2082 POSTER

Fatigue and depressive symptoms influence quality of life in breast cancer survivors

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Background: Due to early detection since the introduction of breast cancer screening programs and the improvements in treatment, breast cancer has become a chronic disease for many women. Attention for quality of life (QoL) should, therefore, not stop after treatment. To assess the long-term QoL after breast cancer treatment, a cohort study was performed including women who remained disease-free for 5 years after treatment. The outcomes of this study provide an indication for the necessity of psychosocial support after treatment.
Methods: Women who were treated for early stage breast cancer between January 2000 and December 2001 were eligible for the study. Exclusion criteria were local recurrence or development of systemic disease, dementia, and no choice between breast conserving therapy (BCT) and mastectomy (MTC) at time of diagnosis.
Out of 251 women, 178 were eligible for participation. They were all contacted by phone and 140 women agreed to participate. They completed questionnaires assessing QoL (WHOQOL-100), depressive symptoms (CES-D), and fatigue (FAS).
Results: Overall QoL for breast cancer survivors was comparable with the reported QoL of a healthy reference population. There were no significant differences between the three age-groups (younger than 50 years, 50−70 years, and older than 70 years at time of diagnosis) and the two treatment groups (BCT and MTC) concerning overall QoL and depressive symptoms. Fatigue was positively correlated with age. Regression analyses showed a significant influence of both depressive symptoms and fatigue on overall QoL for both treatment groups and the three age groups.
Conclusion: Breast cancer survivors reported an overall QoL that is comparable with the QoL of healthy women. The presence of depressive symptoms and fatigue contributed to an impaired QoL. Age at diagnosis and type of surgical treatment did not influence QoL. Depressive symptoms and fatigue are amenable to psychosocial intervention and this may be worthwhile to improve QoL in patients experiencing depressive symptoms and fatigue.

2083 POSTER

Adjuvant delivery of a dose-dense, sequential FEC-docetaxel regimen to patients with high-risk breast cancer is feasible – results of a randomized, open-label Phase II study

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Methods: In this prospective, open-label, Phase II study, high-risk primary operable breast cancer patients were recruited at 2 Belgian centres (09/05–07/06). They were randomized (1:1:2:2) to Conventional-A: 3 cycles Q3W FEC (F 500 mg/m^2, E 100 mg/m^2, C 500 mg/m^2) then 3 cycles Q3W Doc 100 mg/m^2; Conventional-B: reverse sequence (Doc–FEC); dd-C: 4 Q10–11day cycles FEC (E 75 mg/m^2) then 4 cycles Q2W Doc 75 mg/m^2; dd-D: reverse sequence (ddDoc–ddFEC). In dd arms, pegfilgrastim was given on Day 2 of each cycle, but was given only as secondary prophylaxis in conventional arms. The primary endpoint was the proportion of patients completing intended cycles at relative dose intensity (RDI) $\geqslant$ 85%.

	Conventional		Dose dense	
	A. FEC–Doc (n = 19)	B. Doc–FEC (n = 20)	C. ddFEC–ddDoc (n = 39)	D. ddDoc–ddFEC (n = 39)
Target cycles	100%	95%	97%	92%
FEC target dose	79%	90%	82%	72%
Doc target dose	79%	95%	67%	90%
All CT target dose	74%	85%	67%	72%
RDI $\geqslant$ 85%	95%	95%	95%	90%

Results: 117 patients were randomized: mean$\pm$SD age 48.8$\pm$9.1 yrs, 87% ductal carcinoma, 58% stage IIa-b, 4.0$\pm$7.0 lymph nodes involved, 72% estrogen receptor positive. In conventional groups (A+B), 31% received pegfilgrastim secondary prophylaxis. Chemotherapy (CT) delivery is summarized in the table; a high proportion of all groups achieved RDI $\geqslant$ 85%. In all, 53%, 25%, 38% and 23%, of groups A, B, C and D had a related grade 3/4 CTC toxicity. Grade 3/4 neutropenia was significantly more frequent in conventional arms (8 [21%] for A+B vs 5 [6%] for C+D; P = 0.03), while fatigue and hand–foot syndrome may be more common with dd. Skin toxicity was minimal.
Conclusions: Delivery of adjuvant sequential ddFEC–Doc to breast cancer patients is feasible with appropriate growth factor support. Target dose was more easily achieved in the first CT cycles of the dd sequence. There was no clinically relevant increase in toxicity with dd therapy. Further studies are needed to see if this dd regimen confers a survival benefit over conventional delivery.

