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The influence of three years adjuvant anastrozole on conventional and independent biochemical risk factors for coronary heart disease in elderly breast cancer patients

J. Wojtacki[1], A. Markowicz[2], M. Piotrowska[3]. [1]*Medical University of Gdansk, Dept. of Propedeutics of Oncology, Gdansk, Poland;* [2]*Medical University of Gdansk, Dept. of Orthopedics and Traumatology, Gdansk, Poland;* [3]*Division of Chemotherapy, Cancer Center of Gdynia, Gdynia, Poland*

Background: Aromatase inhibitors, such as anastrozole, reduce the effects of estrogen on cancer and other estrogen-dependent cells by potent preventing their biosynthesis from androgens. Since they might reduce estrogen level even to undetectable values, aromatase inhibitors are anticipated to exert adverse effect in estrogen-sensitive targets, including lipid/lipoprotein metabolism. Sub-protocols of large clinical trials provide solely results on the influence of anastrozole on basic lipid parameters [i.e. total- (TCH), high density lipoprotein (HDL-CH)-, low density lipoprotein (LDL-CH)-cholesterols and triglycerides (TG)], whereas data on changes in the concentrations of independent biochemical risk factors for coronary heart disease [apolipoprotein A-I (APO-A) and B (APO-B) as well as C-reactive protein (CRP)] under anastrozole treatment are scarce. Moreover, although the age is the risk factor for cardiovascular disease by itself, elderly patients, though commonly treated with aromatase inhibitors, are under-represented in trials and there are no data concerning the relationship between aromatase inhibition and lipid metabolism in the subpopulation of breast cancer patients over 70 years of age.

Patients and Methods: This prospective study enrolled fifty seven consecutive postmenopausal women (median age: 78 years, range: 71−94) with histologically confirmed estrogen- and/or progesterone-receptors positive early breast cancer. All the patients primary underwent surgery with curative intent and then some of them adjuvant chemotherapy and/or loco-regional radiation therapy. Following a twelve-hour fast, blood samples were analyzed for lipid (TCH, HDL-CH, and LDL-CH, TG) and lipoprotein (APO-A, APO-B) profiles as well as CRP serum levels; all the parameters were measured at baseline and then after 1, 3, 6 months of therapy and every 6 months afterwards.

Results: Three years of adjuvant therapy with anastrozole in elderly breast cancer women did not have a significant impact on any parameter analyzed in the study, i.e.: 1) basic serum lipid profile: TCH ($p = 0.78$), HDL-CH ($p = 0.67$), LDL-CH ($p = 0.77$) and TG ($p = 0.49$); 2) serum lipoproteins (APO-A; $p = 0.88$ and APO-B; $p = 0.71$) and CRP ($p = 0.89$) thought to be an independent risk factors for coronary heart disease; 3) atherogenic risk ratios: APO-B to APO-A ($p = 0.75$), TCH to HDL-CH ($p = 0.69$), LDL-CH to HDL-CH ($p = 0.73$) as well as BMI values ($p = 0.81$).

Conclusions: Three years of adjuvant anastrozole therapy appears to have a neutral effect on conventional and independent biochemical risk factors for coronary heart disease in elderly breast cancer women – an ideal target population for endocrine therapy. The study is being continued to assess the influence of 5 years adjuvant anastrozole on lipid/lipoprotein profile and answer the question whether certain biochemical parameters may serve as surrogate endpoint for assessment of cardiovascular risk in breast cancer women treated with aromatase inhibitors.

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Factors affecting DFS in triple negative early breast cancer patients – a single institution experience

D. Donat[1], J. Pesic[1], J. Trifunovic[1], L.J. Muzikravic[1], S. Tesanovic[1], D.D. Donat[2]. [1]*Institute of Oncology, Clinic of internal Oncology, Sremska Kamenica, Serbia;* [2]*Medical Faculty Novi Sad, Postgraduate study, Novi Sad, Serbia*

Introduction: Breast cancer patients with negative ER, PR, and HER2 are termed as triple negative (TN) patients and they belong to a group of patients with worse prognosis.

Patients and Methods: Disease free survival (DFS) was retrospectively analyzed in breast cancer patients treated at our Institute from December 2004 to December 2006. Out of 1,184 patients treated for early breast cancer, 138 (11.65%) patients were TN. The average follow-up period was 23.4 months (range, 12−33 months). Sixty-one (44.20%) patients were treated with conservative surgery and irradiation combined with adjuvant chemotherapy. FAC regimen was administered in 40 (65.57%) patients while 21 (34.43%) patients received CMF chemotherapy. Seventy-seven (55.80%) patients underwent radical surgery and 28 of them received radiotherapy. There were 64 (43.38%) premenopausal and 74 (53.62%) postmenopausal patients. Grade 3 malignancy was found in 61 (44.20%) patients. Negative finding of axilla was in 32 (23.19%) patients. Out of 106 (76.81%) patients with positive finding of axilla, 71 (66.98%) patients had more than three positive lymph nodes. All patients were alive through the entire study period.

