breast cancer, advanced

### 140 SERUM HER-2/NEU DECLINE PREDICTS IMPROVED RESPONSE TO TRASTUZUMAB-BASED THERAPY (SERUM HER-2/NEU STUDY GROUP)


Penn State Univ./Hershey Medical Center/Lexion VA Medical Center, Hematology-Oncology, Lebanon, PA, 2MD Anderson Cancer Center, Breast Medical Oncology, Houston, TX, 3Memorial Sloan Kettering Cancer Center, Department of Oncology, New York, NY, 4Yale University, Pathology, New Haven, CT, 5University Hospital of Geneva, Division of Oncology, Geneva, Switzerland, 6Tenon Hospital, Service d’Oncologie Médicale, Paris, France, 7Humboldt Univ., Hematology-Oncology, Berlin, Germany, 8University of Geneva School of Medicine, Vaud, Switzerland, 9Penn State Univ./Hershey Medical Center, Hematology-Oncology, Hershey, PA

Background: Trastuzumab (Herceptin) monotherapy has a 34% objective response rate (ORR) in patients with HER-2/neu 3+ or FISH-positive first-line metastatic breast cancer (C. Vogel et al, JCO 20:719-726, 2002). Predicting response and survival to trastuzumab-based therapy is an unsolved problem. The HER-2/neu extracellular domain (ECD) is released after cleavage by the ADAM metalloproteinases, and the remaining membrane-bound internal domain is constitutively activated. Trastuzumab inhibits cleavage of the HER-2/neu ECD.

Material and methods: A pooled analysis of 7 trials of first-line trastuzumab therapy (with or without chemotherapy) with serial serum HER-2/neu levels were included. The FDA-approved HER-2/neu ELISA (Oncogene Science/Bayer HealthCare) was used to determine serum HER-2/neu levels. A pretreatment and post-treatment serum (16-120 days) from 307 patients was available. 236 patients had data on overall survival. Kaplan Meier life table analysis was performed to compare duration of response (DRP), time to progression (TTP), and overall survival (OS).

Results: The median decrease in serum HER-2/neu levels for all patients was 31.0%. Patients who had a greater than 20% decrease in serum HER-2/neu levels had significantly higher ORR, and longer DRP, TTP, and OS, regardless of the remaining membrane-bound internal domain (ECD) is released after cleavage by the ADAM metalloproteinases. The FDA-approved HER-2/neu ELISA (Oncogene Science/Bayer HealthCare) was used to determine serum HER-2/neu levels. The median decrease in serum HER-2/neu levels for all patients was 31.0%. Patients who had a greater than 20% decrease in serum HER-2/neu levels had significantly higher ORR, and longer DRP, TTP, and OS, regardless of the remaining membrane-bound internal domain (ECD) is released after cleavage by the ADAM metalloproteinases. The FDA-approved HER-2/neu ELISA (Oncogene Science/Bayer HealthCare) was used to determine serum HER-2/neu levels.

**Table 1:**

<table>
<thead>
<tr>
<th>Time to 2nd serum HER2 levels (Baseline to followup)</th>
<th>ORR% (N)</th>
<th>DRP Median (Days)</th>
<th>TTP Median (Days)</th>
<th>OSMedian (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 days &lt;20% Decrease</td>
<td>20.6 (68)</td>
<td>245 (14)</td>
<td>198 (68)</td>
<td>521 (47)</td>
</tr>
<tr>
<td>20% Decrease</td>
<td>55.9 (102)</td>
<td>383 (57)</td>
<td>320 (102)</td>
<td>1077 (72)</td>
</tr>
<tr>
<td>&gt;20% Decrease</td>
<td>39.6 (48)</td>
<td>189 (19)</td>
<td>173(48)</td>
<td>617 (39)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0001</td>
<td>0.05</td>
<td>0.01</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Conclusion: Patients with <20% decrease in serum HER-2/neu levels have decreased benefit from trastuzumab therapy. Patients who do not have a significant decrease in serum HER-2/neu levels should be considered for additional HER-2/neu-targeted therapies.

### 1410 LAPATINIB IN COMBINATION WITH CAPECITABINE DEMONSTRATES SUPERIOR EFFICACY COMPARED WITH CAPECITABINE ALONE IN ERBB2+ ADVANCED OR METASTATIC BREAST CANCER (MBC) PATIENTS (PTS) PRETREATED WITH CHEMOTHERAPY AND TRASTUZUMAB


1Western General Hospital, Division of Medical Oncology, Edinburgh, United Kingdom, 2Allegheny General Hospital, Division of Medical Oncology, Pittsburgh, PA, 3Nottingham City Hospital, Division of Medical Oncology, Nottingham, United Kingdom, 4Cancer Center, Division of Medical Oncology, Warsaw, Poland, 5CRCC, Division of Medical Oncology, Val d’Aurelle Paul Lamarque, France, 6CZN MSWiA, Division of Medical Oncology, Olkusz, Poland, 7St. Vincent’s University Hospital, Division of Medical Oncology, Dublin, Ireland

Background: Lapatinib (TYCERB/C210) is an oral small molecule inhibitor of ErbB1 and ErbB2 tyrosine kinase receptors. The primary objective of the study was to evaluate and compare time to progression (TTP) in pts with recurrent IBC, illustrating the importance of selecting pts based on biology rather than histology alone, in order to maximize the clinical efficacy of ErbB kinase inhibitors in breast carcinomas.

