Conclusions: These data indicate that the triple combination is very active and safe in the primary treatment of the operable HER-2 positive breast cancer. A phase II study is ongoing.

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Implementation of adjuvant trastuzumab in breast cancer patients in the Netherlands

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Background: Recent studies have shown that trastuzumab combined with adjuvant chemotherapy improves outcome in women with HER2-positive breast cancer. Based on these results, a new national guideline was released in the Netherlands on September 15th 2005 stating that adjuvant chemotherapy should be combined with trastuzumab for women with HER2-positive breast cancer. This study evaluates the implementation of trastuzumab in clinical practice, guideline compliance and regional differences between the eight Comprehensive Cancer Centre regions in the Netherlands.

Methods: All women diagnosed with breast cancer between September 2005 and January 2007 were selected from the population based Netherlands Cancer Registry (NCR), covering all 16.4 million inhabitants. Women without surgery, with metastases at diagnosis or who received neoadjuvant chemotherapy were excluded. HER2 overexpression was recorded in the NCR based on IHC scores or FISH if indicated.

Results: The study included 14,934 patients. Of those, 1,928 (13%) had a tumour which overexpressed HER2. HER2 overexpression decreased with age from 22% in women under 40 years to 9% in women $\geqslant$70 years. Of all 1,928 women with HER2 overexpression, 1,114 (58%) received adjuvant chemotherapy. This percentage decreased from 93% among women <40 years to 8% among women 70−79 years of age. Of 1,585 women <70 years with HER2 overexpression, 1,095 women received adjuvant chemotherapy. Of these, 6% did not receive trastuzumab (regional range: 3−16%, p = 0.001). This percentage decreased from 9% in the first 4 months after release of the new guideline (regional variation 0−24%, p = 0.029) to 3% in the last trimester of 2006 (regional variation 0−12%, p = 0.517). Most common reasons for women not to receive trastuzumab were cardiotoxicity (29%) and patient refusal (21%). In 8% others reasons were given, in 42% no reason was given in the medical chart.

Conclusion: The percentage of women with HER2-positive breast cancer is markedly lower than the assumed 25% in the Netherlands. Of women with HER2 overexpression treated with adjuvant chemotherapy, 6% did not receive trastuzumab. The implementation of trastuzumab in clinical practice was rapid, with significant regional variation. One year after introduction in the guideline, regional differences disappeared. There was a known legitimate reason not to give trastuzumab in 58% of the 61 patients who did not receive trastuzumab.

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A validated analytical method for the simultaneous quantification of tamoxifen, endoxifen, anastrozole and letrozole

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Background: Liquid chromatography hyphenated to tandem mass spectrometry (LC/MS/MS) represents a powerful analytical method for the quantification of drugs in patients. Concerning the endocrine therapy of breast cancer, LC/MS/MS methods have been developed for therapeutic drug monitoring. However, none of the published methods allows for the simultaneous analysis of estrogene receptor antagonists as well as aromatase inhibitors. Thus, our aim was to develop and to validate a LC/MS/MS method covering drugs frequently prescribed in the endocrine therapy of breast cancer (tamoxifen, anastrozole, letrozole) allowing for a convenient pharmacokinetic drug monitoring.

Material and Methods: Blood plasma samples were collected from 320 patients undergoing endocrine breast cancer therapy and stored at −20ºC. To prepare a sample for LC-MS/MS analysis, 1 ml plasma was treated with a solid phase extraction procedure using a cation mixed-mode polymeric sorbent phase (Strata-X-C cartridges, Phenomenex, Torrance, CA). Chromatographic separation was accomplished on a reversed-phase column (200 mm $\times$ 0.5 mm, Eurosphere-C18, 5 μm, Knauer, Berlin) by using a gradient of acetone in an aqueous hexafluorobutyric acid solution. Mass spectrometric detection was performed on a quadrupole-quadrupole-linear ion trap instrument (Q Trap 3200, Applied Biosystems, Foster City, CA).