Results: The relapse occurred in 27 (19.57%) patients. Average DFS period to the occurrence of relapse was 17.4 months (range: 7−31 months). The relapse occurred in breast in case of six (22.22%) patients, nodal disease recurrence was found in five (18.51%) patients, and distant metastases in 16 (59.25%) patients. No difference was found between the patients treated with conservative or radical surgery, i.e. radiotherapy. The relapse frequency was slightly higher in premenopausal than in postmenopausal patients but the finding had no statistical significance. In the group of patients with the relapse, 13 (56.52%) patients received CMF regimen and 16 (59.25%) patients received FAC ($p = 0.02$). The size of primary tumor had no statistical significance but the status of axillary lymph nodes was statistically significant. In patients with 3 or more positive lymph nodes DFS was shorter and in average it was 12.6 months (range: 3−26 months) ($p = 0.002$). The patients with G3 tumor had experience relapse more frequently. Out of 61 patients 17 (27.86%) of them relapsed ($p < 0.001$).

Conclusion: Although the study group was small and follow-up period was short, it can be said that TN early breast cancer patients present a risk group with short DFS. It was particularly observed in patients with G3 tumor, in patients with three or more positive lymph nodes, and in patients treated with CMF chemotherapy. The risk is primarily associated with the appearance of distant metastases.

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Feasibility of adjuvant treatment with docetaxel/doxorubicin/ cyclophosphamide (the TAC regimen) in routine clinical practice

I. Gounaris[1], S. Kelly[1], P. MacLeod[1]. [1]*Plymouth Hospitals NHS Trust, Plymouth Oncology Centre, Plymouth, United Kingdom*

Background: The TAC regimen improves survival when used for the adjuvant treatment of node-positive breast cancer. Many oncologists, especially in the UK are reluctant to use this regimen though, because of toxicity concerns. We examined the feasibility of using this regimen in routine UK clinical practice.

Materials and Methods: We audited the treatment of all women diagnosed with node-positive breast cancer over a 6 month period. Out of 44 eligible women, 25 were treated with the TAC regimen. Differences between these women and those that received other regimens were explored. For women on TAC, retrospective information was retrieved regarding hospitalisations, dose reductions, cycle delays, regimen changes, achieved dose intensities and adjunctive treatments such as antibiotics and haematopoietic growth factor use.

Results: Women that received TAC were younger (mean age 52.7 years) than women that received other regimens (mean age 59.4 years) or did not receive chemotherapy (mean age 73.2 years). No differences regarding tumour size, grade, number of involved lymph nodes, hormone receptor or HER2 status were found. 21 of the 25 women received the full 6 planned cycles of the regimen. Out of 136 cycles of TAC administered, 3 (2.2%) resulted in hospitalisation. 9 (6.6%) cycles were delayed and in 28 (20.6%) cycles one or more drugs were administered in less than full dose. For all 25 patients the achieved chemotherapy dose intensity was 93.84%. The mean delivered dose of docetaxel was 404 mg per patient (89.8% of the planned dose). The impact of prophylactic G-CSF and antibiotic support was significant. 36% of the cycles with inadequate support were complicated by hospitalisation, cycle delay, subsequent need for dose reduction or an alternative regimen. These complications were seen in only 7% of cycles with adequate cover.

Conclusions: The TAC regimen is feasible for fit women with node-positive breast cancer in routine clinical practice. Complications are minimised with adequate haematopoietic growth factor and prophylactic antibiotic administration.

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Skeletal events of Anastrazole versus Tamoxifen on bone mineral density and bone biomarker Osteocalcin in post menopausal women with early breast cancer

M. Abdel Wahab[1], L.R. Ezz Elarab[1], K. Maher[1]. [1]*Ain Shams Universty, Radiation Oncology, Cairo, Egypt*

Introduction: Post Menopausal women with breast cancer are at increased risk of bone loss because of age-related estrogen deficiency face which accelerated with the use of aromatase inhibitors (AI's). we aimed to study the effect on bone mineral density (BMD) and bone formation biomarker Osteocalcin level in post menopausal breast cancer patients, for the first 3 years of adjuvant hormonal treatment of both groups Tamoxifen versus Anastrazole.