**Table 2:**

<table>
<thead>
<tr>
<th>Time to 2nd serum HER2 levels (Baseline to followup)</th>
<th>ORR% (N)</th>
<th>DRP Median (Days)</th>
<th>TTP Median (Days)</th>
<th>OSMedian (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 days &lt;20% Decrease</td>
<td>20.6 (68)</td>
<td>245 (14)</td>
<td>198 (68)</td>
<td>521 (47)</td>
</tr>
<tr>
<td>20% Decrease</td>
<td>55.9 (102)</td>
<td>383 (57)</td>
<td>320 (102)</td>
<td>1077 (72)</td>
</tr>
<tr>
<td>&gt;20% Decrease</td>
<td>39.6 (48)</td>
<td>189 (19)</td>
<td>173(48)</td>
<td>617 (39)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0001</td>
<td>0.05</td>
<td>0.01</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Conclusion: Patients with >20% decrease in serum HER-2/neu levels had decreased benefit from trastuzumab therapy. Patients who do not have a significant decrease in serum HER-2/neu levels should be considered for additional HER-2/neu-targeted therapies.
Background: Lapatinib (TYCERRB®) is orally bioavailable reversible, dual tyrosine kinase ErbB1 and ErbB2 inhibitor. Trastuzumab, an ErbB2 inhibitor, has been associated with cardiotoxicity. Methods: Left ventricular ejection fraction (LVEF) was monitored every 8 weeks using MUGA or echocardiogram. Cardiac risk factors including age, underlying CV disease, previous exposure to AC, trastuzumab, or mediastinal/left sided radiation (XRT) were also collected. LVEF data were evaluated for ≥ NCI CTG C grade 3, or ≥ 20% decline relative to baseline (≤ below institutional LLN). Results: 1.3%, 42 of the 3127 subjects who received lapatinib in all trials to date experienced isolated LVEF decrease ≥ 20% of pts received lapatinib monotherapy, the remaining 19 received lapatinib in combination with other chemotherapeutic agents. 69% (294/2) of pts were female, median age 59 years. Decreased LVEF occurred within 9 weeks of treatment onset in 69% of cases. The event resolved/improved in 62% in 42 of these, lapatinib treatment was continued. Average event duration was 4 weeks. Four of 42 pts were symptomatic (0.1% incidence). Most symptomatic events responded promptly to standard CHF therapy. The majority of pts (90%, 3842) had confounding factors that may have contributed, including previous exposure to AC, trastuzumab or XRT, and/or medical history. 9 of 38 pts had a positive lapatinib challenge (LVEF recovered): 5 were symptomatic (sign of CHF) and 6 asymptomatic. 4 pts had no contributing factors: 1 experiencing asymptomatic decrease LVEF, 1 had an asymptomatic decrease 3 weeks after last lapatinib dose, the remaining 2 died due to disease progression whilst LVEF decrease was ongoing. 17 of 1492 pts participating in placebo-controlled studies experienced decreased LVEF. Of these 8 are known to have received lapatinib, giving an incidence of 1.0% (8/744). Conclusions: Lapatinib-associated LVEF decrease is rarely symptomatic and generally reversible/non-progressive. Incidence was 1.3% in our series. Efforts are underway, including pharmacogenetic studies on ErbB1 polymorphism, to determine predictive markers.

A RANDOMIZED PHASE III STUDY COMPARING THREE ANTHRACYCLE-FREE TAXANE-BASED REGIMENS, AS FIRST LINE CHEMOTHERAPY, IN ADVANCED BREAST CANCER (ABC)

George Fourtatzis, Meltemis A. Dimpoulos, Urania Dathi, Dimoterisis V. Skarlos, Papageorgiou Papanakia, Heiner Goggas, Helen Lianitis, Epanrommadas Sarantias, Dimitros Pectasides, Haralampos P. Kalofonos
Hellenic Cooperative Oncology Group, Data Office, Athens, Greece

Background: Advanced breast cancer (ABC) is an incurable disease. Anthracyclines are an integral part of adjuvant chemotherapy in patients with high-risk disease. However, their re-introduction in advanced stages is limited due to increased risk of cardiomyopathy. Taxanes are active in ABC and their use as first line chemotherapy is theoretically attractive. The purpose of this study is primarily to compare the survival of patients with ABC treated with 3 different anthracycline-free taxane-based regimens. Secondary endpoints included time to progression (TTP), overall response rate (ORR), toxicity, quality of life and cost assessment. Patients and methods: Patients with ABC were randomized to receive either 6 cycles of paclitaxel 126 pts were treated; median age 51 yrs (range 30–78) and KPS 70–100%. Baseline treatments were 20% prior to lapatinib. The interim analysis, the decision was reached to continue the study to completion, since no significant difference in ORR, TTP or survival between the three groups was found. Severe myelotoxicity was significantly higher in group B (13% vs 31% vs 10%, P<0.001), while severe peripheral neuropathy was present as expected only in the arms that included paclitaxel (5% vs 0% vs 8%, P=0.008). No other significant difference in toxicity was found between the three groups. Conclusion: In view of no difference in survival or unexpected toxicity, results of quality of life and cost analyses will guide us to select the optimal regimen for further development.
were sensory peripheral neuropathy (14%), fatigue (19%), myalgia (7%) and stomatitis (6%). Sensory neuropathy was cumulative and reversible; 2 pts discontinued due to neuropathy. Median time to resolution of G3 neuropathy (to G1 or baseline) was 5.4 wks. Sensory neuropathy in 23 pts (18%) was managed by dose reduction and of these pts, 20 (87%) had their neuropathy improve or not worsen. Promising activity and a manageable safety profile were achieved with I in this highly refractory population.

**Methods**

This open label phase II study enrolled a total of 109 EP-CAM-positive breast cancer patients. An initial restriction to allow for a maximum of one previous chemotherapy for metastatic disease was subsequently removed during the study. Patients were stratified into low/middle and high-level EP-CAM expression according to their primary tumour IHC estimated staining intensity (Spizzo et al., 2004); and subsequently randomised to receive either high-dose (6 mg/kg) or low-dose (2 mg/kg) adecatumumab i.v. every other week until disease progression.

**Results**

This report summarizes the results of a pre-specified interim analysis on the first 67 evaluable patients. Patients receiving high-dose adecatumumab (n=35) showed a higher rate of AE as compared to patients (n=32) in the low-dose group (97% vs 92% of patients), with no significant increases in serious AE (33 vs 26 SAE). Gastrointestinal (nausea, vomiting, diarrhoea, constipation) and constitutional symptoms (chills, fatigue, headache) were reported as the most common toxicities and were mostly mild to moderate. A longer time-to-disease progression (TTP) was observed in patients receiving high-dose adecatumumab as compared to the low-dose group (median TTP: 78 vs 43 days; p=0.0384), with the longest TTP seen in patients expressing high levels of EP-CAM and receiving high-dose adecatumumab (n=21; median TTP: 90 days; p=0.0238).

**Summary**

This interim analysis demonstrates the safety and feasibility of adecatumumab treatment in patients with metastatic breast cancer. Moreover, there is suggestive evidence for clinical efficacy of the high-dose adecatumumab regimen, which appears to be more pronounced in patients with high EP-CAM expression.
Bmi-1 oncogene, one of the cell cycle regulators, is observed in several tumor tissues and is known to be involved in tumorigenesis and cancer progression. To clarify the roles of Bmi-1 in breast carcinoma, we examined the expression of Bmi-1 in 970 tissue samples of breast carcinoma patients by immunohistochemistry using anti-Bmi-1 monoclonal antibodies that have BCS. In univariate and multivariate analysis, Bmi-1 overexpression was significantly correlated with favorable prognostic indices and clinical outcome. Strong staining was defined as the presence of Bmi-1 monoclonal antibody and correlated their expression with the pathologic prognostic indices and clinical outcome. Favorable prognosis in breast carcinoma.