Results: We have developed a fully validated method for the simultaneous quantitative analysis of tamoxifen, its active metabolite endoxifen, and the non-steroidal aromatase inhibitors anastrozole and letrozole in human plasma. Validation was accomplished according to published guidelines [1] for a concentration range of 25–500 ng/ml for tamoxifen, 10–200 ng/ml for endoxifen, 5–200 ng/ml for anastrozol and 10–300 ng/ml for letrozol. The applicability of the method has been demonstrated by analyzing plasma samples of 320 patients treated with tamoxifen, anastrozole and letrozole.

Conclusion: The developed method represents a reliable and convenient tool for the simultaneous quantitative analysis of tamoxifen/endoxifen, anastrozol and letrozole allowing for convenient pharmacokinetic drug monitoring in the endocrine therapy of breast cancer.

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Adjuvant endocrine therapy in premenopausal women − toxicities and adherence rates from a tertiary care centre

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Background: Multiple randomized trials have demonstrated the efficacy of aromatase inhibitors (AIs) in postmenopausal women with hormone receptor positive (HR+) early-stage breast cancer (EBC). Ongoing clinical trials are examining the role of AIs given concurrently with ovarian suppression (OS) in premenopausal women with HR+ EBC. This study reports on toxicities and adherence rates observed in premenopausal women treated with OS and tamoxifen (Tam)/AIs in an academic cancer centre.

Material and Methods: Premenopausal women with HR+ EBC were identified through a home LHRH antagonist injection registry from Jan/05 to May/09. Data collected included: demographics, treatments, choices of endocrine therapies, treatment toxicities and adherence rates.

Results: 84 eligible patients (pts) were evaluated. Median age at diagnosis was 44 years (range: 24−53). Stage was I/II/III in 14/47/23 pts and 32 (38%) pts had her2/neu positive disease. Median BMI was 25.6. The majority of pts (90%) received chemotherapy. Initial endocrine therapy choices included Tam alone/AI+ OS/Tam+OS in 14/62/8 pts. Of the Tam alone group, 93% of pts switched to AI+OS and 7% switched to Tam+OS. The AI+OS group had 90% adherence rate at the time of evaluation. Few pts switched from AI+OS to Tam (1.6%) and Tam+OS (4.8%). Most pts (19/23) with stage III stage were on AI+OS. 79 pts had evaluations on BMD with 33 pts having follow-up BMD studies. 44% pts proceeded to have bilateral oophrectomy. Common toxicities for pts on AI+OS were arthralgia/myalgia (40%), hot flushes (35%), fatigue (19%), vaginal symptoms (18%), weight gain (15%), sleep disturbances (10%) and psychosocial issues (7%).

Conclusion: The use of AI+OS is not the current standard hormonal treatment in premenopausal women with HR+ EBC. In our experience, it is unclear if this choice has been driven by patient choice or physician advice. The 90% adherence rate in AI+OS group seems to be higher than the clinically observed AI adherence rates in postmenopausal women despite significant toxicities from treatment. Survivorship issues are complex in premenopausal woman and require careful attention and standardized approach.

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Actual or adjusted surface area: which should we use?

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Background: Calculation of chemotherapeutic drugs doses was standardized to Body Surface Area, with the aim to produce optimum systemic drug level & minimize drug toxicity; it also can be very challenging in obese cancer patients. Obesity represents a condition of excessive adipose tissue with its currently accepted definition is defined as Body Mass Index >30 kg/m^2); it once believed that obese patients who received chemotherapy on their actual body weight would result in increased toxicity, secondary to distribution of lipid soluble drugs into the adipose tissue. By using Adjusted Body Weight it's assumed that cancer patients would receive a dose of a particular cytotoxic drug associated with an acceptable degree of toxicity without reducing its therapeutic effect. The aim of this study is considering the use of adjusted body weight for calculation of chemotherapeutic drugs

doses and its impact on the disease free survival in obese female breast cancer patients.

