Friday 18 April 11:00–13:00

KEYNOTE SYMPOSIUM

Late breaking session

1LB Late Breaking

Neoadjuvant treatment of HER2 overexpressing primary breast cancer with trastuzumab given concomitantly to epirubicin/ cyclophosphamide followed by docetaxel ± capecitabine. First analysis of efficacy and safety of the GBG/AGO multicenter intergroup-study "GeparQuattro"

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Background: Trastuzumab has shown high efficacy in combination with neoadjuvant chemotherapy (NACT). We have prospectively investigated the efficacy of trastuzumab in a large controlled multicenter study.

Material: Patients (pts) were eligible in whom adjuvant chemotherapy would be considered otherwise and received 4 cycles of epirubicin/cyclophosphamide (EC) (90 mg/m^2/600 mg/m^2) and were then randomized to either 4 cycles of docetaxel (D) (100 mg/m^2), standard arm or 4 cycles of D-capecitabine (DX), (75 mg/m^2/1800 mg/m^2), combination arm or 4 cycles of D (75 mg/m^2) followed by 4 cycles of X (1800 mg/m^2) (D $\rightarrow$ X), sequential arm. Pts with HER2-positive tumors received trastuzumab 6 (8) mg/kg every 3 weeks concomitantly with all NACT before surgery and for up to 1 year after surgery. The second co-primary aim of this trial was to compare the pathologic complete response (pCR) rate in pts with HER2-positive tumors receiving NACT plus trastuzumab to the response rate in pts with HER2-negative tumors receiving the same NACT without trastuzumab.

Results: Within 15 months 1510 pts (453 HER2-positive) entered and after receiving 4 cycles EC, 1421 (427 HER2-positive) were randomized to D (N = 471; 147 HER2-positive), or DX (N = 471; 144 HER2-positive), or D $\rightarrow$ X (N = 479; 136 HER2 positive). Safety interim analysis of the HER2 positive pts revealed no increase in toxicity for NACT + trastuzumab compared to NACT alone. In 97% of HER2 positive and 96% of HER2 negative pts LVEF was >55%. No patients developed a loss in LVEF below 45%. During simultaneous treatment with trastuzumab and chemotherapy no CTC grade 4 cardiac event occurred, CTC grade 3 cardiac events were observed in two HER2 positive pts and in two HER2 negative pts. There were no congestive heart failures and no cardiac related deaths. The pathologic complete response rates (pCR) including residues of carcinoma in situ was 19.5% without trastuzumab and 41.3% with trastuzumab ($p < 0.001$); the rates of breast conserving surgery (BCS) were 63.1% without trastuzumab and 61.8% with trastuzumab (not significant).

Conclusions: The addition of trastuzumab to epirubicin/cyclophosphamide followed by docetaxel with and without capecitabine is feasible without clinically relevant cardiotoxicity. The pathologic complete response rate in patients with Her 2 neu overexpressing tumors was significantly increased by the addition of trastuzumab. Further follow up of this study will analyse the correlation of this result to patient outcome.

2LB Late Breaking

Breast conservative surgery with and without radiotherapy in patients aged 55−75 with early stage breast cancer – a prospective randomised multi-centre trial

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Breast conserving therapy (BCT) including postoperative irradiation of the remaining breast tissue is generally accepted as the treatment of choice for the vast majority of patients with early stage breast cancer, resulting in advantages of improved cosmesis and quality of life (QOL) as compared to mastectomy (MX). The question whether post operative irradiation is mandatory in all patients and, herewith, over-treating almost a half of them, remains one of the most controversial issues in BCT. To properly answer this question a randomised prospective multi-centre study was launched in January 2001 based on long-term follow-up data of the Milan III trial comparing BCT with or without postoperative irradiation. Those data demonstrated a significant lower risk of local recurrence in patients older than 55 years in comparison to the younger age group. Moreover, in patients older than 65 years the risk of local recurrence was similar in the irradiated and the control group.

Aims of the study: The main aim was to assess the cumulative incidence of local recurrence after conservative surgery with (CS+RT) vs without breast irradiation (CS). Added values of the study were to avoid the inconvenience and the risk of side-effects of radiation therapy and to prevent unnecessary mastectomies in hospitals where the facilities for radiation treatment are not available.

