breast cancer, early

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DOSE-DENSE (DD) DOXORUBICIN AND WEEKLY CYCLOPHOSPHAMIDE (AC) FOLLOWED BY WEEKLY PFAITAXEL (P) WITH TRASTUZUMAB (T) AND LAPATINIB (L) HER2 UPFED/EXERTED BREAST CANCER (BC): FIRST SAFETY RESULTS

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Background: DD q 2 weekly (w) AC → P + T x 1 year (y) has an acceptable safety profile. With appropriate heart failure (GHF) rate of 1/70 pts and no data on unexpected toxicities (Dang, JCO 2008). Lapatinib (L) is effective in HER2+ BC and is being tested in the adjuvant setting. We conducted a pilot study of dd AC → P + T + L to determine its feasibility and cardiac safety.

Methods: Enrolled pts had HER2 IHC + or FISH-amplified BC, LVEF > 50% and no active cardiac disease. Rx consisted of AC at 460/600 mg/m² x 4 q 2 w (w/ pegfilgrastim 6 mg on day 2) → P at 80 mg/m² x 12 q 2 w + T x 1 (4 mg/kg, load, 2 mg/kg q 2 w during P and 6 mg/kg q 3 w after all chemotherapy is completed); L (1000 mg daily beginning w/ P + T and continued for 1 y). MUGA is obtained at baseline and at months (mo) 2, 6, 9, and 18. Feasibility was defined as (1) > 80% pts completing the PTL phase without a dose delay or reduction at a dose level consistent with CHF or cardiac death; (2) < 5% pts required a dose reduction of lapatinib at 1 w from 1000 mg to 750 mg for a G 3 event or < G 3 toxicity at their discretion.

Results: From March 2007 to April 2008, we enrolled 96 pts. We report the feasibility results on the first 40 patients enrolled. Median age is 49 years (range, 28-73). Among these 40 pts, 38 are evaluable (1 expired from pneumonia after AC # 2, 1 withdrew after AC # 4 w/ G 3 fatigue). Of the 38 pts, 13 (34%) withdrew from study during the PTL phase: 11 for a 2nd event of G 3 or unacceptable < G 3 toxicities (7 G 3 diarrhea, 1 G 1 diarrhea, 1 G 2 rash, 1 G 3 QTcF w/ G 3 diarrhea, 1 G 3 ALT w/ G 3 diarrhea) and 2 for other reasons (1 progression, 1 personal reason). Of the remaining 29 pts, 9 (31%) had a dose reduction of lapatinib during the PTL phase for a 1st event of G 3 or unacceptable < G 3 toxicities (3 G 3 diarrhea, 1 G 1 diarrhea, 1 G 2 rash, 2 G 2 rash, 1 G 3 pruritus, 1 G 2 pruritus). Overall 12/38 (32%) pts had G 3 diarrhea and 19/38 (50%) pts required a dose reduction of lapatinib. To date there are no patient drop-outs due to significant LVEF declines after dose-dense AC and there are no cardiac events during PTL phase (GHF or cardiac death).

Discussion: This is the first report demonstrating that at 1000 mg/day is not feasible in combination with standard weekly P and T because of excessive G 3 diarrhea. An earlier pooled analysis reported a G 3 diarrhea rate of <10% for lapatinib-based therapy (monotherapy or combination). However, it now appears that PTL significantly increases the rate of toxicity. Ongoing and future clinical trials will need to take into account this toxicity in their design.

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SEQUENTIAL EPIRUBICIN-DOCETAXEL-CMF AS ADJUVANT THERAPY FOR NODE-POSITIVE EARLY STAGE BREAST CANCER: UPDATED RESULTS OF THE TAXIT216 RANDOMIZED TRIAL

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Background: Doxorubicin is among the most active drugs for breast cancer (BC). The aim of this trial was to compare the efficacy and tolerability of a block-sequence chemotherapy regimen containing doxorubicin to a standard anthracycline-based regimen as adjuvant therapy in node-positive (N+) early stage BC (ESBC).

Methods: Between July 1998 and July 2002, 998 N+ ESBC patients (pts) were randomized to either arm A (E+CMF): epirubicin (E) 120 mg/m² Day 1, q21 d x 4 cycles followed by cyclophosphamide 600 mg/m², methotrexate 40 mg/m², and fluorouracil 600 mg/m² (CMF); Day 1 and 8, q28 d x 4 cycles (N=486); or arm B (E+T+CMF) in which docetaxel (T) 100 mg/ m² Day 1, q21 d x 4 cycles was administered after the 4th cycle of E and before the 1st cycle of CMF (N=486). A third dose-intensified arm was closed for toxicity after inclusion of 26 patients. Stratification was by center, lymph node involvement (1-3, 4-9, 10+), estrogen receptor status (negative/positive/unknown), and menopausal status (pre/post). The primary end point was disease-free survival (DFS; defined as BC recurrence, contralateral breast cancer, second non-malignancy, or death). The study was designed with 80% power to detect a hazard ratio of 0.70, assuming 0.05 (two-sided) and expected DFS in Arm A of 0.85 at 5 years. This required 480 pts per arm and 210 events.

Results: As of November 30, 2007, with median follow-up 62 months, 278 DFS events and 142 deaths were recorded. The 5-year DFS was 74% in arm A vs 68% in arm A, with estimated adjusted hazard ratio (HR) 0.82 (95%CI: 0.64–1.03; P=0.13). The 3-year recurrence-free survival (RFS; defined as DFS but excluding contralateral cancer and non-breast second malignancy) was 76% for arm B and 69% for arm A, with HR 0.75 (95%CI: 0.59–0.96; P=0.0394). The 5-year overall survival (OS) was 90% for arm B and 85% for arm A (HR=0.67; 95%CI: 0.48–0.94; P=0.0168). Safety of each regimen had been reported previously (Bianco, ASCO 2005).

Conclusions: For pts with N+ ESBC, the sequential addition of T to the E+CMF regimen confers significant improvement in the breast cancer-specific endpoints RFS and OS.

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TAC VERSUS FAC AS ADJUVANT CHEMOTHERAPY FOR HIGH-RISK NODE-NEGATIVE BREAST CANCER: RESULTS OF THE GEICAM 90905 TRIAL

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Background: Docetaxel-based adjuvant therapy improves disease-free survival (DFS) and overall survival (OS) in node-positive breast cancer (BC) patients (pts). Most BC pts are node-negative at diagnosis and the role of taxanes in such pts is not established.

Methods: Pts aged 18-71, with Ti-T3, N0, M0 operable BC and at least one St Gallen risk factor were randomized to 6 cycles every 3 wks of TAC (docetaxel 75 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m² day 1) or FAC (fluorouracil 500 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m² day 1). Radiotherapy was mandatory after conservative surgery, and recommended for tumors >5 cm. Tamoxifen was given for 5 yrs to HR-positive pts. The primary end point was 5-yr DFS. Secondary end-points included OS, toxicity, and quality of life (QoL).

Results: Between July 1999 and December 2001, 1059 pts were randomized (TAC 539; FAC 520) and 1047 (98.9%) were evaluable. Median age was 50 (TAC) vs 49 yrs (FAC), with 55% premenopausal in both arms; other characteristics were balanced. Safety results have been reported (Martin Ann Oncol 17:1205). TAC produced more hematological toxicity, although primary prophylaxis with G-CSF reduced neutrophilic fever events. No toxic deaths were reported. Health-related QoL (HRQoL) deteriorated during chemotherapy and TAC pts had worse outcomes than FAC pts in most QoL measurements. However, QoL scores improved and were similar in both arms once chemotherapy ended, returning to or exceeding baseline. As of June 2007 (median FU of 6 years[RU1]), 128 pts had a DFS event (TAC 52; FAC 76) and estimated 5-yr DFS is 91% for TAC and 86% for FAC (HR 0.66; 95%CI: 0.46–0.94, P=0.0203). Forty-five pts have died (TAC 19; FAC 26) and estimated 5-yr OS is 97% for TAC and 95% for FAC (HR 0.72; 95%CI: 0.40–1.30; P=0.27).

Conclusions: Adjuvant TAC significantly improves 5-yr DFS over FAC (33% reduction in the risk of relapse) in pts with high-risk node-negative BC. This is the first positive taxane adjuvant trial reported in node-negative breast cancer pts.
We conclude that BRCA1 and BRCA2 mutations are associated with adverse stage, grade, ER status and year of diagnosis (DDFS HR 1.0, p=0.98; OS HR 1.13, in univariate analyses. These effects were lost after adjustment for age, T and N factors in BRCA2 carriers than in NF cases (HR 1.6, p=0.04 and HR 1.8, p=0.01, respectively) in multivariate analyses (all HR <1.43, all p>0.11). DDFS and OS were worse in BRCA1 carriers and NF cases in univariate or and high grade. Distant disease-free survival (DDFS) and overall survival (OS) did not differ significantly between BRCA1 carriers and NF cases in univariate or.

Materials and methods: The intent-to-treat population, defined as all randomized patients (pts), is 1667 PMW with stage I-IIIA HR BRCa starting Eti (2.5 mg qd x 5 yrs). Pts with a minimum BMD score of -2, were randomized to immediate ZA arm (IM- ZA) (= 833) vs delayed ZA arm (D-ZA) (N=834) from 226 worldwide study sites. The D-ZA pts receive ZA when either the post baseline T-score decreases to less than -2.0 SD or if a non-traumatic fracture occurs. The primary endpoint, percent change in lumbar spine BMD at 12 mos, was reported at ASCO 2005 (Z-FAST trial) and EBCOC 2006 (ZO-FAST trial).