Patients and methods: Thirty-three taxane resistant metastatic breast cancer patients were treated with gemcitabine 1250 mg/m² IV infusion over 30 minutes on days 1 and 8, and with cisplatin 75 mg/m² by IV infusion for 1 hour on day 1 in 21 day cycles. Results: Of the 30 evaluable patients, there were 9 (30%) partial responses and no complete responses, an overall objective response rate of 30%. Median time to progression and median survival duration for all study subjects were 7 (95% CI, 5.1–8.9 months) and 15 months (95% CI, 10.5–19.3 months), respectively. Toxicities included grade 3 and 4 leukopenia in 10 (30%), thrombocytopenia in 6 (18%), anemia in 2 (6%) and oral mucositis in 2 (6%). No grade 3 or 4 peripheral neuropathy, renal dysfunction, hepatic dysfunction, or nausea/vomiting was observed, and there were no treatment-related deaths.

Conclusion: The described gemcitabine plus cisplatin combination is active and tolerable salvage regimen in patients with taxane resistant metastatic breast cancer.

Background: The combination of doxetaxel (D) and trastuzumab (H) is considered to be active for HER2-overexpressing (HER2+) breast cancer in both the metastatic and adjuvant setting. The purpose here was to evaluate the rate of pathological complete response (pCR) with this combination as it is often used as an early surrogate marker of treatment efficacy.

Patients and methods: 21 pts with HER2+ (>30% by IHC) breast cancer were enrolled at 6 cancer centers in Japan. We administered the combination of D (70 mg/m² every 3 weeks) and H (4 mg/kg loading dose and thereafter 2 mg/kg weekly). Four cycles of chemotherapy were repeated every 5 weeks and followed by surgery. The primary endpoint was pCR rate.

Results: The median age was 54 years (range, 35-69). The median tumor size was 54 mm (range, 13-150). PS (ECOG): 0/1 (18/3). Clinical node status: N0/N1/N2 (8/12/1). Hormone receptor status: ER+/-/ER- (9/47/65), PgR+/-/PgR- (24/36/19). The pCR rate was 9% (95% CI 67%–99%), with 5 CR, 12 PR and 2 SD. Breast conservation surgery (BCS) rate was 58%. Nine pts who had planned for mastectomy were able to have BCS. The most common Grade 3 or 4 adverse events were leukopenia 48%, neutropenia 43%, febrile neutropenia 10% and anemia 5%. All non-hematological toxicities were mild and manageable.

Conclusion: The combination of D and H produced a high clinical and pathological response which allowed for BCS in the majority of patients. The combination was well tolerated. The predictive value of ER, PgR, and degree of HER2 and MYC amplification will be analyzed and reported for all patients.

Background: Despite the progress in early detection of breast cancer, there is still a sizable proportion of patients in which the diagnosis is made when the tumor is already locally advanced. In this setting not only long-term survival is a problem, but also a high risk of loco-regional failure. Thus, it is important to consider the patient management by a multimodality treatment approach.

Patients and methods: We analyzed the results of the multimodality treatment of 240 patients diagnosed with locally advanced breast cancer (Stage III A B, ACC 2002) treated from February 1990 until June 2004. Median age was 51 years (range 21–70), and 94% were postmenopausal. ER receptor status was (>50%) in 29%, progesterone receptor status was (>50%) in 29% and HER2 was not determined in 20%. In 205/240 (85%) the clinical tumor size was larger than 5 cm. After incisional or core biopsy, 3 to 4 cycles of neo-adjuvant chemotherapy was given (FAC, FEC50 AC), followed by local treatment, surgery and loco-regional radiotherapy (pretreatment with taxane in 90%, post operative in 45%, not given in 5%). After local treatment, patients with (+) hormone receptors tumors received tamoxifen for 5 years.

Results: After neo-adjuvant chemotherapy clinical tumor size shrunk down to 5 cm or less in 91% of the patients allowing in 99/240 patients (41%) a breast conserving surgery. 56% underwent mastectomy and in 8 patients no surgery was undertaken because of patient’s refusal or tumor progression. With a median follow-up of 82...
Chapter 1: Introduction

Background: Addition of X to T significantly improves response rate, time to progression and overall survival vs T alone in MBC. X and T are synergistic with H in HER2-positive tumours. We assessed the efficacy and safety of neoadjuvant XT in pts with LABC.

Methods: Pts with newly diagnosed stage III inoperable BC (CT4 and/or CN2) received XT (36 mg/m² iv d1 & 8) q3w x6, followed by surgery and radiotherapy. Pts with HER2-positive tumours (IHC 3+ or FISH+) also received H (8 mg/kg on 1 of the 1st 3w cycle and 6 mg/kg on subsequent cycles). Assessments: safety after each cycle; clinical response after cycles 3 and 6; pathological complete response (pCR, defined as no residual invasive tumour in breast and axilla) postoperatively.

Results: Baseline characteristics: median age 50 years (range 25–74), median ECOG PS 0 (range 0–1), ER/PR/HER2 status 74/61/16%. Neoadjuvant chemotherapy and surgery are complete in 30/30 planned pts (XT n=26; XT+H n=14). The most common grade 3/4 treatment-related toxicities were diarrhoea (16%), stomatitis and HFS (10% each). Dose was reduced because of grade 2–4 toxicities (stomatitis, HFS, diarrhoea, vomiting, peripheral neuropathy and skin rash) in 11 pts and neutropenic fever in 2 pts. Treatment was discontinued prematurely because of disease progression (1 pt), capillary leak syndrome (1 pt), infection (1 pt), fever of unknown origin (1 pt) and psychological intolerance (1 pt). Overall response rate was 99%, including 2 CRs (7%) and 25 PRs (83%). A further 2 pts had stable disease (7%). pCR was seen in 2 pts who completed 6 cycles of XT (18%) and in 24 pts (50%) after 6 cycles of XT+H. Most pts received postoperative anthracycline-based chemotherapy (4–6 cycles of FEC100/110) without unexpected toxicity. All pts with hormone receptor-positive tumours received adjuvant hormone therapy.

Conclusions: XT+H appears to be reasonably tolerated as neoadjuvant therapy for LABC, with promising pCR rates in the XT+H arm. Combining H with XT avoids the risk of overlapping cardiac toxicity with anthracyclines, which can be problematic in HER2-positive BC.