2084 POSTER

Acute myeloid leukaemia and myelodysplastic syndrome after taxane-based adjuvant chemotherapy for early breast cancer: an exploratory meta-analysis

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Background: Acute myeloid leukemia (AML) and the myelodysplastic syndrome (MDS) are rare but life-threatening side effects of breast cancer chemotherapy. The taxanes, docetaxel and paclitaxel, have recently emerged as effective agents for the adjuvant treatment of early stage breast cancer. We performed an exploratory meta-analysis to investigate whether the incidence of AML/MDS differs between patients treated with taxane- or anthracycline-based regimens.
Methods: We searched the MEDLINE database, the online proceedings of the American Society of Clinical Oncology and the San Antonio Breast Cancer Symposium to identify trials randomizing patients with early stage breast cancer to either taxane- or anthracycline-based chemotherapy regimens after surgery. Trials with treatment arms differing solely regarding the administration of taxane, with doses of all other drugs being identical across treatment arms, were analyzed separately. We abstracted data on AML and MDS incidence. Fixed effects meta-analysis was performed to estimate combined odds ratios (OR) and their confidence intervals, with values higher than one indicating that AML/MDS is more common in patients receiving a taxane. Continuity correction, proportional to the relative size of the opposite of the study, was used for studies with zero events in one arm. Sensitivity analysis was performed using different correction methods or no correction. Results are presented in accordance with the QUOROM guidelines.
Results: Out of nine eligible trials (15,960 patients), one did not report on AML/MDS incidence. The eight trials included in this analysis allocated a total of 14,605 patients to docetaxel-based (3,663), paclitaxel-based (3,654) or anthracycline-based (7,288) regimens. 24 cases of AML/MDS occurred in patients who received a taxane and 22 in those who did not. Overall, we found no difference in AML/MDS incidence between taxane- and anthracycline-based regimens (OR, 1.08; 95% CI, 0.59 to 1.96). This held true when trials evaluating docetaxel (OR, 0.93; 95% CI, 0.38 to 2.25) and paclitaxel (OR, 1.22; 95% CI, 0.54 to 2.75) were analyzed separately. Four trials had arms deferring solely regarding taxane administration (10,549 patients; 5,259 receiving anthracycline-based and 5,290 receiving taxane-based regimens). Analysis of those trials revealed no correlation between taxane administration and AML/MDS development (OR, 1.24; 95% CI, 0.66 to 2.33). Sensitivity analysis revealed no inconsistencies between different calculation methods.
Conclusion: The incidence of AML/MDS following treatment with taxane-based regimens was low. We found no evidence of increased incidence of AML/MDS events in patients receiving taxane-based regimens for early stage breast cancer, when compared to patients receiving anthracycline-based regimens. AML/MDS is a serious consequence of adjuvant chemotherapy, given that treated patients achieve long-term breast-cancer specific survival, and long term surveillance is warranted.

2085 POSTER

Stage migration in breast cancer: a trend towards better disease free survival for N0 patients since the introduction of the sentinel lymph node (SLN) procedure

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Background: The extensive pathologic examination following introduction of the SLN procedure in breast cancer patients has resulted in the more frequent finding of limited lymph node involvement in breast cancer

patients. We evaluated the stage migration effect on prognosis by comparing the outcome of "SLN-N0"patients to N_0 breast cancer patients that were treated in the "pre-SLN" era.
Method: Two groups of patients were evaluated: a prospective cohort of 245 consecutive patients that were staged as N_0 based on pathologic assessment (HE and IHC-staining) of the SLN, and a cohort of 182 patients treated before 2000 for unifocal cancers and staged as N0 based on axillary lymph node dissection (ALND) specimens. Patients who had chemotherapy (in the SLN group) and patients who would nowadays have had chemotherapy (in the ALND-group) were excluded. Median follow-up was 4 years for the SLN-group and 9 years for the ALND group.
Results: The SLN group and the ALND group were comparable for tumor size, the proportion of high grade cancers and the proportion that received hormonal therapy.
2- and 4-year cumulative overall survival was 95 and 91% for the ALND group and 98 and 93% for the SLN group (P=ns). 2- and 4-year disease free survival was 93 and 86% for ALND-group and 97 and 91% for the SLN group (P = 0.1)
Conclusion: Stage migration appeared to have an effect on prognosis. Although not statistically significant, patients who were staged as N_0 based on SLN assessment seemed to have more favorable disease free survival.

2086 POSTER

Clinical implications of the MDR1 1236C>T polymorphism: influences on doxorubicin pharmacokinetics and myelosupression in Asian breast cancer patients