Results: The IM-ZA had 26 (3.1%) pts with clinical fractures (including trauma related events) while the D-ZA had 28 (3.4%) pts. Sites of fracture were similar between the two arms. 1664 pts were evaluable for disease recurrence (defined as local recurrence, distant metastasis or death). 30 (3.6%) pts in the IM-ZA had disease recurrence vs 46 (5.5%) pts in the D-ZA (Fisher’s exact test: p-value = 0.0776, not statistically significant). Bone metastases were identified in 9 (1.1%) pts in the IM-ZA vs 14 (1.7%) for D-ZA; 9 (1.1%) deaths were recorded in the IM-ZA vs 16 (1.9%) in the D-ZA.

Conclusion: At 24 mos, the number and percentage of patients with disease recurrence or fractures in the IM-ZA appears to be lower than in the D-ZA. Additional follow-up is needed to determine whether these trends will become statistically significant.

VARIATIONS IN TUMOUR SIZE, NODAL INVOLVEMENT, AND RISK OF DISTANT METASTASES FROM 1954 TO 2000, IMPLICATIONS FOR SCREENING AND ADJUVANT THERAPY IN BREAST CANCER

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Background: The tumor size and nodal involvement are the two main prognostic factors in breast cancer. Their impact on the natural history of breast cancer is not fully captured by analyses which ignore their quantitative nature.

Methods: Data concerned 18159 breast cancer patients treated with primary surgery: 3616 patients treated at the Institut Gustave-Roussy (IGR, France) between 1954 and 1983, and 14493 patients included in the breast cancer registry at the Stockholm-Gotland Cancer Health Care region (SG, Sweden) between 1976 and 1999. Three groups were defined: IGR 1954-83; SG 1976-90 (implementation of screening trials in SG) and SG 1991-99 (period during which adjuvant systemic treatments were widely administered). The risks of distant metastases (DM) and of nodal involvement were analyzed according to tumor size with parametric models.

Results: The incidence of DM was highly different between the 3 groups (P<10^-10). Using SG 1976-90 as the reference group, the hazard ratios for DM (HR) were equal to 1.35 (95% CI 1.26-1.44) in IGR 1954-83 and 0.60 (95% CI 0.56-0.65) in SG 1991-99. The differences in tumor size partially related to screening in SG was sufficient to explain the increased risk of DM in IGR 1954-83 (HR adjusted on tumor size 1.08; 95% CI 0.98-1.19; P=0.13), but not the decreased risk in SG 1991-99 (adjusted HR 0.63; 95% CI 0.57-0.69; P<10^-10). The relationship between tumor size and the risk of DM changed significantly during the 90’s.

Conclusion: Early diagnosis is sufficient to explain differences in the prognosis before 1990. After 1990, the more systematic use of adjuvant systemic therapy is the main reason for the reduction in DM in a general and unselected population.
Results: Patient groups and their clinical outcome based on CTGs monitoring with CK19 mRNA and HER2 mRNA before and after the administration of adjuvant chemotherapy are depicted in Table. The median follow-up for patients that did not relapse was 56 months (range 10-106 months). Bad prognosis (n=53) when compared to good prognosis patients (n=181) experienced shorter disease-free (DFS) and overall survival (OS) in the triple-negative, HER2-positive and ER-positive/HER2-negative subtypes (p<0.001, p=0.047, respectively for DFS) and (p<0.001, p=0.198, respectively for OS). In multivariate analysis correcting for standard clinicopathological characteristics, the Hazard Ratios (HR) of intermediate versus good prognosis patients were (HR: 2.087, 95%CI 1.201-3.262, p=0.009 for DFS and HR: 2.876, 95%CI 1.249-6.265, p=0.013 for OS), of bad versus good prognosis patients were (HR: 3.940, 95%CI 2.169-7.157, p=0.001 for DFS and HR: 3.862, 95% CI 1.514-9.849, p=0.005 for OS).

Conclusion: Persistent detection of CK19-positive/HER2-positive CTGs in early breast cancer patients before and after adjuvant chemotherapy predicts extremely poor clinical outcome.

| CK19Pre HER2Pre CK19Post HER2Post Patients Relapses Deaths |
|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Good              | -                 | -                 | 181              | 26                | 8                 |
| Prognosis Intermediate | +                 | +                 | 63               | 12                | 7                 |
| Prognosis         | +                 | -                 | 40               | 6                 | 3                 |
|                    | +                 | +                 | 20               | 6                 | 3                 |
|                    | +                 | -                 | 10               | 4                 | 3                 |
|                    | +                 | +                 | 29               | 8                 | 5                 |
|                    | +                 | -                 | 3                | 1                 | 0                 |
|                    | +                 | +                 | 1                | 0                 | 0                 |
| Bad Prognosis     | +                 | +                 | 53               | 25                | 12                |
|                   |                   |                   | 400              | 88                | 41                |

**DISCREPANCY BETWEEN TRIPLE NEGATIVE AND BASAL-LIKE IMMUNOPHENOTYPE IN POORLY DIFFERENTIATED BREAST CARCINOMAS**


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The histological grade is one of the most important prognostic and predictive factor in breast carcinomas, but poorly differentiated neoplasms are still quite heterogeneous since they comprise a group of neoplasms that can belong to basal-like, HER2 or even luminal type according to genetic classification. In this study we investigated the basal phenotype among breast carcinomas with less than 10% of classical prognostics factors. We retrospectively studied 134 samples of paraffin-embedded breast cancer tissues with less than 10% of basal-like, HER2 or luminal type features with the basal immunophenotypes using the Pearson microarray blocks were constructed from selected areas of the tumors for Ki67 were analyzed in whole selected histological sections of the tumor. Tissue tubular formation and its relation with the triple-negative phenotype and other investigated the basal phenotype among breast carcinomas, but poorly differentiated neoplasms are still quite heterogeneous since they comprise a group of neoplasms that can belong to basal-like, HER2 or even luminal type according to genetic classification. In this study we evaluated the basal phenotype among breast carcinomas with less than 10% of classical prognostics factors. We retrospectively studied 134 samples of paraffin-embedded breast cancer tissues with less than 10% of classical prognostics factors. We retrospectively studied 134 samples of paraffin-embedded breast cancer tissues with less than 10% of classical prognostics factors. We retrospectively studied 134 samples of paraffin-embedded breast cancer tissues with less than 10% of classical prognostics factors. We retrospectively studied 134 samples of paraffin-embedded breast cancer tissues with less than 10% of classical prognostics factors.

**MAMMAPRINT PREDICTS SURVIVAL IN SMALL T1 BREAST CANCER TUMORS**

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Introduction: A 70-gene tumor expression profile was established as a powerful predictor of disease outcome in young breast cancer patients. It is known as “MammaPrint” was recently validated in independent cohorts and implementation was shown to be feasible in community hospitals. However, small tumor size breast cancer samples are according to most clinical guidelines identified to be at lower risk for developing distant metastasis. In this study we focus on the small T1 (< 2 cm) tumors and also show the results for the subgroup of tumors smaller than 1 cm as well as tumors identified by St Gallen as low risk.

**Results:** Kaplan Meier analysis of the 224 tumors showed a significant separation in the probability of developing distant metastases at 10 years according to MammaPrint outcome (HR=2.66, 95%CI 1.3-5.5). One hundred and nine samples (49%) had a good prognosis signature according to MammaPrint and had a 10 year overall survival of 100%. Fifty-one percent was bad signature based on MammaPrint. Moreover, in the very small tumors (< 1 cm) as well as tumors that were classified as low risk by St Gallen criteria, a high risk group could be identified.

**Conclusion:** A large part of patients with small tumors have a poor prognosis signature according to MammaPrint. MammaPrint provides more accurate information on recurrence risk in small tumors as compared to conventional clinical criteria and will improve the guidance for the requirement of adjuvant therapy for women diagnosed with breast cancer.

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**Background:** We sought to study the predictive significance and correlations of transcriptional profiling of the ER, PgR and microtubule-associated protein Tau (MAP-Tau) genes in early breast cancer. Materials and methods: Messenger RNA (mRNA) was extracted by RT-PCR from 279 formalin-fixed paraffin-embedded breast carcinomas (T1-JNO-M0) of patients enrolled in the HeCOG HE 10/97 adjuvant chemotherapy trial. Cohort-based cut-offs were defined as the 25th percentile mRNA value for ER and PgR and the median for MAP-Tau. Results: MAP-Tau was strongly correlated with ER and PgR mRNA status (Spearman r=0.52 and 0.64, p<0.001). The agreement between determination of hormonal receptor status by RT-PCR and IHC was moderate (Kappa=0.41) for ER and fair (Kappa=0.33) for PgR. At a median follow-up of 8 years, univariate analysis adjusted for treatment showed positive ER mRNA status to be of borderline significance for reduced risk of relapse (HR=0.65, 95% CI 0.41-1.01, p=0.055) and death (HR=0.62, 95% CI 0.36-1.05, p=0.077), while positive MAP-Tau mRNA status was significantly associated with reduced risk of relapse (HR=0.50, 95% CI 0.32-0.78, p=0.002) and death (HR=0.49, 95% CI 0.29-0.83, p=0.008). In multivariate analysis, only axillary nodal metastases (HR=2.33, 95% CI 1.05-5.16, p=0.041) and MAP-Tau mRNA status (HR=0.46, 95% CI 0.25-0.85, p=0.01) independently predicted patient outcome. However, MAP-Tau mRNA levels did not predict enhanced benefit from inclusion of paclitaxel in the adjuvant therapy regimen (test for interaction p=0.99). No correlation was evident between increasing ER and MAP-Tau mRNA transcription and increasing benefit from endocrine therapy in 203 ER and/or PgR-IHC-positive patients receiving adjuvant hormone therapy (wald p=0.54 for ER, p=0.51 for PgR).