Chapter 2: DISSEMINATED TUMOUR CELLS (DC) IN THE BONE MARROW (BM) IN ADJUVANT BREAST CANCER – A FREQUENT EVENT WITH PROGNOSTIC AND THERAPEUTIC RELEVANCE?

Chapter 3: A PHASE I/II STUDY ON DOSE-DENSIFICATION OF CYCLOPHOSPHAMIDE, METHOTREXATE AND S-FLUOROURACIL (CMF) CHEMOTHERAPY WITH SUPPORT OF G-CSF IN LOCALLY ADVANCED OR METASTATIC BREAST CANCER

Chapter 4: SAFETY AND EFFICACY RESULTS

Chapter 5: MULTICENTRE PHASE II STUDY OF CAPECITABINE (X), DOCTAXEL (T) ± TRASTUZUMAB (H) AS NEOADJUVANT TREATMENT FOR PATIENTS (PTS) WITH LOCALLY ADVANCED BREAST CANCER (LABC): PRELIMINARY SAFETY AND EFFICACY RESULTS

Chapter 6: DOSE-ESCALATED VINORELBINE-CAPECITABINE IN ELDERLY METASTATIC BREAST CANCER PATIENTS. A SIGCO PHASE II STUDY

Chapter 7: CONCLUSIONS

Chapter 8: DISSEMINATED TUMOUR CELLS (DC) IN THE BONE MARROW (BM) IN ADJUVANT BREAST CANCER – A FREQUENT EVENT WITH PROGNOSTIC AND THERAPEUTIC RELEVANCE?
Introduction: The recommended dose of capecitabine is 1250 mg/m² bid, D: 1–14 q3w but this dose is difficult to administer in a relevant percentage of BC pts. The objective is to evaluate the efficacy and safety of an alternative schedule of continuously administration of C in lower daily doses but keeping the same cumulative dose per cycle as in the standard schedule.

Methods and patients: Pts with MBC previously treated with chemotherapy (anthracyclines and/or taxanes), ECOG PS ≤2, at least one measurable lesion and adequate bone marrow, renal and hepatic functions were randomized to Arm A (A, C 1250 mg/m² bid, D:1–14 q4w) or Arm B (B, C 800 mg/m² bid continuously).

Results: 28 pts have been randomized. 14 pts are eligible for toxicity analysis, and 8 for response evaluation. Median age 57 (range=46–70) yrs, ECOG PS 1.1 (range=0–2). Median PS 0.100%. Histology: 43% ductal carcinoma and 27% lobular carcinoma in both arms. 9% with HR+ (E and/or P) 10% arm A and 8% arm B. 86% of pts in both arms had previously failed to anthracyclines and/or taxanes. Metastatic sites were: arm A: lung 4 (57.1%), breast 4 (57.1%), skin 2 (28.6%), bone 4 (28.6%), liver 1 (14.3%). Pts received 37 cycles in arm A and 42 cycles in arm B with a median of 3 cycles respectively. 6 cycles (16.2%) were delayed in arm A and 4 in arm B (9.5%) in both due mainly to non haematological toxicity. Dose was reduced in 6 (16.2%) cycles in arm A and 4 (9.5%) cycles in arm B. Median RD: arm A: 73% and arm B: 93%. Grade 3–4 main toxicities by pt were by arm A: arm B: asthenia 43/30%, hand and foot syndrome 43/30%, febrile neutropenia 14/3% (all these due to sensory neuropathy). Leukopenia and neutropenia were the most frequent toxicity with a very high incidence in the 2 arms. Grade 3–4 neutropenia occurred in 9/19 pts (47.4%) and in arm B: lung 4 (57.1%) and breast 4 (57.1%) in the other case).

Efficacy: 4 pts are evaluable for response. Arm A: 1 PR, 2 SD and 1 PD. Arm B: 1 PR, 1 SD and 2 PD.

Conclusions: Our very preliminary data show that the continuous regimen of C seems to be associated with less G3-4 toxicity, in particular asthenia, HFS, diarrhea, stomatitis and/neutropenia. The study is ongoing.

In ixabepilone (I), a semi-synthetic analog of natural epothilone B, has shown antitumor activity in a broad range of tumor types including taxane-resistant breast cancer. Differing mechanisms of action and minimally overlapping toxicities provide the potential for synergy between I and other antineoplastics. Breast cancer pts who are ER, PR and HER-2 negative (triple negative) have fewer treatment options and pose particular treatment challenges. This open-label Phase III trial was conducted to determine the Phase II and III doses of I and capcitabine (C) using a 3-h infusion of I on Day 1 (Schedule A) or a 1-h infusion of I for 3 days (Schedule B) with C given orally on Days 1-14 q21d in pts with metastatic breast cancer (MBC) previously treated with a taxane and an anthracycline. Pts were excluded if they had received >3 prior chemotherapy regimens in the metastatic setting. Result from the 62 pts treated with I 400 mg/m² and a 1-h infusion and C 2000 mg/m² are shown. 48% of pts were triple negative. Pts received a median of 4 cycles (range 1-20).

Toxicity in the total population was notable for peripheral neuropathy (Grade ≥2: 19 pts [31%] vs Grade 0–1: 28% [19%]; sensory neuropathy 12 pts; motor neuropathy 1 pt). Neuropathy resolved in 94% of pts with a median time to resolution of 2.6 weeks (95% CI 1.1–6.9%). In the total population, hand-foot syndrome, reported in 39 pts (63%), was primarily Grade 2 (26%) or 3 (34%). 27% of pts discontinued due to adverse events (11% of these due to sensory neuropathy). Leukopenia and neutropenia were the primary hematologic abnormalities (primarily Grade 1-3). G4 leukopenia and neutropenia were observed in 12 and 26 of pts, respectively. I/C combination demonstrated antitumor activity and a manageable safety profile in the total population and triple negative pts with MBC previously treated with a taxane and an anthracycline.

Conclusion: Our preliminary data show that the continuous regimen of C seems to be associated with less G3-4 toxicity, in particular asthenia, HFS, diarrhea and neutropenia. The study is ongoing.

In ixabepilone (I), a semi-synthetic analog of natural epothilone B, has shown antitumor activity in a broad range of tumor types including taxane-resistant breast cancer. Differing mechanisms of action and minimally overlapping toxicities provide the potential for synergy between I and other antineoplastics. Breast cancer pts who are ER, PR and HER-2 negative (triple negative) have fewer treatment options and pose particular treatment challenges. This open-label Phase III trial was conducted to determine the Phase II and III doses of I and capcitabine (C) using a 3-h infusion of I on Day 1 (Schedule A) or a 1-h infusion of I for 3 days (Schedule B) with C given orally on Days 1-14 q21d in pts with metastatic breast cancer (MBC) previously treated with a taxane and an anthracycline. Pts were excluded if they had received >3 prior chemotherapy regimens in the metastatic setting. Result from the 62 pts treated with I 400 mg/m² and a 1-h infusion and C 2000 mg/m² are shown. 48% of pts were triple negative. Pts received a median of 4 cycles (range 1-20).