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Background: This exploratory study aims to identify predictive biomarker polymorphisms in the ABCB1 gene and their relation to doxorubicin pharmacokinetics and pharmacodynamics in Asian breast cancer patients undergoing adjuvant chemotherapy.
Methods: Patients (N = 32) who have had curative surgery for histologically confirmed Stage I to III breast cancer were recruited. Doxorubicin was administered at 60 mg/m^2 and cyclophosphamide at 600 mg/m^2 every 3 weeks. DNA was extracted from the blood lymphocytes for analysis of the 1236C>T, 3435C>T and 2677G>T/A polymorphisms in the MDR1 gene. The incidence of treatment related toxicities were recorded. The nonparametric Mann-Whitney U test was used to detect significant differences between paired groups and the Kruskal-Wallis test to assess genotypic-phenotypic correlations.
Results: The median age was 48.5 years (range 31.2−66.8). Majority were Chinese (84%); 12.5% Malays and 3.1% were Eurasian. Patients harboring the reference genotype for the 1236C>T polymorphism were found to have significantly lower exposure levels to doxorubicin compared to patients who were heterozygous [CC vs. CT, AUC0-inf/dose/BSA(h*m-5): 10.95±3.9 vs 22.10±5.7, P = 0.0001] or carried the homozygous variant allele [CC vs. TT, AUC 0-inf/dose/BSA(h*m-5): 10.95±3.9 vs 19.01±5.8, P = 0.011]. The exposure levels for doxorubicinol were also significantly lower in patients who had the reference genotype when compared to the patients who were heterozygous [AUC 0-inf/dose/BSA(h*m-5); 7.04±2.6 vs 11.60±3.4, P = 0.011] or of the variant genotype [AUC 0-inf/dose/BSA(h*m-5); 7.04±2.6 vs 11.59±4.1, P = 0.019]. The presence of at least one T allele was associated with an approximately 5-fold odds ratio of developing grade 3/4 febrile neutropenia [CC vs CT+TT; OR = 4.8, 95% CI; 0.5 to 45.5]. No significant correlations were observed between 3435C>T and 2677G>T/A polymorphisms and pharmacokinetics of doxorubicin and neutropenia.
Conclusions: The present exploratory study showed that the 1236C>T MDR1 polymorphism may influence doxorubicin pharmacokinetics and is a potential predictive biomarker for severe myelosuppression in patients on adjuvant chemotherapy. Accrual is ongoing.

2087 POSTER

Saline instillation into the cavity after conservation surgery for breast cancer is a safe way of improving cosmesis

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Background: To demonstrate that saline instillation is a safe and simple procedure for volume replacement after wide local excision in breast surgery.
Materials and Methods: We performed a pilot study over a 12 month period at the Chase Breast Unit. 106 patients who underwent wide local excision for breast cancer had saline instilled into the surgical cavity at the time of wound closure. This was to maintain the volume and shape of the breast after removal of significant amounts of tissue. 75 mg of local anaesthetic (10 mls Ropivacaine hydrochloride 7.5 mg/ml) was added and included in the volume. We measured the volume instilled and monitored the wound and breast post-operatively at 1 week, 2 weeks and 3 months. As is our normal practice, all patients had peri-operative antibiotics.
Results: The volume of fluid instilled varied between 30–180 mls. The weight of tissue removed was in the range of 12–116 gms. The fluid was retained within the cavity. However, in one case the wide local excision cavity unexpectedly communicated with the axillary clearance cavity and all the fluid was evacuated spontaneously through axillary suction drain with a resultant visible reduction in the volume of the breast. There were no complications of saline instillation. In particular, there was no early or late infection in any of the 106 patients. None of the patients reported any additional discomfort or pain. There were no visible abnormalities apart from a subjective enhancement in the shape and volume of the breast. This improvement in shape and volume was maintained for the entire length of assessment (3 months).
Conclusions: Saline instillation is a simple and safe method of replacing volume after removal of significant amounts of breast tissue. Surprisingly, the benefits seem to persist. We are now proceeding to fully evaluate this technique in a formal prospective trial.

2088 POSTER

Efficacy in terms of local control, cosmetic outcome and late toxicity in 536 women treated with interstitial brachytherapy boost for breast conserving therapy

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Background: The aim of this study is to report local control, cosmetic outcome and late toxicity in women with early breast cancer treated with brachytherapy boost after external beam irradiation following breast conserving surgery.
Materials and Methods: During 1980–2000, 536 women received tumor bed boost with brachytherapy after external beam radiation therapy. The median pathological T size was 3 cm and the lymph nodes were positive in 198 (37%) women. Adjuvant chemotherapy was given to 228 women while 85 received adjuvant hormonal therapy. Three hundred and eighty three women were treated with low dose rate brachytherapy (LDR) to a dose of 15−20 Gy and 153 received high dose rate brachytherapy (HDR) to a dose 10 Gy (optimised) in single fraction. The median follow up for the entire group was 52 months.
Results: Actuarial 5 year local control rate was 90% for LDR group and 92% for the HDR group. Cosmesis at the last follow up was good or excellent in 83% women. Post radiation worsening of cosmesis was observed in 11.5% women and was similar in the 2 boost groups. Moderate to severe late breast sequelae were observed in 22% women in the HDR group and was significantly higher 12% in the LDR group (p = 0.002). Fibrosis was the most common late sequelae of radiation and 14% women had moderate to severe fibrosis in HDR group as compared to 7% in the LDR group (p = 0.01). Other late sequelae included breast oedema observed in 6% women in the HDR group and 4.5% women in the LDR group.
Conclusion: The local control was comparable for LDR and HDR brachytherapy boost. Type of tumour bed boost did not have a significant impact on worsening of cosmetic outcome. The late breast sequelae were however significantly higher in women treated with single fraction HDR implant.

2089 POSTER

Clinical impact of upfront adjuvant AI therapy on the early risk of recurrence

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Background: In postmenopausal women (PMW), most early breast cancer (BC) is hormone-dependent (HD), with a very heterogeneous natural history. During the first 2 years post surgery, there are more distant metastases (DM) events than locoregional or contralateral BC events. DM account for approximately 75% of all recurrences in patients taking