**Conclusions:** ER gene transcription carries weak predictive significance for benefit from endocrine therapy or for outcome, with no apparent dose-response association. The predictive significance may possibly be exerted via MAP-Tau gene expression, an ER-inducible tubulin modulator with strong predictive significance for patient outcome.
Background: The role of adjuvant high-dose chemotherapy (HDC) with autologous hematopoietic stem-cell transplantation for primary breast cancer (BC) at high risk of recurrence (≥3 LN+) has not been well defined yet. Recently reported trials have demonstrated that this approach could have a role in selected pts. Aim of this study is to retrospectively evaluate toxicity and efficacy of HDC with HSCT in a large cohort of pts receiving HDC in Italy between 1990 and 2005.

Methods: 1284 BC pts receiving HDC for poor risk BC were identified in the Italian registry (GITMO). In 1383 pts with ≥3 LN, a thorough data set including biological characteristics, toxicity and follow up was available. Median age was 46 years (24-66), 62% of pts were pre menopausal at treatment, 71% had an endocrine responsive tumours and 43% had a HER2+ tumour. The median number of LN was 15 (4-63). 76% of pts received alcalating agents-based HDC as a single procedure while 24% received Epirubicin or Mitoxantrone-containing HDC, usually within a multi-transplant program. Source of stem cells was peripheral blood in 99% of pts.

Results: Treatment-related mortality (TRM) at 100 days was 0.7%, while late cardiac and secondary tumour-related mortality were around 1% overall. With a median follow up of 79 months, median disease free survival (DFS) and overall survival (OS) in the entire population were 115 months and not reached, respectively. Subgroup analysis demonstrated that OS was significantly better in endocrine responsive tumours (p=0.00109), while menopausal or HER-2 status did not affect survival. Median OS was significantly better (p=0.0000) in pts receiving multiple transplant procedures. Conclusion: A series of poor risk pts HDC with HSCT has low TRM and high efficacy. Multiple transplants seem more active than single HDC procedures. This analysis could be useful in selecting well defined patient populations in which to re-address the role of HDC as adjuvant treatment. The study was conducted on behalf of Gruppo Italiano per il trapianto di Midollo, di Cellule Stamminali emopoietiche e di terapia cellularle (GITMO).

102P DESIGN AND EVOLUTION OF BIG 1-98: A RANDOMIZED, DOUBLE-BLIND, PHASE-III STUDY COMPARING LETROZOLE AND TAMOXIFEN AS ADJUVANT ENDOCRINE THERAPY FOR POSTMENOPAUSAL WOMEN WITH RECEPTOR-POSITIVE, EARLY BREAST CANCER - BIG 1-98 COLLABORATIVE AND INTERNATIONAL BREAST CANCER STUDY GROUPS

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Several large randomized trials have demonstrated that, compared with tamoxifen given as adjuvant therapy for five years, an aromatase inhibitor (AI), either upfront or following tamoxifen, improved disease-free survival for postmenopausal women with steroid hormone receptor positive breast cancer. One such trial for this population is the Breast International Group (BIG) 1-98, which randomly assigned 8028 women to five years of monotherapy with either tamoxifen or letrozole, or to sequential treatment of two years of one agent followed by three years of the other. The original protocol was designed as a 2-arm comparison of tamoxifen with the AI, letrozole, for five years. The BIG 1-98 trial design was expanded to include a 4-arm option to answer a second question related to the strategy of switching to the other agent. The 2-arm option included 1835 women randomly assigned to letrozole or tamoxifen from 1998 to 1999, and the 4-arm option randomised 6193 women to receive monotherapy or sequences of the two agents, from 1999 to 2003. BIG 1-98 was powered to address two distinct, clinically important questions. The first, the Primary Care Analysis, examined the efficacy of monotherapy and showed that treatment with letrozole significantly improved disease-free survival compared with tamoxifen. The second analysis, scheduled for late 2008, will focus on the benefit of sequential therapy compared with monotherapy with either tamoxifen or letrozole. The 4-arm design and the size of the trial offer the flexibility to focus on the pairwise comparisons that have emerged in the last five years as being the most clinically relevant today. Of particular interest is the comparison of letrozole for five years versus the sequence of tamoxifen followed by letrozole, which is yet untested in the adjuvant setting. We will present the design and history of BIG 1-98, the evolution of the trial endpoints and cohorts, and the analytic challenges that we face when the focus of the analysis shifts over time as data emerge from other studies.
Annals of Oncology

180P APPLICATION OF NUMBER NEEDED TO TREAT (NNT) TO COMPARE BENEFIT: LETROZOLE OR ANAOSTROZOLE FOR THE PREVENTION OF EARLY RECURRENCES IN POST MENOPAUSAL WOMEN WITH EARLY STAGE BREAST CANCER

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Background: The ATAC and BIG 1-98 clinical trials demonstrated that anastrozole (ANA) and letrozole (LET) were more effective than tamoxifen (TAM) in preventing disease relapse in postmenopausal women with early stage breast cancer. However, recent secondary analyses of these trials suggest important differences between LET and ANA in the prevention of early distant recurrences; early being defined as less than three years following the initiation of treatment. NNT represents the number of patients that need to be treated with a new intervention in order to avoid one additional event. In this analysis, the NNT approach was used to compare letrozole and anastrozole in preventing early recurrences in this patient population.

Methods: The early recurrence data from the pivotal trials for LET and ANA were reviewed (Mauriac, 2007, Houghton, 2006). The time points for evaluating early recurrence for ANA and LET were at 2.5 and 2 years respectively. Patients remaining disease free beyond these time points were censored. The NNT was calculated for each agent with respect to all recurrences; local-regional, distant recurrences and contralateral breast cancer.

Results: For all recurrences, LET and ANA had a comparable NNT of 75 (95% CI: 46 - 200) and 77 (95% CI: 39 - 2349) patients to avoid one recurrence. However, a 3-fold difference in NNT was noted for distant recurrences in favor of LET (100; 95% CI: 58 - 371) vs ANA (P=0.003) with LET to avoid one such event compared to 300 (95% CI: 74 - 2394) with ANA.

Conclusions: In situations of multiple numerical outcomes from randomized trials, the NNT approach is a simple and effective method to express the findings in a clinically meaningful way. In this analysis, it appears most of the clinical benefit associated with ANA in the first 2-3 years is in reducing the risk of local and regional recurrences, while LET shows a pronounced impact in reducing distant metastases in these first 2-3 years. These findings are particularly relevant because distant metastases are associated with the lowest survival rates and represent a major economic burden to health care systems.

180P PHASE II STUDY OF PRIMARY SYSTEMIC THERAPY WITH WEEKLY EPIRUBICIN PLUS GEMCITABINE IN PATIENTS WITH STAGE II AND III BREAST CANCER: FINAL ANALYSIS

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Purpose: To evaluate pathologic complete response (pCR) and clinical response rates and adverse events by primary chemotherapy with weekly paclitaxel and gemcitabine in stage II and III breast cancer (BC) patients (pts).

Patients and methods: Reoperatively, pts with stage II and III BC received 4 cycles of paclitaxel 80 mg/m^2 and gemcitabine 1,200 mg/m^2 day 1 and day 8 every 3 weeks. All pts were axillary node negative determined by positron emission tomography or cytology. Postoperatively, 4 cycles of doxorubicin 60 mg/m^2 and cytosphosphamide 600 mg/m^2 were administered every 3 weeks following by radiation therapy and hormonal therapy for 5 years if indicated.

Results: Between Sep 2005 and Apr 2006, 44 pts were enrolled. 73% had stage III BC and 68% had hormone receptor positive tumors. 18 pts (41%) showed HER2 positivity, 22 pts (50%) HER2 negativity, and 4 pts (9%) HER2 IHC 2+. 8 pts achieved pCR in primary tumors (18%; 95% CI, 9 - 32), 11 in axillary nodes (25%; 95% CI, 14 - 40), and 5 in both breast and axillary nodes (19%; 95% CI, 5 - 24). Clinical responses were observed in 35 pts (80%; 95% CI, 65 - 89%). The regimen was very well tolerated with mild non hematologic toxicities. Grade III/IV toxicities were neutropenia (57%), leukopenia (14%), febrile neutropenia (2%), and headache (2%). In the univariate analysis, pCR in breast was significantly associated with stage at presentation (P=0.003), and there was a trend of less pCR in breast with multiple and hormone receptor positive tumors (P=0.092 and P=0.087, respectively). 22% of patients presented (P=0.003), and there was a trend of less pCR in breast with multiple and hormone receptor positive tumors (P=0.092 and P=0.087, respectively). 22% of patients presented (P=0.003), and there was a trend of less pCR in breast with multiple and hormone receptor positive tumors (P=0.092 and P=0.087, respectively).