Method: We compared disease free survival between two groups of female breast cancer patients receiving adjuvant chemotherapy, both groups received FEC 100 regimen (Epirubicin 100 mg/m^2, 5-FU 500 mg/m^2, Cyclophosphamide 500 mg/m^2) for 6 cycles in the period between 2000–2008. Group A: (149 patients) received their regimen based on their actual body weight calculation of body surface area (BSA [m^2] = vHt. [cm]·Wt. [kg]/3600). Group B: (100 patients) received their regimen based on their adjusted body weight. (Adjusted Body Weight = Ideal Body weight + 0.4(Actual Body Weight − Ideal Body Weight.) Ideal Body Weight for females = 45 + 2.3kg for each inch >60 inches [60 inches = 152 cm]). Correlation with age, T & N status, hormonal status and HER2 status was done in the two groups.

Results: At median follow up period of 17 months there was statistical significance of disease free survival in favor of group B (70.3 months Vs. 52.4 months, p = 0.004). Both groups showed non-significant difference as regards correlation with other parameters: ER, PR, HER2 status, Age, T & N.

Conclusion: Using adjusted body weight is considered a proper alternative method for the calculation of anti-cancer drugs doses. An effort is currently using the substantial information to retrospectively examine outcome with respect to toxicities.

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Adjuvant taxane chemotherapy is associated with a significant risk of febrile neutropenia

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Background: Taxane based adjuvant chemotherapy has shown benefit in terms of overall survival when compared to non-taxane containing regimens and is increasingly used in high risk patients. The risk of febrile neutropenia (FN) is known to be higher with taxane based chemotherapy. In South West Wales, taxane based chemotherapy is recommended for node positive and selected high risk node negative patients. Commonly used regimens include TAC (docetaxel, doxorubicin, cyclophosphamide x6q3w), FEC 100-D (fluorouracil, epirubicin, cyclophosphamide ×3q3w − docetaxel ×3q3w), AC-T (doxorubicin, cyclophosphamide ×4q3w − docetaxel ×4q3w) or dose dense AC-P (doxorubicin, cyclophosphamide ×4q2w − paclitaxel ×4q2w). Where anthracyclines are contraindicated, TC (docetaxel, cyclophosphamide ×4) or TCH (docetaxel, carboplatin, herceptin ×6) are used. Only patients receiving TAC or AC-P receive primary prophylaxis as routine. This study was peformed to determine the incidence of febrile neutropenia in patients receiving adjuvant taxane based chemotherapy.

Materials and Methods: A retrospective analysis of all patients who received adjuvant taxane based chemotherapy at Singleton Hospital and Prince Philip Hospital between January 2007 and Sept 2008 were included. FN was defined as fever >38ºC (single reading) and neutrophil count $<1\times10^9$. Admissions for FN and use of secondary GCSF were recorded.

Results: 135 patients were identified, including 2 male patients. 29 patients were admitted with FN (21%). 23 were receiving a taxane at the time of the episode with 6 patients receiving either FEC100 or AC. The median duration of hospital stay was 6 days. 2 patients had grade 4 toxicity requiring intensive support and >60 day hospital stay. There were no deaths.

96% of patients who did not receive primary prophylaxis, received pegylated GCSF with subsequent cycles and only 1 patient (4%) had a further episode of FN.

FN rates according to regimen are summarised in the table.

Chemotherapy regimen	No. of patients	Rate of FN (%)	Published FN rate (%)
AC-T	44	5(11)	16 (ECOG 1199)
AC-P	3	1(33)	3 (CALGB 9741)
FEC100-D	32	7(21.8)	11.2 (PACS-01)
TAC	29	6(20.7)	24.7 (BCIRG 001)
TC	18	6(33)	8 (US Oncology)
CH	7	3(42)	9.8 (BCIRG 006)
TH	1	1(100)	

Conclusion: The FN rate following taxane based adjuvant chemotherapy in our population is higher than expected according to published trial data. Most admissions were short in duration. The use of secondary GCSF is effective at reducing subsequent episodes.