Methods: Pts with anthracycline- and taxane-pretreated MBC received X 1250 mg/m² twice daily on days 1-14 every 3 weeks for a median of 6 cycles (range 1-15).
A PHASE II TRIAL OF CAPECITABINE AND VINORELBINE AS FIRST-LINE TREATMENT IN PATIENTS WITH METASTATIC BREAST CANCER (BC)

Raffaella Palumbo1, Antonio Bernardo2, Maria Rosa Stradai1, Guido Pogli1, Angelo DeMorti1, Cristina Teragni1, Mara Frascaroli2, Giovanni Bernardo1

Background: Both Vinorelbine and Capecitabine have shown significant activity as single agents in patients with advanced BC, and recent data suggest the feasibility of this drug combination in patients pretreated with anthracycline- and/or taxane-based chemotherapy. A prospective phase II study was designed to verify the activity and safety a combined regimen of Vinorelbine and Capecitabine as first-line treatment in metastatic BC patients.

Patients and methods: Thirty-two consecutive patients with histologically confirmed, measurable or evaluable metastatic BC, entered the study. Median age was 54 years (range 30–72), 91% of them had previously received anthracyclines as neoadjuvant or adjuvant treatment, and 24% had been treated with taxanes; no patient had prior chemotherapy for the metastatic disease. Visceral metastases were present in most patients (liver 65%, lung 43%). Treatment consisted of Capecitabine given at the fixed dose of 1000 mg/m² orally twice daily for 14 consecutive days followed by one week rest plus Vinorelbine given intravenously at 25 mg/m² on day 1 and 8 of a 21-day cycle. Cycles were repeated every 3 weeks.

Results: A total of 136 cycles of treatment were administered (median 4 per patient range 2–6). Neutropenia was the main toxicity, with grade 3 or 4 NCI-CTC occurring in 19% and 9% of patients, respectively, with no severe documented infection; grade 2 hand/foot syndrome occurred in 2 patients, gr.1–2 diarrhea in 4 patients; alopecia did not exceed gr.2. Twenty-three patients achieved a documented objective response, for an overall response rate of 73% (95% CI 54%–84%) including 4 complete responses (3 in the liver, 1 in the lung). Median time to progression and overall survival was 9 and 23 months, respectively

Conclusions: Our results confirm that Capecitabine/Vinorelbine combination has significant antitumor activity in non-pretreated metastatic BC patients. A phase II trial of all oral combination therapy in chemonaive patient with metastatic BC was started.

CAPECITABINE (X) PLUS VINORELBINE (N) AS SECOND-LINE THERAPY IN CHINESE PATIENTS (PTS) WITH METASTATIC BREAST CANCER (MBC)

Binghe Xu1, Qing Wu1, Meizhen Zhou1, Zhongsheng Tong1, Hecheng Li1, Li Li2, Guoxian Du1, Jinyu Tian1, Jinyu Sh1, Lejing Li1

Background: Breast cancer is one of the most common malignancies among Chinese women and the incidence continues to rise, particularly in large cities such as Shanghai. X monotherapy is consistently effective and very well tolerated in pretreated MBC. N is also commonly used in this indication. In several studies, the combination of X + N led to response rates ranging from 43-67% in first-line MBC. As there are few data on this combination in pretreated MBC, we evaluated the efficacy and safety of X + N in Chinese pts with MBC refractory to anthracycline or taxane treatment in a phase II trial.

Methods: 77 pts (planned population 60 pts) were enrolled between Feb 2003 and Nov 2004. All pts had measurable MBC (WHO) recurrent after anthracycline or taxane treatment, Karnofsky PS 20-80, adequate bone marrow, renal and hepatic function. Pts received 3-weekly cycles of oral X 1000mg/m² bid d1-14 + N 25mg/m² d1-8, for at least 2 cycles. Pts with progressive disease went off study while those with complete response (CR), partial response (PR), or stable disease (SD) continued treatment for a maximum of 6 cycles.

Results: Baseline characteristics of the 77 pts evaluable to date: median age 51 years (range 29–68); median Karnofsky PS 90 (range 70–100). Previous chemotherapies received were: anthracycline 87%, paclitaxel/docetaxel 52% Principal tumour sites were: lung 40%, liver 39%, lymph nodes 33%, thoracic wall 12%, breast 7%, other 3%. All pts received at least 2 cycles, 20 received 4 cycles and 47 received 6 cycles of X + N. The overall response rate was 22%, including 5 CRs and 12 PRs. At a median follow-up of 6 months (95% CI, 4.2–9.0), the median time to progression (TTP) is 6 months (95% CI, 5.3–9.0). The most common (210%) pts-related grade 1 adverse events were: HFS 16%, nausea 12%, and SGPT abnormality 10%. Most adverse events improved or resolved after dose adjustment and/or suitable treatments. There were very few grade 3/4 adverse events, the most common being leukopenia 12%.

Conclusions: X + N is active in pretreated MBC and its efficacy is confirmed in this Chinese pts. The combination is also well tolerated.

EFFICACY AND TOLERABILITY OF CAPECITABINE (X) MONOTHERAPY IN METASTATIC BREAST CANCER (MBC)

Nickie Vasconcelos

Background: Objective measures of response rate (RR), survival and quality of life are used to select therapy for MBC. X is a rationally designed oral, tumor-activated fluoropyrimidine carbamate with high activity in MBC both in combination with taxanes and as monotherapy. This study was designed to further evaluate the efficacy (response rate, duration of response, survival rate) and safety of X as monotherapy.

Methods: The study included 61 patients (pts) treated for MBC at our institution between 2002 and 2005. All had received prior adjuvant chemotherapy. We administered capecitabine monotherapy (1250 mg/m² twice daily, days 1–14 of every 21-day cycle) until grade 3/4 toxicities or progression.