Materials and Methods: One hundred post menopausal early breast cancer were prospectively randomized to receive either Tamoxifen

20 mg/day (n = 50), or Anastrazole 10 mg (n = 50). Both BMD and Osteocalcin were assessed initially before treatment then at regular intervals for both groups. Use of Tamoxifen was associated with significant annual decrease in Osteocalcin. P = 0.001, whereas Anastrazole group had gradual increase of the annual levels P < 0.01. BMD decreases significantly in Anastrazole group versus Tamoxifen 2.6%, 0.4% respectively (P < 0.001). Osteoporosis T < −2.5 was reported significantly higher in Anastrazole group (P < 0.01). Women with initial osteopenia in Anastrazole group showed significant decrease in BMD P < 0.05. The addition of bisphosphonate for patients with early osteoporosis markedly improved both Osteocalcin level and BMD.

Conclusion: Tamoxifen preserves BMD in post menopausal breast cancer patients whereas Anastrazole accelerates age associated fall in BMD especially in the first year of therapy, more over the addition of bisphosphonate can help to decrease the skeletal related events associated with treatment to ensure better quality of life with treatment.

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The association of HER-2 status with disease outcome in premenopausal early breast cancer patients treated with adjuvant ovarian ablation

S. Susnjar[1], T. Vujasinovic[2], Z. Abu Rabi[2], D. Gavrilovic[3], Z. Neskovic-Konstantinovic[1], D. Jovanovic[4], N. Borojevic[5]. *[1]Institute for Oncology and Radiology of Serbia, Dpt for Medical Oncology, Belgrade, Serbia; [2]Institute for Oncology and Radiology of Serbia, Dpt for Experimental Oncology, Belgrade, Serbia; [3]Institute for Oncology and Radiology of Serbia, Data Center – Dpt for Medicine Statistics, Belgrade, Serbia; [4]Institute for Oncology and Radiology of Serbia, Dpt for Pathohistology and Cytology, Belgrade, Serbia; [5]Institute for Oncology and Radiology of Serbia, Dpt for Radiology, Belgrade, Serbia*

Background: Steroid receptor (SR) – positive breast cancer (BC) patients (pts) have better prognosis and higher response to endocrine therapy, although some of them experience early relapse. We investigated the influence of HER-2 gene amplification on disease outcome in premenopausal women with SR-positive BC treated with adjuvant ovarian ablation (A-OA).

Patients and methods: One hundred and forty eight premenopausal pts with progesterone receptor (PgR)-positive BC were treated from 1988 to 1993 with A-OA only. The guidelines for the treatment of BC at that time proposed adjuvant endocrine therapy only in PgR-positive grade 3 node-negative BC pts and 1−3 node-positive pts, irrespective of tumor grade. SRs were determined prospectively by the classical biochemical DCC method, while HER-2 gene amplification was determined retrospectively by CISH in 66 women whose archival paraffin tissue samples were retrieved. Log rank test, cumulative hazard function (Peterson's method) and Cox regression models were used for statistical analysis.

Results: Sixty-six premenopausal BC pts, median age of 45 years (range 35−54), were treated with A-OA by irradiation after the radical mastectomy. The median SR contents were: estrogen receptor (ER) 22 fmol/mg protein (range 0–199) and PgR 65 fmol/mg protein (range 14–511). Median follow-up was 156 months (range 12–234). Disease relapse experienced 35 patients, while 26 women died, all from BC. According to HER-2 status, HER2 positive subgroup (10/66 pts) had almost similar risk of disease relapse [Hazard ratio (HR): 1.17; 95% CI: 0.512−2.69; Likelihood ratio test: p = 0.71)] and death (HR: 1.09; 95% CI: 0.411−2.90; Likelihood ratio test: p = 0.86) as HER-2 negative subgroup (56/66 pts). The ratio of hazard functions of disease relapse and death between HER-2 negative and HER-2 positive groups ranged from 1.46 to 3.68 at 3−10 years of follow-up and from 1.66 to 3.59 at 6−10 years of follow up, respectively.

Conclusion: There is no strong association of HER-2 status with disease outcome in SR-positive early premenopausal BC pts treated with A-OA, although the likelihood of disease recurrence from 3−10 years of follow up seemed to be higher for HER-2 negative in comparison to HER-2 positive pts. According to our opinion, the potential of oestrogen deprivation therapy in premenopausal SR positive/HER-2 positive BC pts deserve further investigation within randomized clinical trials.