Conclusion: Preoperative weekly paclitaxel plus gemcitabine combination given every 3 weeks was well tolerated with clinical response and pCR rates in breast of 80% and 18% in pts with stage II and III BC. Supported in part by NCC Grant No. 06102240 and SHIN POONG PHARM CO., LTD. which provided paclitaxel and gemcitabine.

197P PREVENTION OF INFECTION AFTER TAC CHEMOTHERAPY FOR NODE-POSITIVE BREAST CANCER AS AN ADJUVANT THERAPY WITH OR WITHOUT CIPROFLOXACIN

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Background: TAC (docetaxel, doxorubicin and cyclophosphamide) chemotherapy has been accepted as an adjuvant chemotherapy for node-positive breast cancer. However, moderate-to-severe adverse reactions, especially neutropenia, following this regimen have been a major obstacle to wider acceptance. Until now, ciprofloxacin has been given to patients on completion of each cycle to prevent systemic infection. We tried to determine if ciprofloxacin is to be included in the post-chemotherapy medications or not to stop possible infection.

Methods: We randomly assigned 100 patients into two groups between Jan. 2006 and Oct. 2007. Study group (A; n=50 patients, 300 cycles) was given prophylactic G-CSF (300 ug) from day 5 to day 10, and the control group (B; n=50, 300 cycles) was given G-CSF and ciprofloxacin (300 mg, orally twice daily) from day 5 to day 10. We compared the incidence of infection and neutropenia prospectively. This study was reviewed by the IRB and informed consent from the patient was compulsory for her to be included in this trial.

Results: The incidence of infection in group A was 0.5% and in group B was 0.4% (P=0.14). The incidence of febrile neutropenia was 12% (A) versus 10% (B) (P<0.09). We could not find the significant differences in grade 4 neutropenia nor leukopenia after G-CSF with without ciprofloxacin.

Conclusions: The use of ciprofloxacin was not helpful to reduce systemic infection nor neutropenia after TAC chemotherapy. Even though larger number of patients should be enrolled to get the definite power to delineating the protective role of ciprofloxacin against infection or neutropenia, we do not think that ciprofloxacin itself gives additional advantage to patients having TAC chemotherapy to go through all cycles with fewer adverse reactions.

198P WEEKLY EPIRUBICIN IN PREGNANT BREAST CANCER PATIENTS: A COOPERATIVE STUDY ON 20 PATIENTS

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Background: Gestational breast cancer (GBC) is a rare disease, with less than 3% of breast cancers diagnosed during pregnancy.

Methods: Single agent weekly Epirubicin, at an average dose of 35 mg/m^2 was administered because of shorter terminal half-life and lower cardiotoxicity compared to Doxorubicin. Patients (pts) were eligible if they had locally advanced or metastatic disease, high risk of recurrence after surgery and pregnancy between 16 and 30 weeks of gestational age.

Results: 20/88 pts with GBC were treated with weekly Epirubicin since 1.2002. Median maternal age was 37 years (23-42). Median gestational age at chemotherapy was 19 weeks (16-30). 13/20 pts were treated after surgery because of high risk of relapse. 5/13 pts had positive axillary nodes, with 3 having >5 positive nodes. 6/20 pts had locally advanced tumours and 1 patient had a locally advanced tumour with synchronous liver metastases. 10/20 pts had endocrine responsive diseases, with 4/20 over expressing HER-2. Ki-67 was >20% in 13/15 pts. Mean total Epirubicin dose was 420 mg/m^2 with a median number of 12 (4 -16) administrations. No G3-4 toxicities were observed. Chemotherapy was administered with thorough fetal monitoring, and no adverse fetal effects were observed, but 1 premature delivery at 28 weeks. Births were induced by caesarean section in 12/20 pts at a median gestational age of 35 weeks (28-40). 2/20 newborns required neonatal intensive care, but none had pulmonary, cerebral or infectious complications. No malformations were observed, except 1 newborn with polycystic kidney. With a median age of 2 years (0-4), neurological and immunological development was normal in all 20 children, as reported by parents. In the 7/20 pts with evaluable disease, 5/7 had an objective response. With a median follow-up of 38 months, 17/ 20 pts are alive, 14/17 disease free.

Conclusions: Weekly Epirubicin is a safe and effective in pregnant breast cancer pts who need chemotherapy, with low acute toxicity for the fetus. A cardiology follow up is planned for all children, to exclude late onset of cardiac damage.
abstracts

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ANTHRACYCLINE-BASED CHEMOTHERAPY FOR BREAST CANCER - PREDICTIVE FACTORS OF DOSE INTENSITY REDUCTION

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Introduction: Adjuvant chemotherapy with an anthracycline-based regimen is considered standard for treatment of breast cancer (BC). There is good evidence that reduction in relative dose intensity (RDI) result in loss of clinical benefit. This study was undertaken to define predictive risk factors for reduced RDI.

Methods: A retrospective study was conducted between 1998 and 2007. Information on 631 BC patients (pts) was available. Pts under anthracycline based-chemotherapy regimens were not candidates for primary G-CSF prophylaxis. DIEEE® software (Dose Intensity Evaluation Programme) was developed to allow calculation of RDI, and includes demographic data, clinical and treatment characteristics, chemotherapy dose modifications and delays, haematological toxicities and patterns of use of G-CSF. Univariate and multivariate analysis was employed to identify factors related to RDI < 90% of standard. A value of p < 0.05 was considered of statistical significance.

Results: Pts distribution according to chemotherapy: doxorubicin/cyclophosphamide (A06 C400) - 17%, 5-fluorouracil/cyclophosphamide (F500 E100 C500) - 22.5%, 5-fluorouracil/adriamycin/cyclophosphamide (F500 A50 C500) - 60, 5%. Median RDI was 97% in AC, 94.6% in FEC and 97.1% in FAC. RDI < 90% was delivered in 139 (22%) pts. According to univariate analysis, factors related to reduction of RDI were: age > 65 years (p = 0.035), number of patients with at least one G-CSF administration on secondary prophylaxis (p = 0.013), number of patients with at least one G-CSF administration due to neutropenia or febrile neutropenia (p = 0.001) and FEC regimen (p < 0.001). In multivariate analysis, independent predictors of RDI < 90% were: FEC regimen (p < 0.001), age > 65 years old (p = 0.027) and secondary G-CSF prophylaxis (p = 0.002).

Conclusion: A significant proportion of BC pts treated with anthracycline based-chemotherapy, in particular older pts and those treated with FEC regimens, have an important reduction of RDI. G-CSF secondary prophylaxis does not avoid dose reduction. These subgroups of BC pts might be candidates for primary G-CSF prophylaxis.

Acknowledgments: The authors wish to thank AMGEN (Portugal) for supporting the DIEEE database.

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PRELIMINARY DATA OF GENE EXPRESSION PROFILING FOR THE PREDICTION OF RESPONSE TO ANASTROZOLE IN PRIMARY BREAST CANCER

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Background: We evaluated the potential role of oligonucleotide microarrays in patients receiving primary endocrine therapy (ET) to identify the molecular signatures associated with tumor sensitivity/resistance and the changes in the gene expression profile after ET.

Methods: In post-menopausal women with large (>2.5 cm) ER positive breast cancer we administered anastrozole 1 mg/d for 12 weeks before surgery. Clinical response was evaluated by breast ultrasound measurements during the neoadjuvant treatment.

Expression profiling analysis was conducted on pre-treatment and post-treatment biopsies. Sample pairs from 16 patients provided sufficient and good quality RNA for hybridization on human whole genome 44K oligonucleotide microarrays (Agilent Technologies), using a pool of tissues as common reference and a dye-swap duplication scheme.

Results: Nine out 16 patients obtained a PR and 7 were stable after primary ET according to RECIST criteria. Conservative surgery was performed in 14/16 patients.

Unsupervised analysis revealed the presence of specific patterns of differential expression, one of which showed a slight association to clinical response. In particular, sensitive tumors had higher expression of a group of genes involved in estrogen metabolism and response to xenobiotic stimuli. Changes in gene expression were seen before and after anastrozole treatment and during the presentation this analysis will be updated and presented.

Conclusion: Our findings identify a possible transcriptional signature associated with anastrozole sensitivity in breast cancer patients. Further analyses are needed to confirm this preliminary data.

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COMPARISON OF ADJUVANT! ONLINE SURVIVAL PREDICTION WITH THE 10-YEAR FOLLOW-UP RESULTS ACCORDING TO THE PR-STATUS IN SLOVENIAN EARLY BREAST CANCER PATIENTS

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Background: In the era of targeted therapy it is difficult to make an appropriate decision for individualized treatment of early breast cancer (EBC) patients. Adjuvant online computer program can make this decision easier. It is well known that HR influence EBC prognosis and treatment results; however, Adjuvant! takes into account only ER but not PR. Aim: To evaluate the difference between predicted overall survival by Adjuvant! and observed OS on the overall data set of Slovenian EBC patients, and also according to the PR status.

Methods: 245 EBC patients diagnosed and primary treated in the year 1997 at the Institute of Oncology Ljubljana were included. All patients had radical local therapy, and adjuvant systemic therapy was given according to the then current guidelines. The basic clinicopathological characteristics were assessed routinely. HR was determined biochemically (cutoff 10 fmol/mg protein). For the overall data set and for both PR-defined subsets the 10-year OS were calculated. For the same data, the average Adjuvant! (Version 8.0) predicted OS were calculated, and the observed and predicted OS were compared.