Results: Baseline characteristics: mean age 56.1 years ± 10.9 SD (range 30–77), mean KPS 90% ± 10.7 SD (60–100%), mean disease-free interval from diagnosis of MBC 24 months ±22.6 SD). More than two-thirds (73%) of pts had prior anthracycline therapy, 57% had 2-involved sites. Prior first-line treatment consisted of CMF in 12 (20%), taxanes in 5 (8%) and anthracyclines in 19 (31%). Median of no. of cycles was 14 ± 8.4 SD (443, Wts 79%) received >8 cycles of X, 33 (54%) received >12 cycles and 27 (44%) received >15 cycles.

Efficacy: There are 40 complete and 11 partial responses so far, giving an overall RR of 83.6%. The remaining 10 pts had disease stabilisation. Median duration of response to date is 6.94 months (± 5.6 SD); 6-month survival rate is 100%. X therapy is ongoing in 40 pts (66%). Safety: Predominant toxicities were hand-foot syndrome (13%, of which <5% grade 3) and gastrointestinal adverse events (6.6%). Grade 4 toxicities were rare (1.6%). Dose reduction was (by 10–25%) in 25% of patients.

Conclusion: This study confirms that X achieves a high tumour control rate and long-lasting responses in pts with MBC. X monotherapy was well tolerated. The evidence suggests that therapy should be continued until disease progression or development of unacceptable toxicities.

MULTICENTER PHASE II STUDY OF EFFICACY, SAFETY, AND PHARMACOKINETICS OF VINORELBINE AND TRASTUZUMAB AS FIRST-LINE THERAPY FOR HER2-OVEREXPRESSING METASTATIC BREAST CANCER

Kenjiro Aogi1, Masakazu Toi2, Hiroji Iwata3, Yoshinori Ito4, Muneaki Sano5, Tamayo Sado1, Toshiaki Sawai6, ShigemiTsuchida7

Background: This study was designed to evaluate the efficacy and safety of vinorelbine (VNB) and trastuzumab combination regimen as first-line chemotherapy in Japanese patients with HER2-overexpressing metastatic breast cancer (MBC) and to determine the pharmacokinetics of VNB in this setting.

Methods: This multi-center study was conducted at 6 medical institutions in Japan. From March 2003 to March 2005, 23 patients with HER2-overexpressing MBC who had received no prior chemotherapy for metastatic lesions were enrolled. Treatment consisted of VNB at 25 mg/m² plus trastuzumab at 2 mg/kg (initial dose level: 4 mg/kg) once weekly. The neutrophil count was set to be greater than or equal to 1000/mm³ before VNB administration. Patients were given VNB alone on Day 1,
trastuzumab alone on Day 1, and the two drugs in combination on Day 8 or later. In the first 5 of the 23 patients, VNB pharmacokinetic data were evaluated during the first two cycles of therapy.

Results: The co-administration of trastuzumab did not affect the pharmacokinetics of VNB. Terminal half-life (t1/2) was 11.6 ± 0.5 h (mean ± standard deviation) in the first cycle and 11.2 ± 0.9 h in the second, and the area under the plasma concentration-time curve (AUC) was 275 ± 38 ng·h/mL and 268 ± 29 ng·h/mL, respectively. The response rate was 73% (2 CRs and 14 PRs/22) with a median time to progression (TTP) of 12.0 months (1.9–13.3 months). The median dose per week was 16.9 mg/m2 for VNB and 1.90 mg/kg for trastuzumab. 4. The most common Grade 3 or 4 adverse events were neutropenia (83%), leukopenia (79%), and febrile neutropenia (4%). Left ventricular ejection fraction (LVEF) was decreased in 6 patients (26%); however, all of them were of Grade 1 or 2, with only one declining to below 50%. Subset analysis showed that the incidence of decreased LVEF was 4% (3/77) in patients with prior anthracycline exposure and 15% (4/27) in patients without it. The combination of VNB and trastuzumab did not cause any unexpected adverse reactions. Conclusion: These results suggest that this combination regimen as first-line chemotherapy can be safely administered with a favorable efficacy profile.
Methods: 90 pts of a planned population of 100 pts were enrolled between Mar03 and Feb05. All pts had measurable (WHO criteria) HER2-positive (IHC 3+ or IHC 2+ FISH positive) and untreated MBC, KPS ≥60, and adequate organ function. H was administered as a 4 mg/kg loading dose followed by 2 mg/kg i.v. weekly (until disease progression) and X 1250 mg/m² bid d1-14 q3w (max 6 cycles). The primary endpoint was progression-free survival (PFS).

Results: Baseline characteristics of the 43 pts currently evaluable are: median age 49 years (range 27-74), median KPS 90 (range 60-100). Principal tumour sites: lymph nodes 49%, lung 33%, liver 28%, breast 14%, thoracic wall 9%, chest 9%, other 12%. Prior treatment: surgery 3%, radiotherapy 39%, chemotherapy 41%, hormone therapy 68%. At a median follow-up of 6 months, median KPS has not yet been reached. The most common grade 1/2 adverse events (AEs) were hand-foot syndrome (HFS) 14%, neutropenia 14%, SGOT abnormality 16%, and SGPT abnormality 14%. Grade 3 HFS occurred in 4 pts (9%) with grade 3 myelosuppression in 1 pt (2%). AEs resolved in all pts.

Conclusions: H + X is highly active and well-tolerated as first-line treatment for HER2-positive MBC. Updated data will be presented.

170P TRASTUZUMAB BEYOND PROGRESSION IN METASTATIC BREAST CANCER
Mustafa T. Yarnaz1, Mustafa Ozoguzgil2, Betul Cettik3, Kazem Uygur3, Gul Basaran1, Hande Turan1, Ozcan Yildiz4, Ahmet Baran1, Golkan Demir1, Evrim Buyukalp1, Istanbul University, Cerrahpasa Medical Faculty, Medical Oncology, Istanbul, Turkey.

Background: Trastuzumab, a humanized anti-HER2 monoclonal antibody, extends the survival of women with HER2-positive metastatic breast cancer. However, there is no standard approach about the duration of therapy. Only a few retrospective analyses showed its feasibility and safety, but not efficacy, when continued beyond progression. We retrospectively reviewed 33 metastatic breast cancer patients who received trastuzumab beyond progression.

Methods: We evaluated 33 metastatic breast cancer patients. There were 14 premenopausal and 19 postmenopausal women. 29 patients were HER2 neu positive with immunohistochemical staining. Trastuzumab was combined with taxanes (docetaxel 8, paclitaxel 3), capecitabine (10 patients), vinorelbine (9 patients), cisplatin (1 patient) and hormonotherapy (2 patients) beyond progression.