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Strong age dependent increase in the use of adjuvant systemic treatment for early stage breast cancer in the period 1990–2006: a population based analysis

M.P.P. Sukel[1], L.V. van de Poll-Franse[2], G.A.P. Nieuwenhuijzen[3], A. Vreugdenhil[4], R.M.C. Herings[1], J.W.W. Coebergh[2], A.C. Voogd[5]. *[1]PHARMO Institute for Drug Outcomes Research, Research, Utrecht, The Netherlands; [2]Comprehensive Cancer Centre South, Research, Eindhoven, The Netherlands; [3]Catharina Hospital, Surgery, Eindhoven, The Netherlands; [4]Maxima Medisch Centrum, Internal Medicine, Veldhoven, The Netherlands; [5]Maastricht University, Epidemiology, Maastricht, The Netherlands*

Background: This study evaluated the impact of changing guidelines on the patterns of adjuvant systemic treatment for patients with early stage breast cancer from 1990 through 2006. Special attention was paid to patients aged 70 years and older due to absence of clear guidelines for this age group.

Methods: Patients diagnosed with early stage breast cancer (stage I−IIIa) in the period 1990–2006 were selected from the cancer registry of the Comprehensive Cancer Centre South (n = 8,261). Based on the publication date of the guidelines and the changing indications for adjuvant systemic treatment, results were shown separately for the periods 1990–1997, 1998–2001, 2002–2006 and the age groups $\leqslant$35, 36−49, 50−69 and $\geqslant$70 years. To determine probability ratios (PR) of receiving adjuvant systemic therapy per tumor and patient characteristic, multivariate analyses were performed by SAS Proc Genmod using a modified Poisson regression approach.

Results: The use of any adjuvant systemic treatment increased significantly over time: 37% in 1990–1997, 51% in 1998–2001 and 53% in 2002–2006 (p for trend <0.0001). Patients aged $\geqslant$70 years compared to patients aged $\leqslant$35 years had less chance of receiving chemotherapy, or a combination of hormonal and chemotherapy (PR = 0.01; 95% CI, 0.01−0.02 and PR = 0.01; 95% CI, 0.00−0.02, respectively), and a higher chance of receiving hormonal therapy alone (PR = 2.39; 95% CI, 1.94−2.95). Tumor size, positive nodal status and undifferentiated tumors were positively associated with the probability to receive adjuvant systemic treatment. Patients with ER- and PR-negative tumors were more likely to receive chemotherapy (PR = 1.59; 95% CI, 1.47−1.71) and less likely to receive hormonal therapy (PR = 0.28; 95% CI, 0.23−0.33) or both chemotherapy and hormonal therapy (PR = 0.13; 95% CI, 0.08−0.20).

Conclusions: Trends in adjuvant systemic treatment over a large period of time (1990–2006) showed that treatment with hormonal therapy and chemotherapy increased significantly. The use of chemotherapy, alone, or in combination with hormonal therapy decreased strongly with age, while the use of hormonal therapy alone increased with age. Part of these age-related differences is attributed to the absence of clear guidelines for patients aged 70 years and older.

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Prognostic relevance of hormone receptor and HER2 status in T4 breast cancer patients who failed to receive a pathological complete response following primary chemotherapy. Long term results from a single institution

M. Ionta[1], V. Pusceddu[1], B. Frau[1], M. Murgia[1], M. Barca[1], M. Murru[1], D. Guerzoni[1], A. Chiappe[1], L. Minerba[2], B. Massidda[1]. *[1]University of Cagliari, Medical Oncology, Cagliari, Italy; [2]University of Cagliari, Biostatistics, Cagliari, Italy*

Background: Pathological Complete Response (pCR) following primary chemotherapy in both the breast and the axilla is the main determinant for improved DFS and OS in patients (pts) with breast cancer, irrespective of hormone receptor (HR) status, HER2 or chemotherapy regimen. On the contrary, failure to achieve a pCR (<pCR) identifies an heterogeneous group of pts with different risks of recurrence and death even if they received the same standard neoadjuvant chemotherapy. The aim of our study was to evaluate the prognostic relevance of HR and HER2 status in terms of survival in <pCR T4 breast cancer patients.

Material and Methods: We analysed 58 of 74 consecutive stage T4 patients, observed between 1996 and 2007, who achieved <pCR following primary PEV regimen (cisplatin 50 mg/m^2; epirubicin 100 mg/m^2; vinorelbine 25 mg/m^2) for up to 6 cycles (4−6). All pts, subsequently, received surgery, radiation, adjuvant chemotherapy and hormone therapy when indicated. Median age was 51years (29−70); 45 pts (78%) were T4abc and 13 pts (22%) were T4d; 52 pts (90%) had clinical axillary nodes involvement; 39 pts (67%) were ER+, 19 pts (33%) were ER−; 23 pts (40%) were PgR+, 35 pts (60%) PR−; 18 pts (31%) ER−/PR−; 22 pts (38%) ER+/PgR+; 6 pts (10%) HER2+, 40 pts (69%) HER2−, 12 pts (21%)