwiennej serca.

Cel pracy. Ocena wpływu krótkotrwałego leczenia anastrozolem, inhibitorem aromatazy trzeciej generacji, na podstawowy profil lipidowy kobiet chorych na raka piersi, u których dotychczas podawano tamoksyfen.

Materiał i metody. Oceną objęto grupę 44 pomenopauzalnych chorych w wieku od 47 do 75 lat (mediana: 64,5), które zakwalifikowano do podawania anastrozolu. Wszystkie chore uprzednio otrzymywały tamoksyfen jako leczenie uzupełniające (n=31) lub paliatywne w chorobie zaawansowanej (n=13). Podstawowe parametry lipidowe krwi oraz wartość wskaźnika masy ciała (waga w kilogramach podzielona przez wzrost w metrach do kwadratu) oceniono przed włączeniem anastrozolu i po 12-32 tygodniach (mediana: 13, średnia: 16,2) podawania preparatu w dawce 1 mg dziennie doustnie.

Wyniki. W trakcie stosowania anastrozolu nie zaobserwowano statystycznie znamiennych zmian stężeń cholesterolu całkowitego (p=0,50), cholesterolu – LDL (p=0,51), cholesterolu – HDL (p=0,69), trójglicerydów (p=0,95) oraz odsetka chorych z poziomem cholesterolu całkowitego powyżej normy (> 5,7 mmol/l, p=0,85). Nie wykazano również wpływu leku na średnie wartości wskaźnika masy ciała (p=0,94).

Wnioski. Krótkotrwałe podawanie anastrozolu nie wpływa na podstawowy profil lipidowy i wartości wskaźnika masy ciała u chorych na raka piersi dotychczas leczonych tamoksyfenem. Badanie jest kontynuowane celem oceny wpływu długotrwałego stosowania na parametry lipidowe i lipoproteinowe.

Key words: anastrozole, breast cancer, cholesterol, triglycerides, body weight
Słowa kluczowe: anastrozol, rak piersi, lipidy, cholesterol, trójglicerydy, masa ciała

Introduction

Estrogens play an important part in the regulation of lipid metabolism – they decrease the serum concentration of total- and low-density lipoprotein (LDL) cholesterol and elevate the concentration of high-density lipoprotein (HDL) cholesterol [1-3]. Hormonal treatment of breast cancer is aimed at eliminating the influence of estrogenes on neoplastic cells [4]. Tamoxifen, the most frequently applied drug in breast cancer hormonotherapy, is a non-steroidal antiestrogen which blocks intracellular estrogen receptors (ER) [4]. The drug is, however, known not to be a simple antiestrogen; apart from an antiestrogenic effect it is also an ER agonist in postmenopausal women. It has been found to decrease the loss of bone tissue and prevent osteoporosis [7, 8]. In adjuvant treatment of breast cancer cases with tamoxifen there is a decrease in the total concetrations of cholesterol (by 10-20% on avarage) and LDL-cholesterol (by some 15-20%), whereas the level of HDL-cholesterol either increases, or remains unchanged [4, 6, 9]. Clinically this involves a significant reduction in the incidence and mortality from ischaemic heart disease [10]. The same agonist properties, that provide the beneficial effect of tamoxifen, to a certain extent limit its clinical value. The drug and its derivates stimulate the proliferation of the endometrium [11] and are associated with an increased risk of endometrial cancer [11, 12]. Moreover, some authors suggest that late failure of adjuvant tamoxifen therapy or *de novo* resistance to the drug may be related to its estrogen-like activity [4, 13-16]. These observations form a theoretical basis of the studies aimed at discovering the merits of sequential adjuvant treatment of breast cancer cases, where, after the previous use of tamoxifen, aromatase inhibitors are intentionally administered. Scheduled application of aromatase inhibitors in sequence to tamoxifen is expected to reduce a probability of side effects caused by its estrogen-like properties [16]. There are some concerns, however, that decreasing estrogene concentration to an indeterminable level may suppress the beneficial effects tamoxifen has on lipid metabolism and, consequently, increase the risk of hypoestrogenic-related diseases, including myocardial ischaemia. The current study is aimed at determining the effect of short-term anastrozole therapy on the lipid profile in patients previously on tamoxifen.