Results: Response rates of 60 lines of trastuzumab therapy were evaluated. There were 20% (n=12) partial responses, 32% (n=19) stable disease and 48% (n=29) progressive disease. The best response of each patient showed partial response in 30% (n=10), stable disease in 33% (n=11) and progressive disease in 37% (n=12). At present 23 patients are alive. 10 patients died due to the disease progression. Median overall survival is 43 months (11-75).

Conclusion: Our results suggest that use of trastuzumab beyond progression may have some additional benefit in some patients. Randomized trials are warranted in this controversial issue.

171P TO ANALYZE THE EFFICACY, TOLERABILITY AND PHARMACO ECONOMICS OF LETROZOLE VS. TAMOXIFEN AS FIRST LINE THERAPY IN POST MENOPAUSAL, HORMONE POSITIVE FEMALES WITH METASTATIC OR RECURRENT BREAST CANCER

Aim: To analyze the efficacy, tolerability and pharmacoeconomics of Letrozole vs. Tamoxifen as first line therapy in post menopausal, hormone positive females with metastatic or recurrent breast cancer.

Patients and methods: 100 patients with metastatic or recurrent Breast Cancer were included in the study. They were randomised to receive either Letrozole 2.5 mg or Tamoxifen 20 mg daily. Patients with CNS metastasis, more than 1/3 liver involvement, estimated life survival less than 6 months and patients who had received tamoxifen in the last 12 months were excluded. The primary end point was to assess TTP (time to progression), toxicology profile, QOL (quality of life) as well as to analyze the pharmacoeconomic feasibility of both therapies. Patients were evaluated before treatment and subsequently every 12 weeks till disease progression. EORTC QLQ 30 questionnaire was administered. Pharmacoeconomic feasibility was determined using cost of drug and management of complications.

Results: Both the groups were evenly matched for age, number of patients, hormonal status and site of metastases. The median TTP was 35 weeks in the Letrozole group and 31 weeks in Tamoxifen group. The overall response rates were 33% in Letrozole group and 28% in Tamoxifen group. The QOL was similar in both the groups. Overall, adverse events were seen at a similar incidence in both the Letrozole and Tamoxifen groups. Tamoxifen group had a marginally higher incidence of hot flushes and vaginal bleeding (6.2% vs 4.9%) whereas Letrozole group had a higher incidence of bony pains and nausea (15.2%). The cost of treatment in the Letrozole arm was 20 times more as compared to Tamoxifen arm.

Conclusion: Although Letrozole had a superior efficacy and longer TTP as compared to Tamoxifen, the high cost of treatment precludes its widespread use and Tamoxifen still continues to be the treatment of choice in postmenopausal women with hormone positive metastatic or recurrent breast cancer in third world countries like India.

172P CLINICAL BENEFIT OF FULVESTRANT IN POSTMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER (ABC) AND PRIMARY OR ACQUIRED RESISTANCE TO AROMATASE INHIBITORS (AIS): FINAL RESULTS OF PHASE II SAKK TRIAL 21/00
Khalil Zamani1, Robert Pariando2, Hanne Hlawke1, Franco Noil, Hans Wildiers2, Maryse Fiche1, Daniel Dietrich1, Aron Goldhirsch3, Beat Thuerlimann1, Lucien Perry1
1Swiss Group for Clinical Cancer Research, Sankt, Bern, Switzerland, 2University Hospital Giessen, Department of Internal Medicine, Oncology, Leuven, Belgium, 3European Institute of Oncology, Unit for Medical Care, Department of Medicine, Milan, Italy

Introduction: The development of new non cross-resistant endocrine agents is urgently required, especially as tamoxifen, AI s or both are now increasingly used in the adjuvant setting. We evaluate the efficacy and tolerability of fulvestrant (Fadodo®), an estrogen receptor pure antagonist, for the treatment of ABC in postmenopausal women with hormoneresponsive tumors progressing after AI treatment.

Patients and methods: The trial was a phase II, open, multicenter, non-comparative study. Two patient groups with ABC were prospectively considered: Group A (n=70) with AI-responsive disease, Group B (n=20) with primary AI-resistant disease. Fulvestrant 250 mg was administered every 28 days (8x). Tumor samples were analyzed centrally for HER2 status. As an exploratory analysis, Fisher's exact test was performed to investigate the association between clinical benefit (CB; defined as objective response or stable disease [SD] for ≥24 weeks) and selected baseline characteristics.

Results: All patients were pretreated with AI and 84% also with tamoxifen or toremifene; 67% had bone metastases and 45% liver metastases. Fulvestrant administration was well tolerated and yielded a CB in 28% (90% confidence interval [CI]: 19 to 39) of patients in group A and 57% (90% CI: 39 to 58) in group B. Median time to progression was 3.6 months (95% CI: 3.0 to 4.8) in group A and 3.4 months (95% CI: 2.5 to 6.7) in group B. This treatment seemed to be most effective for older women and for those with a lower tumor burden. Only six patients out of 54 presented HER2-positive disease and none obtained CB with fulvestrant.

Conclusions: By inducing a CB in 30% of patients having received prior steroidal and non-steroidal AI and most of them having also been exposed to tamoxifen, fulvestrant emerges as an important player in the sequential endocrine treatment of ABC. In this population of older women, delaying the use of chemotherapy by using monthly injections of fulvestrant is a valuable approach to keep an optimal quality of life. Prior response to an AI did not appear to be necessary for benefit with fulvestrant.

173P EFFECTS OF LETROZOLE ON PLASMA LIPIDS, TRIGLYCERIDES AND ESTRADIOL IN WOMEN WITH METASTATIC BREAST CANCER
Jamarl Zoban1, Gazzalah Tafesh, BSS* Jorjet Tafesh2, Liqa Chetuer3, Jula Shrader1, Waild Bashir1, Sajjat Tamin3, Arrohan Albo5
1Ziv Hospital, Oncology, Zefat, Israel, 2ORT Braude College, Medical Biotechnology, Karmiel, Israel

Objective: Estrogen has beneficial effects on lipid metabolism in postmenopausal women, decreasing total cholesterol and low-density lipoprotein cholesterol and increasing high density lipoprotein. Letrozole and other aromatase inhibitors are more effective than tamoxifen in all stages of breast cancer, decreasing circulating estrogen in postmenopausal women to very low levels. We evaluated effects of letrozole on breast cancer and plasma lipids, triglycerides and estrogen.

Methods: Letrozole 2.5 mg/day was given to 30 postmenopausal women with metastatic breast cancer, previously untreated for metastases. All had measurable disease. Non-fasting clotted blood samples for assessment of serum levels of estradiol, lipid profiles (TC, LDL-C, HDL-C), triglycerides and LDH were taken from patients at baseline, 3, 6 and 12 months.