Results: The predicted 10-year OS for the overall data set of 245 EBC patients (median age 56 years) was 64.5%, while the observed OS was 62.4%. The predicted 10-year OS for PR-positive (n=133) was 68.4% and the observed OS was 69.2%. The predicted 10-year OS for PR-negative patients (n=112) was 60.0% and the observed OS was 54.5%. The differences between predicted and observed OS were within tolerable limits for the overall data set and for the PR-positive subset (2.1% and 8.8%, respectively), but no so for the PR-negative subset (5.5%).

Conclusions: Adjuvant! is a reliable tool for prognosis assessment of Slovenian EBC patients. However, our data also indicates that Adjuvant! seems to overestimate OS for PR-negative patients. While it is not realistic for PR status to be included into the Adjuvant! model due to lack of data, the clinicians should be aware that Adjuvant! predictions can be misguided when they are evaluating prognosis and deciding on treatment for PR-negative EBC patients.

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FEASIBILITY OF USING CORE NEEDLE BIOPSIES FOR THE 70-GENE PROGNOSIS SIGNATURE

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Introduction: A 70-gene microarray prognosis signature was previously discovered to improve the selection of patients with lymph-node negative disease for adjuvant therapy. This diagnostic test known as “MammaPrint™” was recently validated in an independent cohort and implementation was shown to be feasible in community hospitals. However, most breast cancer patients will undergo core needle biopsies. We investigated whether the 70-gene prognosis signature could be assessed from core needle biopsies.

Patients and methods: We determined the negative and positive predictive value of the MammaPrint assay in patients with breast cancer stage II-IIIII presenting to 4 ONCAMI hospitals from November 2006 up to present who had core needle biopsies (14-gauge) and subsequent neo-adjuvant treatment with 6 courses of doxorubicin (50 mg/m2) plus docetaxel (75 mg/m2) given every 21 days with G-CSF support. Core needle biopsies from 52 patients before treatment were subjected to microarray expression analysis using the 70-gene prognosis signature and were classified as being at either low or high risk. The results of this study have been broadened the clinical applicability of the MammaPrint prognosis signature.
MAMMAPRINT®: PREDICTIVE TOOL OF RESPONSE AND RESISTANCE TO PRIMARY CHEMOTHERAPY IN ELDERLY BREAST CANCER (BC) PATIENTS

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Background: gene expression analyses, such as Mammaprint®, are a promising approach for predicting future behaviour of tumours and for defining responsiveness to chemotherapy by interrogating the molecular signature of BC. The neoadjuvant approach for predicting future behaviour of tumours and for defining responsiveness to chemotherapy is currently the groundwork to developing a novel platform for micrometastasis detection with potential predictive and prognostic role. However, more studies are warranted.

Methods: 13 women with T2-4 N0-1, estrogen receptor positive BC were treated with Letrozole (U 25 mg/daily) and oral "metronomic" cyclophosphamide (50 mg daily [LC]). Mammaprint® test was performed by Agenda on tumour tissues, previously stored in RNA later, obtained at the diagnosis through incisional biopsy. Clinical response was measured by caliper by the same clinician, before and after treatment. All tested tumours were ductal and G3.

Results: 7 out of 13 valuable patients attained a clinical complete response (CR) whereas 5 did not respond (NR). Mammaprint® classified 4 patients as "low risk" and 9 women as "high risk". The "low risk" was confined to T2C to T2G cm. All patients underwent to a CR (1 pCR) and a great reduction of Ki67 after treatment (median BT: 16.7; AT: 2.3). The "high risk" profile was linked to T2-2 cm. 5 patients out of 9 showed NR with low reduction of Ki67 expression after treatment. 4 patients obtained a CR but with less pronounced reduction of Ki676 expression as compared to "low profile" (median BT: 9.5; AT: 4). 2 patients classified as "high risk" showed a disease progression at bone level after 2 months.

Conclusions: Small sample size limits the generalization of the results but our observations suggest that Mammaprint® assay can be not only a promising prognostic but also a predictive factor for cytotoxic drug activity. Moreover, the microarray gene expression profiling can be used to develop models with the ability to optimize the decision-making process for the appropriate application of adjuvant therapy. However, more studies are warranted.

A COMPARISON OF 18F FDG -PET AND MRI IN THE PREDICTION OF PATHOLOGICAL RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER (BC): FINDINGS FROM THE ARIANNA 01 PROJECT

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Background: Pathological complete remission to primary chemotherapy (PST) correlates with a better prognosis. The primary aim of this study is to compare FDG PET and MRI in the prediction of pathological response to primary anthracycline- and taxane-based PST for BC.

Patients and methods: Thirty T2-4 N0-3 BC pts were enrolled. MRI and PET scan were done at baseline, every 2 courses and at the end of PST. Metabolic response was measured by SUVmax within the primary lesion and by % SUVmax decrease. According to ROC curves analysis we considered as PET response a decrease >25% and >20% of SUV max after the 2nd cycle and the end of PST. MRI response was defined as partial or complete remission according to WHO criteria. Pathological response was evaluated according to Miller and Payne, from grade 1 (no response) to grade 4-5 (only small clusters or no malignant cells).

Results: After PST we observed 40 % grade 4-5 pathological responses. A PET response was observed in 63% and in 66% of pts after 2 cycles and at the end of PST. The corresponding figures for MRI were 37% and 88%. PET responses after 2 cycles of PST (83% vs 33%, p<0.01) and at the end of PST (100% vs 55%) were more frequent in pts who obtained a grade 4-5 pathological response, while MRI responses were not.

Conclusion: a decrease of SUVmax ≥ 65% after the 2nd cycle of PST is significantly more frequent in grade 4-5 pathological responders (p<0.01) with a PPV of 86%, higher than that of MRI (68%). Therefore we can exclude with high probability an optimal pathological response in pts who do not obtain a 25% reduction in SUVmax after 2 courses of PST. PET is more accurate than MRI also at the end of PST: the absence of a PET response excludes a grade 4-5 pathological response (PPV 100%), but a PET response cannot rule out a cancer residual (NPV 55%).
The VEGF C36T and G634C polymorphisms affect the expression of the vascular endothelial growth factor (VEGF) gene in breast cancer (BC) cells. The cells also produce the angiogenic protein endothelin (ET), which may be involved in the angiogenesis of breast tumors. The polymorphisms may influence the risk of breast cancer development. However, the interaction between VEGF C36T and G634C polymorphisms and breast cancer risk is not well understood. The aim of this study was to investigate the relationship between the VEGF C36T and G634C polymorphisms and the risk of breast cancer in the Italian population. A total of 592 breast cancer patients and 592 healthy controls were included in the study. The genotypes were determined by PCR-SSP assay. The results showed that the frequency of the C36T allele was significantly higher in the breast cancer group compared to the control group (p = 0.03). The frequency of the G634C allele was also higher in the breast cancer group compared to the control group (p = 0.04). The frequency of the TT genotype was significantly lower in the breast cancer group compared to the control group (p = 0.02). The frequency of the CC genotype was significantly higher in the breast cancer group compared to the control group (p = 0.01). The results suggest that the VEGF C36T and G634C polymorphisms may be associated with the risk of breast cancer in the Italian population.
RETURN TO WORK AFTER BREAST CANCER: WHY NOT? PREDICTORS FACTORS AND IMPACT ON QUALITY OF LIFE IN A PROSPECTIVE MONO-CENTRE RESEARCH

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The work experience of women who have had a breast cancer (BC) is still an unexplored area of survivorship research. The purpose of the present longitudinal mono-centre study was to investigate whether socio-economic, disease- and/or treatment-related factors were associated with the ability of returning to work in a sample of 146 consecutive patients treated at our Institution for early BC who were working at the time of diagnosis. The research three main goals were 1) to evaluate the percentage of women returned to work after 24 months from diagnosis in the cohort of survivors, 2) to identify risk factors associated with the ability of patients to continue their employment, 3) to quantify work disability that survivors associated with cancer and its treatments. At 24-month analysis, 97 out of 131 eligible women (74%) had returned to work. Most were state-employed (85%), full-time working in 69% of cases, and > 60% did an intellectual job; 69% benefited from flexible hours working. Discrimination because of cancer diagnosis was reported by 35% of patients and occupational intervention by 25% of re-employed women. Among the 34 women who had not returned to work after 24 months from diagnosis, 35% were sick-listed, 30% received a disability work pension, 23 were early retired, and 12 were out of work. Statistical analysis showed that the duration of disease (odds ratio= 2.96; 95%CI 1.25 to 7.03) and the nature of work (odds ratio= 3.9; 95%CI 1.57 to 9.82) are the strongest predictors of work disability. Analysis of factors related to quality of life and quality of work (EORTC QLQ-C30, EORTC-B23, FACT-an and VBRRA validated questionnaires) suggest that fatigue adversely affected the return to work in our sample, while perceived good quality of job was associated with a greater likelihood of work resumption. Our results confirm that work disability after BC remains a critical issue: strictly disease- and work-related variables can significantly affect the probability of return to work, also involving remarkable socio-economic aspects. There is a need of improving social support and rehabilitation to BC, for which returning to work is an important measure of recovery from the disease and a positive step toward the future.

MUSCULOSKELETAL COMPLAINTS AND ADJUVANT AROMATASE INHIBITOR (AI) THERAPY

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Background: Musculoskeletal complaints are common in postmenopausal women (PMW) and are related to estrogen deprivation. Not surprisingly, these problems are also reported in PMW receiving adjuvant endocrine therapy. These problems are often described differently by patients and reflected in various adverse events reported, making it difficult to evaluate across trials.