Material and methods

Our serial analysis of blood lipid parameters was performed on 44 postmenopausal breast cancer women aged between 47 and 75 years, (median: 64.5), who, due to progressing neoplastic disease, were assigned to receive anastrozole therapy. All the patients had previously received tamoxifen as either adjuvant therapy (31 cases) or as palliative therapy in advanced disease (a total of 13 cases: dissemination to the supraclavicular nodes – 5 patients, to the bones – 6, to the bones and hypodermis – 1, to the ovary – 1). Following tamoxifen treatment of 3 to 51 months (median: 15) progression of the neoplastic disease was diagnosed (in 11 cases – local recurrence, in 33 – metastatic disease: in 21 – bones, in 3 – lungs, in 9 – ipsilateral supraclavicular lymph nodes) and the patients were switched on anastrozole. Anastrozole 1 mg was given orally once a day to all the patients. Median time from tamoxifen discontinuation to the begining of anastrozole therapy was 10 days (range: 2-14; the half-life of tamoxifen is 7 days; its biological effects are maintained approx. 14 days, the half-life of anastrozole is 30 to 60 hours) [13, 16]. In cases of skeletal metastases irradiation was applied to the involved areas. All the cases with local recurrence were initially operated on while radical radiation therapy to the chest wall and to the regional lymph nodes area was applied later. In case of metastases to the supraclavicular lymph nodes palliative radiotherapy was applied to the cervical-supraclavicular areas involved. Table I presents the characteristics of the evaluated population.

Tab. I. Clinical characteristics of the study group

Age – years:	
- average	61.6
- median	64.5
- range	47-75
Initial treatment:	
- chemiotherapy	17
- radical mastectomy	27
Adjuvant treatment:	
- chemiotherapy	11
- hormonotherapy	31
- no treatment	2
Estrogen receptor	
- positive	27
- unknown	17
Menopause:	
- natural	40
- surgical	2
- LHRH analogs*	2
Duration of anastrozole therapy – weeks:	
- average	16.2
- median	13
- range	12-32

* – treatment was continued during anastrozole administration

Women suffering from hypertension, acute and chronic liver failure and biliary tract diseases, endocrinological disorders or treated with drugs that alter the lipid profile were excluded from the study. Basic lipid parameters of blood and body mass index values (weight in kilos divided by squared height in meters) were estimated before administering anastrozole and after 12-32 weeks (median: 13, average: 16.2) of therapy. After an overnight fast, blood was obtained by venipuncture the following morning between 07.00. and 09.00. hours. Serum total- and HDL-cholesterol concentrations were analyzed by enzymatic methods using Abbot VP bichromatic analyzer [17, 18]. HDL-cholesterol was estimated after previous precipitation of apoprotein B containing lipoproteins with dextrane sulfate (0.1 mg/ml, MW 5 x 10^5; Pharmacia) and magnesium chloride (0.05 x 10^{-3} mmol/l) [18]. LDL-cholesterol concentration values were calculated according to the Friedewald formula [19]. The cut off level of total cholesterol to determine hypercholesterolemia was defined at 5.70 mmol/l (220 mg/dl).

Statistical calculations were performed using the paired Student's t test, and chi-square test with Yate's continuity correction. p-values below 0.05 were considered to be significant.

Results

There was no statistically significant change over time in basic lipid parameters, i.e. total- (p=0.50), LDL – (p=0.51), HDL-cholesterol (p=0.69), triglycerides (p=0.95) as well as the percentage of hypercholesterolemic cases (p=0.85). No effect of anastrozole therapy on the body mass index values (p=0.94) was found. Table II presents the results of the study.

Discussion

Anastrozole, together with letrozole and vorozole, constitute a group of oral non-steroid third-generation aromatase inhibitors [20]. Unlike aminoglutethimide, anastrozole is marked by a better tolerance and greater selectivity of aromatase inhibition [20]. Thus, administering doses even 60 times higher than these clinically applied does not upset the hydroxylation of sterols metabolised by enzymes of cytochrome P-450 and does not necessitate supplementation with glycocorticoids [20]. Application of 1 mg of anastrozole on a daily basis leads to a significant decrease in estrogen concentration within three hours, whereas with three day treatment estradiol concentration falls beneath the level detectable by available tests [20, 21]. It remains in the range of 17% of the initial value throughout the therapy [21]. Although anastrozole applied in short courses causes some inhibition of estrogen synthesis, while, in turn, estrogenes are the main regulators of lipid metabolism, no changes were observed in basic lipid parameters in our pilot group of 44 patients (duration of treatment – median: 13 weeks, average: 16.2, range: 12-32). These results are consistent with our previous observations [22].