Patients and Methods: From January 2001 until December 2005 749 patients from 11 centres in Italy were randomly assigned to CS+RT (radiotherapy: homogenous breast irradiation 50 Guy +10 Guy boost) or to CS. Main patients and tumours characteristics were fairly well balanced between treatment groups. Adjuvant systemic therapy in patients at moderate-high risk of distant recurrence were allowed as per participating center policy.

Results: After a median follow-up of 53 months, the cumulative incidence of local recurrence was 0.7%±0.4 after CS+RT vs 2.5%±0.9 after CS (HR: 4.01, 95% confidence limits 0.85−18.89; P = 0.07). Distant disease-free survival was 96% after CS+RT and 96.5% after CS. Overall survival was 95% vs 96%, respectively. Local-regional treatment was well tolerated and devoid of major side effects.

Conclusion: Present data indicate that breast irradiation after conservative surgery can be avoided in patients aged 55−75 years without exposing them to an increased risk of local recurrence and death. Prolonged follow-up will further clarify possible late sequelae potentially induced by breast irradiation in these patient population. Participating centres:

1. Division of Surgery and Senology, The Maugeri Foundation Pavia, Italy
2. Italian School of Senology, Milano, Italy
3. Division of Surgery General Hospital Alba, Italy
4. Division of Surgery and Senology General Hospital Bergamo, Italy
5. Division of Senology General Hospital Ortona, Italy
6. Division of Surgery Arcispedale Santa Maria Reggio Emilia, Italy
7. Division of Surgical Science and Medical Technology University La Sapienza Roma, Italy
8. Division of Surgery Casa Sollievo della Sofferenza Hospital S. Giovanni Rotondo, Italy
9. Division of Surgery S. Orsola Malpighi Hospital Bologna, Italy
10. Division of Surgery S. Maria della Misericordia Hospital Udine, Italy
11. Division of Gynaecology Cancer Research Centre Torino, Italy
12. Division of Gynaecology General Hospital Cirié, Italy
13. Division of Psychology, The Maugeri Foundation Pavia, Italy
14. Statistical Centre National Cancer Institute, Milano, Italy

3LB Late Breaking

UK TACT trial results – does everyone need adjuvant taxanes?

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Introduction: Initial reports from several trials suggested a modest survival benefit favouring taxanes over anthracyclines for women with early breast cancer (BC). Other trials failed to show such a benefit and uncertainty remains where taxanes are compared with anthracycline regimens of similar duration. The UK TACT Trial, a multicentre phase III randomised trial comparing sequential FEC – docetaxel (FEC-T) to UK anthracycline chemotherapy (CT), provides further evidence with regard to overall benefit, as well as which sub-groups, if any, have more or less to gain.

Materials and Methods: Between Feb 2001 and July 2003 4162 women with node positive or high risk node negative early BC were recruited from 104 centres (103-UK, 1-Belgium). Centres chose FEC (600/60/600 mg/m^2 q3wk $\times$ 8) or E-CMF (Epirubicin 100 mg/m^2 q3wk $\times$ 4 CMF 100 mg/m^2 PO d1−14 or 600 mg/m^2 IV d1&8/40/600 mg/m^2 q4wk $\times$ 4) as the control arm, reflecting standard UK practice. Patients (pts) were randomised to FEC-T (FEC q3wk $\times$ 4 docetaxel 100 mg/m^2 q3wk $\times$ 4) or control. 2523 pts were from FEC centres (FEC = 1265: FEC-T = 1258) and 1639 from E-CMF centres (E-CMF = 824; FEC-T = 815). Tumor blocks were collected prospectively for central HER2 testing and creation of

tumour microarrays. Primary endpoint was disease-free survival (DFS) (time to loco-regional or distant relapse, contralateral invasive BC or death without relapse). Secondary endpoints included overall survival (OS), CT tolerability and quality of life.