Methods: The incidence of musculoskeletal problems in phase 3 clinical trials of AIs (anastrozole [ANA], letrozole [LET], and exemestane [EXE] vs tamoxifen [TAM]) (ATAC, BIG 1-98, IES) or placebo (PLA) (MA.17) and in several small AI studies were evaluated.

Results: Among women taking Ana, ady, stiff joints and joint pain were the most frequent complaints and have been reported to cause discontinuation of AI therapy. The incidence of arthralgia was significantly greater with ANA in ATAC at 68 months (35.6% vs 29.4%; P=0.0001), with LET in BIG 1-98 at 25.8 months (20.3% vs 12.3%; P=0.0001), and with EXE in IES at 55.7 months (18.6% vs 11.8%; P=0.0001). Myalgia was not reported in ATAC, but the incidence was similar with LET vs TAM in BIG 1-98 at 25.8 months (6.4% vs 6.1%; P=0.61). In IES, EXE was associated with more musculoskeletal pain (25.7% vs 20.3%; P=0.0001) and joint stiffness (1.8% vs 1.0%; P=0.009). Carpal tunnel syndrome was more common with ANA in ATAC (3% vs 1%; P=0.0001) and EXE in IES (2.8% vs 0.3%; P=0.001). Compared with PLA in MA.17, there was significantly more myalgia (25% vs 21%; P=0.001) and myalgia (15% vs 12%; P=0.004) with LET, but not bone pain (5% vs 6%; P=0.67). Higher rates of AI-related joint pain (47%) and joint stiffness (44%) have been reported in clinical practice than in clinical trials. Measures can be taken to manage these problems. Results from AIQUOT showed that >50% of patient with joint symptoms on one nonsteroidal AI do not experience symptoms on the other nonsteroidal AI. Analgesics and glucocorticoids may also reduce bone pain.

Conclusions: Musculoskeletal complaints are common but can be managed by analgesics, anti-inflammatory agents, and lifestyle changes. Also, changing from one nonsteroidal AI to another may reduce joint symptoms. Thus, the benefits of adjuvant AI therapy may be maintained.

DEVELOPMENT AND IMPLEMENTATION OF NEW UK NATIONAL CANCER RESEARCH INSTITUTE (NCRI) GUIDELINES FOR PREVENTING AND MANAGING CARDIAC EVENTS WITH TRASTUZUMAB

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Background and aims: The development and introduction of adjuvant trastuzumab (Herceptin™) has significantly improved outcomes for women with HER2+ breast cancer. Current guidelines for identifying and managing cardiac events were developed as part of the adjuvant trastuzumab clinical trial protocols, and are not necessarily appropriate for use in routine clinical practice. Consequently, some women who may benefit from trastuzumab without long term adverse cardiac sequelae do not receive, or do not complete a full course of, HER2-targeted therapy. Trastuzumab is not intrinsically cardiotoxic, and reductions in left ventricular ejection fraction are almost always reversible, yet the cardiac mortality guidelines developed for trial use result in some women failing to benefit fully from trastuzumab treatment.

Methods: A group of specialist breast cancer oncologists, cardiology specialists, and a cardiovascular lead general practitioner reviewed the current guidelines and trastuzumab safety data. Applying the knowledge gained from the clinical trial data and current understanding of the mechanisms of the cardiac effects of trastuzumab, the group set out to draft interventional guidelines that promote a proactive approach to identifying and managing cardiac events in patients with breast cancer who are likely to receive standard cytotoxic chemotherapy and trastuzumab.

Results and conclusions: Key recommendations include a proactive monitoring and cardiac assessment schedule at baseline, (pre-chemotherapy), before and during trastuzumab therapy. Rather than taking the purely observational approach employed in trastuzumab clinical trials, the guidelines advocate a pharmacological intervention strategy for managing alterations in cardiac function before and during treatment, based on a more multidisciplinary approach. Simpler rules are suggested for starting, interrupting and discontinuing trastuzumab. The guidelines have been peer-reviewed and endorsed by the NCRI, and might also be used to monitor cardiac function in patients treated with other HER2-targeted therapies.

TRASTUZUMAB THERAPY FOR EARLY BREAST CANCER IN THE REAL-WORLD

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Background: Various trials have shown substantial benefits of addition of Trastuzumab (Herceptin®) to adjuvant chemotherapy in Early Breast Cancer (EBC). Our breast oncology unit is a tertiary centre catering to screen detected and symptomatic cancers. The target breast screening population is 245,000 women. We analysed our breast cancer population to determine the number of patients eligible for and receiving trastuzumab treatment in EBC.

Methods: Data for all patients diagnosed with EBC in 2006 was recorded prospectively in a database. Case notes were consulted where the HER2 positive patients, determined by a combination of IHC and FISH, had not received trastuzumab, to ascertain the reasons.
Results: A total of 951 patients were diagnosed with Breast Cancer in 2006. 417 (43.9%) of these were screen-detected cancers. There were 123 (12.9%) HER2 positive newly diagnosed Breast Cancers of whom 117 were EBCs. Fifty nine (50.4%) of the HER2 positive EBCs received trastuzumab therapy.

Reason for not receiving trastuzumab: |
<table>
<thead>
<tr>
<th>Reason for not receiving trastuzumab</th>
<th>No. of patients</th>
<th>% of HER2 EBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low risk (tumour ≤ 10 mm / small node negative)</td>
<td>20 (14 / 6)</td>
<td>34.5</td>
</tr>
<tr>
<td>Age and other co-morbidities</td>
<td>7</td>
<td>12.1</td>
</tr>
<tr>
<td>No chemotherapy received</td>
<td>7</td>
<td>12.1</td>
</tr>
<tr>
<td>Patient non-compliance</td>
<td>3</td>
<td>5.2</td>
</tr>
<tr>
<td>Cardiac problems</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Occult primary</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>No surgery</td>
<td>2</td>
<td>3.4</td>
</tr>
<tr>
<td>Total</td>
<td>58</td>
<td>49.6</td>
</tr>
</tbody>
</table>

Conclusions: The HER2 positivity rate is lower than that previously reported. Only 50% of HER 2 positive EBC patients received trastuzumab therapy. Of those who did not receive trastuzumab, the commonest reason was low risk status or age and co-morbidities precluded chemotherapy. HER 2 positivity alone confers high risk irrespective of pathological stage. Further trials are required to evaluate whether the substantial number of patients who are at present not eligible for trastuzumab therapy might also benefit.

ADJUVANT ZOLEDRONIC ACID (ZOL) THERAPY DECREASES THE PREVALENCE OF DISSEMINATED TUMOR CELLS (DTCs) IN BONE MARROW (BM) OF PATIENTS WITH EARLY-STAGE BREAST CANCER (EBC): 2 YEAR RESULTS

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Background: DTCs in BM, particularly after adjuvant therapy, are associated with distant recurrence (DR) and death in EBC patients. Bisphosphonates exhibit antitumor activity via various mechanisms including inhibition of angiogenesis, reduction in tumor cell proliferation, and induction of tumor cell apoptosis. Clodronate reduced the incidence of metastases and improved survival in patients with DTCs in BC diagnosis. This pilot study is designed to evaluate ZOL in patients with EBC with DTC. Decrease in DTCs may serve as a clinical surrogate marker for antitumor effect.

Methods: Eligible patients have stage I-III BC and > 4 DTC/mL BM (2.5 standard deviations > 50 normal BM samples; Park, Proc ASCO, 2002) after neoadjuvant or adjuvant therapy. DTCs are detected by immunomagnetic BM enrichment using anti-epCAM-PE, then by flow cytometry for EPCAM, CD45, and nucleic acid content. Patients receive 4 mg IV ZOL monthly for 2 yr. Concomitant hormone therapy is allowed. Serum creatinine and toxicity are evaluated monthly; urinary N-telopeptide at 0, 2, 4, 6, 12, and 24 mo; peripheral blood (PB) DTCs at 6, 12, 18, and 24 mo. BM aspirations are repeated at 1 and 2 yr for DTC measurement.

Results: 45 patients were enrolled. Interim analysis of baseline, 1-yr, and 2-yr BM data is presented here. Mean baseline DTCs are 25.6/mL (range 4.9-332) and mean follow-up of 15.6 months. At baseline, 12/17 (71%) patients had a DTC decrease (P = .0018). At 2 yr, 12/17 (71%) patients had a DTC decrease (P = .01). 5 BC patients with > 1 yr ZOL, 32 had BM assessments at 1 yr; 25/32 (66%) had a DTC decrease (P = .04). At 2 yr, 12/17 (71%) patients had a DTC decrease (P = .01). 5 BC cases occurred in the first yr (average time to recurrence 5.2 mo); all were node+ and negative for ER, PR, and Her2. 26/43 patients had detectable baseline PB DTCs (mean 0.4/mL; range 0-8.6), and PB-DTC analysis is ongoing. ZOL was well tolerated, with only 1 patient stopping therapy due to side effects.

Conclusions: DTCs can be detected in BM and PB from patients with EBC. High baseline DTCs in BM predict early DR, and DTCs decreased during the treatment period. This 2-yr data suggest that ZOL treatment decreases the prevalence of DTCs in EBC. Updated data from this study will be presented.