All the patients enrolled in the study had previously received tamoxifen for 3 to 51 months (median: 15), prior to anastrozole. The beneficial effect of the former drug on lipid metabolism has been well substantiated [4, 6, 9]. Our observation to the effect that applying

Tab. II. Changes in total-, HDL-, LDL-cholesterol and triglycerides serum concentrations and body mass index in breast cancer patients during anastrozole treatment

Investigated parameters	Mean value before treatment ± SD	Mean values in the course of treatment ± SD	p – statistic significance
Total cholesterol [mmol/l]	5.44 ± 0.79	5.64 ± 0.71	p = 0.50
LDL cholesterol [mmol/l]	2.99 ± 0.90	3.22 ± 0.96	p = 0.51
HDL cholesterol [mmol/l]	1.38 ± 0.27	1.42 ± 0.30	p = 0.69
Triglycerides [mmol/l]	1.71 ± 0.94	1.69 ± 0.90	p = 0.95
Number and (percentage) of hypercholesterolemic patients	18 (40.9%)	20 (45.5 %)	p = 0.85
Body mass index [kg\m^2]	26.79 ± 6.16	26.62 ± 6.08	p = 0.94

SD – standard deviation

anastrozole does not reverse the effect(s) of prior tamoxifen on lipid metabolism is relevant in the sense that aromatase inhibitors are currently investigated for treatment of early breast cancer in adjuvant setting, and in some studies non-steroidal aromatase inhibitors are given sequentially to initial tamoxifen treatment. In ARNO trial (Arimidex *versus* Nolvadex) by the German Breast Cancer Group, after 2 years of tamoxifen patients are randomly assigned either to an anastrozole group, or tamoxifen is continued for three years [16, 20]. The BIG/FEMTA trial (the Breast International Group Femara and Tamoxifen Trial) has side arms of a similar design, but employing letrozole [16, 20]. The MA17 study by the National Cancer Institute of Canada – Clinical Trial Group randomizes recurence-free patients following adjuvant treatment with tamoxifen for 5 years to either placebo or to another 5 year-treatment with letrozole [16, 20].

In view of prospective use of aromatase inhibitors sequentially to initial adjuvant tamoxifen, evaluation of the long-term effects of therapy with these drugs on lipid metabolism seems particularly important. The subject has not been thoroughly discussed in literature. To our knowledge, only one study evaluating the effects of new-generation aromatase inhibitors on the concentration of several blood parameters crucial in defining the possible risk of heart disease has been published [23]. In the study of L. Costa et al. a group of 21 postmenopausal advanced breast cancer patients was estimated for a potential influence of fadrozole, a non-steroidal aromatase inhibitor of second generation, on lipid metabolism [23]. All the patients were previously on tamoxifen, but the treatment was discontinued at least one month before the analysis. In the course of treatment lasting 3 to 24 months (average: 15.8) no statistically significant changes were observed in the concentrations of total cholesterol, triglycerides, high-, low- and very low-density lipoproteins [23]. Similar observations were made during our former study [24]. We evaluated 30 postmenopausal breast cancer patients treated with non-steroidal aromatase inhibitors (anastrozole n=27, letrozole n=3) for at least 24 weeks (range: 25-52, median: 32). All the patients were previously on tamoxifen as adjuvant treatment (n=21), or in palliative setting (n=9). No changes were discovered in levels of the basic lipid parameters of blood (total-, HDL-, LDL- cholesterol and triglycerides), nor in the percentage of patients with elevated values of total cholesterol. However, their body mass index increased significantly (28.4 ± 4.4 vs. 29.5 ± 3.8 kg\m^2, $p=0.048$). Such observations [23, 24], based on the analysis of relatively low number groups suggest, however, that long-term therapy with non-steroid aromatase inhibitors does not have a detrimental effect on the lipid profile in patients with breast cancer.

The question to be answered now is: why a drug, which strongly suppresses estrogen synthesis and is applied after tamoxifen, which in turn positively affects lipid metabolism as an ER agonist, is of no effect on basic lipid parameters? The data from studies conducted in the 90's may offer a potential explanation. Lipid metabolism regulation in tamoxifen patients has been demonstrated to be dominated by other factors than the drug's estrogen-like activity in the liver [25, 26]. Tamoxifen and toremifen (another antiestrogen coumpound in breast cancer treatment) inhibit delta-8 isomerase, and thus block the conversion of delta 8-cholesterol to lethosterol [25, 26]. It leads to decrease in total- and LDL-cholesterol levels caused by the down-regulation of cholesterol synthesis [25, 26]. Such an inhibition, however, does not affect the levels of HDL-cholesterol or triglycerides [26]. So far, non-steroidal aromatase inhibitors have been proven to have no effect on the activity of enzymes in metabolism of cholesterol or other lipids [23].

Conclusions

1. Short-term application of anastrozole does not affect the basic lipid profile nor the body mass index in breast cancer patients, previously on tamoxifen.
2. The study will be continued to evaluate possible effects of long term anastrozole application on lipid and lipoprotein parameters.

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