Results: With a median follow-up of 52 months, 97.3% alive pts have complete follow-up. 957 DFS events have been observed (484 control, 473 FEC-T) giving a Hazard Ratio (HR) = 0.97 (95% CI 0.86−1.10) p = 0.62, with 73.9% control and 74.7% FEC-T pts alive and disease free at 5 years. 639 pts have died (323 control, 316 FEC-T) (7 related to treatment) giving a HR = 0.98 (95% CI 0.84−1.14) p = 0.76 with 81.8% control and 82.0% FEC-T alive at 5 years. Possible differences in treatment effect are suggested by HER2 and ER status, however with low statistical power for formally testing treatment interactions these are not convincing. Analyses according to ER and HER2 will be discussed in the context of findings from similar trials.

Conclusions: With almost 5 years of follow-up, no evidence was observed of an overall benefit of FEC-T. Adding TACT to results of other trials allows consideration of whether any sub-groups can be identified which consistently appear to benefit (or not) from taxane based therapy.

4LB Late Breaking

Long-term mortality results from the UK Breast Screening Frequency Trial

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In the UK Breast Screening Frequency Trial, 49173 women aged 50−62 were randomised to three annual incidence screens after their prevalence screen date (study group) and 50162 to one incidence screen three years after the prevalence screen (control group).

Primary interest was in those who attended the prevalence screen. Results of predicted case survival based on the Nottingham Prognostic Index of the tumours diagnosed were published early in the study and indicated an insignificant 5−11% reduction in breast cancer mortality.

Here we present actual mortality results to the end of 2006 (median follow-up 162 months). There were 373 breast cancer deaths in the study group as a whole and 374 in the control group (RR = 1.02, 95% CI 0.88−1.17, p = 0.8). In the prevalence screen attenders, there were 209 breast cancer deaths in the study group and 231 in the control group (RR = 0.89, 95% CI 0.73−1.07, p = 0.2).

When we consider mortality only from cancers diagnosed during the three-year screening period of the trial, there was no significant difference between the study and control group (RR = 0.96, 95% CI 0.67−1.37, p = 0.8). This remained the case when restricted to those who had attended the prevalence screen (RR = 0.93, 95% CI 0.63−1.37, p = 0.7).

These results indicate that the predicted mortality figures were accurate. There is no evidence in favour of shortening the current three-year screening interval.

5LB Late Breaking

Is mammography screening effective up to 75 years?

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Background: Although there was little evidence of efficacy of mammography screening in women older than 70 years, the Dutch breast cancer screening programme extended the upper age limit from 69 to 75 years in 1998. This decision was based on microsimulation modelling that resulted in a favourable balance of benefits and harms of mammography screening up to at least 75 years. Beyond this age, however, screening might lead to overdiagnosis of breast cancer due to a probable slower tumour growth rate. Based on first results 1998–2000, 75 years appeared to be an appropriate upper age limit for mammography screening. We updated this previous study with screening results up to 2007, and also assessed age-specific breast cancer mortality.

Material and Methods: We used aggregated national data on screening 1998–2006 and age-specific population and breast cancer mortality data 1986–2006 from Statistics Netherlands. Main outcome parameters (as detection rate and breast cancer mortality rates) were compared with model-simulated results for the age categories 50−69 and 70−75.

Results: In 1998–2006, 7.37 million screening examinations were performed, of which 862,655 in women aged 70−75 years. The participation rate was 81.2% for ages 50−69 and 71.9% for ages 70−75. In the latter age category, participation increased from 62.5% in 1998 to 77.6% in 2006. Per 1000 women screened, 12.8 women aged 50−69 were referred for diagnostic assessment, and 16.4 aged 70−75. The breast cancer detection rate was 4.5 and 7.8 per 1000 women screened, respectively, resulting in a positive predictive value of mammography of 36% and 47%, respectively. One-year age-specific detection rates from 70 through 75 years showed a continuous increase, suggesting a gradually slower tumor growth with age. As of 2003, the breast cancer mortality rate among women aged 75−79 (when assuming a lag time of 5 years to take effect) started to decline statistically significantly, and was 29.5% lower in 2006 than the mean rate during 1986–1997. This breast cancer mortality reduction showed a similar pattern as previously found in women aged 50−69.

Conclusions: The results of our study suggest that screening in women aged 70−75 years has a strong impact on breast cancer mortality, and that mammography screening of high quality is effective and appropriate up to 75 years. Since the detection rates gradually increase with age, however, screening beyond 75 years will become less favourable.