Conclusions: High baseline DTCs in BM predict early DR, and DTCs decreased during the treatment period. This 2-yr data suggest that ZOL treatment decreases the prevalence of DTCs in EBC. Updated data from this study will be presented.

BREAST CANCER IN PATIENTS UNDER 35 YEARS OF AGE: OUR EXPERIENCE

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Background: Breast cancer (BC) in young women represents 2% of cases. The presentation, behaviour and prognosis of BC in such patients (pts), when compared with older women, are unclear and conflicting results have been reported.

Objective: To describe clinical, pathological and biological features in women aged 35 and under with BC.

Methods: We reviewed the records of 45 women aged 35 years or less, with diagnosis of BC in our site, between 1999 and 2007. Epidemiological profile, risk factors, diagnosis, treatment, prognosis and mortality of BC was analyzed in this population of young pts.

Results: 22% out of the 45 pts analyzed in this report, had familiar history of BC. The first symptom was a painless lump (73%) with delay in diagnosis in 44% of the cases (mammography or ultrasound interpreted as benign or negative, previous treatments for benign pathologies). Only 13.3% (6 pts) were diagnosed by screening techniques. Tumor stage at diagnosis was stage I 35.3%, stage II 37.7%, stage III 16.7%, and stage IV 10.7%.

Conclusions: Her2 positivity rate is lower than that previously reported. Only 13.3% (6 pts) were diagnosed by screening techniques. Tumor stage at diagnosis was stage I 35.3%, stage II 37.7%, stage III 16.7% and stage IV 10.7% in 84.4% of the pts (breast preservation in 55%). 51% of the women who underwent axillary surgery had lymph node involvement, 44% of the tumors sized between 2cm and 5cm, and 73% were invasive ductal carcinoma. Hormone receptors were positive in 33 cases (73%) and Her2/neu overexpression showed up in 8 tumors (17.7%). Postoperative radiotherapy was given to 28 pts (62%), while 32 (71%) received chemotherapy with anthracylines. Disease free survival (DFS) of 24 months was achieved in 48% of the women in this study, although most of them are still in follow up. Only 4 pts of this group died of BC.

Conclusions: 48% of pts had 2 year DFS, and only 17.7% developed distant metastases (bone and lungs as most frequent sites). Although we found that delay at diagnosis was highly frequent in this population, tumors were not as advanced as expected. In our experience, behaviour of BC in young women is not as aggressive as the literature reports.

BREAST CANCER IN THE ELDERLY: TREATMENT AND SURVIVAL PATTERNS

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Introduction: Breast cancer (BC) is the most common malignancy in women. Half of new cases of BC is diagnosed after 65 years old. We purpose to identify patterns of treatment and follow-up, evaluating differences between younger (65-74 years old) and older pts (≥ 75 years old).

Methods: Retrospective study based on clinical records of pts older than 65 years admitted with BC from January 2003 to January 2005. Demographic and clinical data was collected, including follow-up information. Differences between age groups were evaluated by univariate analysis. Survival analysis was performed by Kaplan-Meyer method, differences between subgroups evaluated by log-rank test and Cox Regression for identification of independent predictors of survival.

Results: Data from 414 pts was analysed. 71% of pts were younger than 74 years old. Median age was 71 years old. There was no difference between groups according to TNM stage and hormonal receptors status. Only 6% of the older group pts was submitted to conservative surgery, comparing to 33% of pts in the younger group (p<0.001). Chemotherapy was administered to 13% pts in the older group, comparing to 40% of pts in the younger group (p<0.001). Overall survival at the end of follow-up was 85%, with a statistical significant difference (p=0.02) between age groups 65-74 (90%) and ≥ 75 (67%). Pts with higher ECOG, with tumours at advanced stage and negative hormonal receptors had worse overall survival (p<0.001). A statistically significant difference persisted in the overall survival for age group adjusted for hormonal receptor (p=0.002) and for stage (p=0.03). A multivariate Cox Regression identified as independent prognostic factors for overall survival: TNM stage (p<0.0001) and hormonal status (p<0.0001), and, for disease free survival: ECOG (p=0.006) and TNM stage (p<0.0001).

Conclusions: For older pts with BC TNM stage is the single more important factor related to survival. Older pts and those with ECOG ≥1 have a dismal prognosis even after adjusted for other prognostic related variables. That may be related to a less aggressive treatment.
FATIGUE, QUALITY OF LIFE (QOL) AND COGNITIVE FUNCTION IN PATIENTS TREATED WITH ADJUVANT CHEMOTHERAPY (ACT) AND/OR RADIOTHERAPY (RT) FOR LOCALIZED BREAST CANCER (LBC): A FRENCH LONGITUDINAL STUDY

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Most LBC patients given ACT complain of fatigue during or after RT. They also report cognitive function disorders and decrease in QoL.

Methods: A longitudinal study was performed to compare QoL, fatigue and cognitive function changes with time after ACT and RT (Group 1) or RT alone (Group 2). Assessments were made before, during, at the end of, 4 and 12 months after RT. Instruments were the FACT-G (Qol) with breast and fatigue modules, and the HADS; the MMSE, Digit Span, Trail Making Test and Rey Auditory Verbal Learning Test were used to assess cognitive functioning. Biological tests were performed included blood count, inflammatory markers (IL6, TNFα, CRP), TSH, FT4 and anti-TPO and anti-TG antibodies.

Patients: From May 2004 to December 2006, 302 patients were enrolled, 161 in Group 1 and 141 in Group 2. At entry, major differences between groups were: mean age 52 vs 58 years; menopause 23% vs 1%, use of psychotropic support 23% vs 8.5% in Group 1 and 2, respectively.

Results: Before RT, 60% of Group 1 patients expressed fatigue vs 33% (p<0.001). After RT, these proportions were 61% vs 33% (p=0.1). Although fatigue improved with time, it remained present in more than 40% of patients at 12 months. No biological disorders were observed in patients with or without chronic fatigue. Anxiety was present before and after RT in 30% of patients in both groups. In contrast, depression was more frequent in Group 1 patients: 28% vs 16% (p=0.03) before RT; at the end of RT, 25% of patients expressed depression in both groups. Fatigue and depression levels correlated (p<0.001). While significant differences (p<0.02) in QoL parameters were present before RT, with better scores in Group 2 patients, differences disappeared at 12 months. Fatigue scores were significantly lower (p<0.01) in Group 2 patients. Results on cognitive functions will be presented at the meeting.

Conclusion: Almost half of breast cancer patients undergoing RT express high fatigue even 1 year after the end of treatment. Fatigue is correlated with depression. However, no biological disorders are observed that can explain chronic fatigue.

HIGH-DOSE CHEMOTHERAPY (HDCT), PERIPHERAL BLOOD PROGENITOR CELL TRANSPLANTATION (PBPC) AND IMMUNOTHERAPY IN THE TREATMENT OF HIGH-RISK EARLY BREAST CANCER (HRBC)

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Background: A meta-analysis has shown that HDCT with PBPC is not superior to standard dose chemotherapy in the treatment of HRBC. The reason for the limited efficacy is due to failure to eradicate all cancer stem cells, resistant to chemotherapy, and capable to reproduce the tumor in immunodecient mice. Lymphopenia has been described after HDCT. We have previously shown that low dose interleukin-2 (IL-2) and oral 13-cis-retinoic acid (RA) improved lymphocyte (L), natural killer (NK) cell count, CD4+/CD8+ ratio and decrease vascular endothelial growth factor (VEGF), of patients with advanced tumors having a clinical beneft from chemotherapy. Primary endpoint of this pilot study was to verify if IL-2 and RA could improve L and NK cell count, CD4+/CD8+ ratio, and decrease VEGF of patients with HRBC (stage III disease with >10 axillary nodes). Secondary endpoints were the evaluation of progression-free survival (PFS) and overall survival (OS).

Methods: From 02-1998 to 02-2003, 30 patients were entered into the study. One month after HDCT, patients received, for 1 year, 5 days/week, 3 weeks/month, subcutaneous IL-2 (1.8 x 107 IU daily) plus RA (6.5 mg/kg body weight).

Immunotherapy was continued, with intermittent schedules, up to 5 years. Estrogen receptor positive (ER+) received hormonal therapy and premenopausal patients a LH-RH analogue for 5 years.

Results: Patients characteristics: median age, 48 years (range 34-68); performance status 0-1 in all patients; median number of positive axillary nodes, 13 (range 10-27); ER/ER+ 20/10. Major adverse effects from IL-2 were fever, rash and autoimmune reactions; no treatment related mortality was seen. After a median follow-up of 41 months, a statistically signifcant improvement of L and NK count, CD4+/CD8+ ratio and decrease of VEGF were observed. 5 years PFS and OS rate were 76% and 85%, respectively.

Conclusions: These data show that IL-2 administration after HDCT and PBPC is feasible, has a moderate toxicity, gives a statistically signifcant improvement of L and NK count, CD4+/CD8+ ratio, a decrease of VEGF, and seems to give an increased expectation of PFS and OS.

BRAIN METASTASES DURING ADJUVANT TRASTUZUMAB TREATMENT

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Background: Approximately 30% of patients with HER-2 positive breast carcinoma develop brain metastases, usually during first two years of metastatic disease. According to the literature data, 3% of all breast cancer patients have brain metastases as first metastatic site. It is speculated that HER-2 positive status is involved in greater risk for brain metastases. To the best of our knowledge, the incidence of brain metastases as the first relapse site during adjuvant Herceptin treatment is not known. The aim of this paper is to explore the incidence of asymptomatic brain involvement in high risk breast cancer patients during adjuvant Herceptin treatment.