ASCO guidelines recommend the use of primary prophylaxis if the FN rate is higher than 20%. This study suggests that primary GCSF should be routine for patients receiving TC and FEC-D. The number of patients receiving AC-P and TCH is too small for recommendations to be made and further data will be collected as these regimens become more common. For patients receiving TAC primary prophlaxis should include the combination of ciprofloxacin and pegylated GCSF.

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Prognostic factors and survival outcome in triple negative breast cancer patients in routine clinical practice in Slovenia

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Background: Triple negative breast cancer (TNBC) is characterized by negative hormonal receptors (ER and PR) and negative HER-2 status. It is a subgroup of breast cancer (BC) with poor survival despite aggressive systemic treatment when compared to other subgroups of BC.

The aim of our study was to analyze clinical and pathological characteristics and to evaluate prognostic significance of some well established prognostic factors in a large group of consecutive TNBC patients (pts) treated in a routine clinical practice.

Methods: Our retrospective study included 269 TNBC pts treated at Institute of Oncology Ljubljana between March 2000 and December 2006. Median age was 55.3 yrs (23–88.5). Most of pts were postmenopausal (58.7%), 41 (15%) were older than 65 yrs. Tumors were mostly IDC (90.7%), larger than 2 cm (59%), grade 3 (80.7%), without lymphovascular invasion (LVI) (73.3%), with high uPA (76.2%) and PAI-1 (60.5%) levels. The lymph node metastases were found in 46.1% of pts. Majority of pts were treated with adjuvant chemotherapy (CT) (80%), only 12% received neoadjuvant CT. Predominant CT regimen was anthracycline based CT (60%), 24.5% of pts received CMF regimen and 14.5% sequential anthracyclines and taxanes and 1% other regimens.

The survival outcomes were computed using the Kaplan-Meier method. Cox proportional hazard model was used in the multivariate analysis.

Results: After a median follow up of 5.9 yrs 6 (2%) pts experienced local, 79 (29%) pts distal recurrence and 66 (24%) pts died. Five-yrs PFS was 68.2% and 5-yrs OS 74.5%. Most of the relapses (72%) and deaths (63.6%) were in the first three yrs after treatment.

The results of Cox analysis are presented in Table 1.

Table 1

Characteristic	PFS			OS		
	univariate	multivariate		univariate	multivariate	
	p	p	HR (95% CI)	p	p	HR (95% CI)
Menopausal status (pre/peri vs. post)	0.172			0.278		
Age ⩾65 yrs vs. <65	0.009	0.012	1.79 (1.14−2.82)	0.035	ns	
Nodal status positive vs. negative	<0.001	<0.001	2.71 (1.64−4.46)	0.001	0.002	2.96 (1.51−5.82)
Size >2 vs. ⩽2 cm	0.004	ns		0.002	ns	
Grade III vs. I+II	0.315			0.917		
LVI yes vs. no	<0.001	ns		0.006	ns	
uPA >3 vs. ⩽3 ng/mg prot.	0.827			0.732		
PAI-1 >14 vs. ⩽14 ng/mg prot.	0.487			0.632		

ns = not significant.

Conclusions: In our series of TNBC pts nodal status and age >65 yrs were found to be an independent prognostic factor for PFS, whereas for the OS nodal status only. We found a pattern of high recurrence rate in the first 3 yrs following diagnosis and a decline in recurrence rate over the next 3 years.

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Magnetic resonance imaging (MRI) evaluation of pathologically residual tumors in breast cancer after neoadjuvant chemotherapy: experience of 2 centres in Spain

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Background: The objective of this study was to evaluate the accuracy of MRI in assessing tumor response following neoadjuvant chemotherapy in patients with locally advanced breast cancer (LABC).