Patients and methods: From September 2006 to March 2008, 99 patients with HER-2 3+ breast cancer were treated with adjuvant three weekly Herceptin. HER-2 status was determined by IHC (Hercept-Test, DAKO). HER-2 3+ was treated by CISH method. (CISH n=119/99 pts. 11,1%). All patients were premenopausal, median age 43 yrs (range 28-53). 29% of patients were node negative, Median number of positive nodes was 4 (range 1-25). Median time to Herceptin initiation was 7 weeks (range 6-9 weeks) after last adjuvant chemotherapy cycle.

Neurological symptoms were present only in one patient. Brain CT was performed in 73/99 patients (73,7%).

Results: At the time of brain CT, median number of Herceptin cycles was 10 (range 1-18). Median time after initial breast cancer diagnosis was 13 months (range 8-25) There are 5 pts. with abnormal brain CT Brain metastases was confirmed in one patient who has a rapid disease progression after 7 doses of Herceptin with lungs and liver metastases, all diagnosed within few days. Another patient has highly suspicious CNS metastases registered after 3 doses of Herceptin. This patient is without any neurological symptoms and close follow up is recommended by neurosurgeon. Third patient is diagnosed with breast tumor, most likely meningoma, with no neurological symptoms, and close follow up is recommended by neurosurgeon.

Conclusion: In our group of high-risk patients only one developed brain metastases during adjuvant Herceptin treatment (1%) and another patient has a highly suspicious CNS metastases that could not be confirmed or ruled-out at this moment.

DETERMINING THE OPTIMAL TIMING AND DURATION OF THE USE OF AN AROMATASE INHIBITOR (AI) IN THE ADJUVANT TREATMENT OF POSTMENOPAUSAL HORMONE RECEPTOR-POSITIVE (HR+)/BREAST CANCER (BC) USING MODELLING ANALYSES

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Introduction: AIs are more effective than tamoxifen (TAM) in the adjuvant treatment of postmenopausal HR+ BC, with a lower overall mortality benefit regarding the efficacy of the different AIs and the timing of treatment. It is unclear if they should be offered as the initial adjuvant treatment or after an initial “priming” with TAM, when relative benefits appear to be larger.

Methods: Models based on published data from 8 trials evaluate the use of an AI upfront vs sequencing it after varying periods of initial TAM treatment. We model recurrence rates for the first 10 and 20 years of follow-up using only the reported hazard ratios. Historically, carryover effect had only been demonstrated with TAM (EBCTCG overview); however, it is now reported to be significantly greater with AIs [1].

Results: Models indicate that initial or early treatment always dominates a strategy of using TAM for 5 years initially. Using current data to estimate hazard ratios suggests that starting with an AI dominates a 2-year initial use of TAM followed by 3 years of an AI, although the reduction in hazard ratios after switching may be larger after the switch has taken place. Based on data from the recent trials and treatment studies of 5 years of an AI after 5 years of TAM, and the ATLAS study of 5 vs 10 years of TAM, we also model a range of 10-year treatment plans.

Conclusions: Current evidence suggests that use of an AI upfront, in the first 5 years of adjuvant treatment, is the best strategy. The BIG 1-98 trial, comparing upfront vs sequencing, will provide additional information regarding the optimal time to introduce an AI. Available evidence also supports continued treatment beyond 5 years in some patients, but no data exist on the optimal duration of treatment with an AI. Reference [1] Aminode, Tamoxifen, Alone or in Combination Trials’ Group; Forbes JF, Cuzick J, Budzar A, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. Lancet Oncol 2008;9:43-55.
Background: HER-2/neu status of breast cancer (BC) is determined by immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH). Numerous reports have been published identifying discrepancies between IHC and FISH methods from different manufacturers, as well as tissue processing, reagent variability, antigen retrieval methods, scoring interpretation, tumor heterogeneity, and the semiquantitative nature of the test. The objective was to compare the results of HER-2 assessment by IHC and FISH in patients (pts) with BC being considered for trastuzumab therapy.

Methods: For HER2 status review, IHC was used with a polyclonal antibody (CB11-1/5000), antigenic recovery, diamino benzidine (Dako) and ENVISION system of detection (DAKO). Manual method per protocol of work was used (National Plan Her2). The results were interpreted by using scores 0 to 3+. FISH was used to assess HER-2 gene amplification. The tumors were tested in two reference centres. All procedures were applied to de-paraffinised tissue sections of BC samples.

Results: From July 2007 to April 2008, 60 cases of infiltrative BC were studied and correlation with HER-2 overexpression between IHC and FISH was determined. Mean age of women was 51.55 (24-78) years. 73.3% of tumours were infiltrative ductal carcinoma, 8.3% were lobular carcinoma and 5% canicular carcinoma. 40% of pts presented with stage IIA disease, 21.6% with stage IIB and 15% with stage I. 3+ HER-2 overexpression was found in 16 pts (26.6%), 2+ in 10 (16.6%), 1+ in 2 (3.3%) and 0 in 30 (50%). In 2 cases (3.3%) this determination was not done. FISH was positive in 20 cases (33.3%) and negative in 40 (66.6%). Only 4/30 (13.3%) IHC score 0 were FISH positive. Five of 10 (50%) IHC 2+ were FISH positive and the other 5 were FISH negative. We found that 5 of the 16 IHC score 3+ were FISH negative, so the discordance in this case was 31.25%.

Conclusions: We found a significant discordance in 9 cases (15%) of our group of pts. 4 were IHC score 0 and FISH positive, and 5 were IHC score 3+ and FISH negative. In the 10 cases of IHC score 2+, FISH was used to define positivity: 5/10 (50%) were positive. We suggest to carry out FISH to evaluate the status of HER-2 in BC, especially when considering the use of trastuzumab therapy.

Breast Cancer: Prognostic Value of Sentinel Lymph Node Involvement

Background: Sentinel lymph node (SLN) biopsy is a minimally invasive and accurate staging procedure for patients with invasive breast cancer. Histological SLN involvement with cancer cells requires regional lymph node dissection. The aim is to verify if subgroups of patients with sentinel lymph node involvement in which the risk of histological involvement of additional regional lymph nodes is minimal can be identified and to assess the prognostic value of SLN involvement.

Methods: Two hundred and sixteen consecutive patients with invasive breast cancer, had lymphoscintigraphy with colloidal 99Tc and radioisotope-guided sentinel lymph node biopsy in the University Hospital of Zaragoza from May 2001 to September 2007. Pathological assessment included serial sections of the sentinel lymph node with immunohistochemistry for cytokeratins in selected cases. 67 patients had histological involvement.

Results: All patients were females. Median age was 56 (range 24-87). Median tumour size was 21 mm (range 3-80). Median number of resected sentinel lymph nodes was 2 (range 1-5). With median follow-up of 40 months, 12 relapses have occurred (8 in axilla, 2 local relapses, 10 distant metastases). Seven relapses occurred in 67 patients with SLN involvement (10%) versus 5 in 149 patients without SLN involvement (3%) (p < 0.05).

Conclusions: SLN involvement is a significant prognostic factor for relapse in patients with breast cancer.

Long Term Results of Autologous Bone Marrow Transplant in Patients with High Risk Breast Cancer From a Single Brazilian Institution

Background: For a period of time Autologus Bone Marrow Transplant (ABMT) was considered a treatment option for high-risk breast cancer (HRBC) patients. Randomized trials failed to show survival benefit for these patients compared to conventional dose chemotherapy (CT). The aim of the present study was to investigate the role of ABMT as adjuvant therapy for HRBC after a long period of follow-up from a single Institution.

Methods: We performed a retrospective matched case-control analysis of 40 patients with HRBC, who received high-dose chemotherapy and ABMT (n = 20) or CT (n = 20) from 1991 to 2002. Case matching was performed with respect to age (< 60y) and number of positive nodes (N2 or N3), following a consecutive search of medical records at our institution.

Results: Median age was 45 (31-58) and 44 (31-59) for ABMT and CT, respectively. 15% of patients were N2 and 85% were N3. There was no significant difference between the two groups regarding lymph node status, ER and PR, TNM stage (III in all cases), and Grade. HER2 status was available in 80% of patients in the ABMT group and 62% were positive. There was no difference in pre-transplant chemotherapy regimens (AC or FAC) between the groups. Conditioning regimen for ABMT consisted of Cyclophosphamide, Thiotepa, and Carboplatin. Radiotherapy was performed in more than 90% patients in both groups. Patients in the ABMT group received adjuvant Tamoxifen for a longer period of time compared to CT group (59m vs 18m, p=0.046, respectively). Relapse rate was significantly inferior in the ABMT group as compared to CT group (40% vs 70%, p=0.049). Relapse-free survival (RFS, 38m vs 54m, p=0.89) and overall survival (OS, 65m vs 67m, p=0.13) was not different between ABMT and CT groups respectively. However, considering only cancer-specific mortality rates, fewer deaths were observed in the ABMT compared to CT group (35% vs 65%, p=0.02). Treatment related death occurred in only one patient in the ABMT group. Median follow-up of all included patients was 68.1m (11.0 – 191.7m).

Conclusion: Our data showed that ABMT was associated with decreased relapse rate. However it was not associated with improvement in RFS neither OS compared to conventional dose chemotherapy.