Results: Average age was 56. Average time in postmenopausal period before starting letrozole was 12 years. Estradiol level was 48 pg/ml in average before treatment, then reduced to 37, 28 and <18pg/ml after 3, 6, and 12 months. There was no change in the levels of TC, LDL-C and HDL-C before and after treatment with letrozole. Levels of LDL and triglycerides were also unchanged. 48 patients are available for response: 6
Background: pegylated liposomal doxorubicin (PLD) is active in metastatic breast cancer (MBC); the aim of this study was to evaluate safety and activity of PLD as first-line chemotherapy in MBC elderly patients (PTS).

Methods: 19 chemonaive PTS entered the study. Treatment was: PLD (Caelyx®), 40 mg/m², i.v. over 90’ in the 1st infusion and over 60’ in the following courses, q 4 weeks, for up to 3 courses. All PTS were offered pyridoxine 150 mg/day orally, during the whole treatment, in order to prevent cutaneous toxicity. PTS achieving response or stabilisation were treated with 3 additional courses. G-CSF and epoetin were administered if clinically indicated.

Results: median age was 75 (r. 71-83). All PTS had measurable disease. A total of 88 courses were delivered, with 52.6% of PTS receiving the planned 6 cycles. Among 18 evaluable PTS (1 early death due to progression before CT), responses were as follows (WHO criteria): 1 patient (5.2%) achieved a CR, 5 PTS (26.3%) a PR, for an overall RR 31.6%.

Conclusion: this study confirmed the liposomal doxorubicin as an active CT for MBC in elderly PTS. Anyway, a particular attention is needed to prevent both allergic and dermatological toxicity of whom, 2 were hospitalized and one experienced permanent disability. After these first adverse events we decided to administer steroids orally, 12 and 1 hour before chemotherapy in order to prevent cutaneous toxicity. 

The table 1 summerize the evolution of CC during the follow-up.

<table>
<thead>
<tr>
<th>n</th>
<th>Mild RF (CC&lt;90ml/min)</th>
<th>Moderate RF (CC&lt;60ml/min)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year follow-up</td>
<td>238</td>
<td>132</td>
<td>0.57</td>
</tr>
<tr>
<td>2 years follow-up</td>
<td>68</td>
<td>68</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

The table 1 summarize the evolution of CC during the follow-up.
Annals of Oncology

benefit from this therapy. In addition, ibandronate provided pain relief for patients who were bisphosphonate naïve and those who switched from other bisphosphonate therapy.

**170P** BREAST CANCER PATIENTS WITHOUT PAIN ARE AT RISK FOR SKELETAL-RELATED EVENTS (SRES) AND MAY HAVE BETTER OUTCOMES WITH ZOLEDRONIC ACID COMPARED WITH PAMIDRONE

Luis Costa1, Yin-Miao Chen2, Nana Shvina3
1Hospital of Santa Maria, Unidad de Oncología, Lisbon, Portugal, 2Novartis Pharmaceuticals Corporation, Statistics, East Hanover, NJ, 3Novartis Pharmaceuticals Corporation, Medical Affairs, East Hanover, NJ

Introduction: Bisphosphonates such as zoledronic acid (ZOL) play an important role in the treatment of bone metastases from breast cancer (BC); however, patients often are not diagnosed with bone metastases or treated with bisphosphonates until they develop bone pain.

Material and methods: Retrospective analyses were performed in patients with bone metastases from BC (n = 702), who received ZOL 4 mg or pamidrone (PAM) 90 mg every 3 to 4 weeks for up to 24 months. Patients were stratified by pain or no pain at baseline using the Brief Pain Inventory. Analyses included percentages of patients with any SRE-defined as pathologic fracture, spinal cord compression, and radiation or surgery to bone-time to first SRE, and skeletal morbidity rate (SMR).

Results: Among patients with no pain at baseline (n = 97), median time to development of pain was 92 days in the ZOL group and 39 days in the PAM group. In the subgroup of patients with pain at baseline (n = 605), 51% of patients in both the ZOL and PAM groups had at least 1 SRE at 25 months, and the mean SMR was 0.93 for ZOL versus 0.51 for PAM. Median time to first SRE was not reached in this subgroup, but 25% quartile was 693 days for ZOL versus 171 days for PAM. Among patients with pain at baseline (n = 605), 51% of patients in both the ZOL and PAM groups had at least 1 SRE at 25 months, and the mean SMR was 1.01 in the ZOL group versus 1.67 in the PAM group. Median time to first SRE was approximately 1 year in both treatment groups.

Conclusions: Although the risk of SREs was lower in BC patients with no pain at baseline, these results suggest that these patients are nevertheless at considerable risk for SRES. Moreover, ZOL may provide greater clinical benefit compared with PAM in the subset of patients without pain at baseline. Therefore, early diagnosis and treatment with ZOL may preserve patients’ functional independence by preventing SREs and delaying the onset of pain.

**180P** RADIOMODIFICATION BY CAPECITABINE AND ARGLABIN IN RADIATION THERAPY OF BREAST CANCER PATIENTS

Nikolay Malyshev1, Alkhan Dosakhyan2, Eugenia Kosirova3, Nataliya Bochkova3, Valentina Sirota4
1Karaganda Regional Cancer Center, Mammology Unit, Karaganda, Kazakhstan, 2National Research Center, Department of Clinical Research, Astana, Kazakhstan, 3Karaganda Regional Cancer Center, Radiology Unit, Karaganda, Kazakhstan, 4Karaganda State Medical Academy, Oncology Department, Karaganda, Kazakhstan

Aim: To assess the effectiveness of capecitabine and arglabin - new chemotherapy drug with radiomodifying option, in altered fractionated radiation therapy of breast cancer patients.

Materials and methods: 103 breast cancer patients were included in this trial. Stage II - 61 patients, stage III - 42 patients, mean age - 50.2 years. All of them were randomly assigned to three groups. The first group - 36 patients treated by prospective course of extra-beam radiation therapy with double daily fractionation by 2 Gy (time between fractions - 4.5 hours, 4 Gy per day), total dose - 32 Gy. The second group - 33 patients treated by the same regimen of radiation therapy, but with the concurrent radiomodification by arglabin (185 mg/sq.m. iv, 13–20 minutes before the first irradiation, 1 time a day, 8 days). In all the three groups the radiation therapy was always followed by radical mastectomy in 1–2 days.

Results: Positive clinical effect (complete remissions, partial remissions and process stabilization) was observed in 33% of the patients in the first group, 45% in the second group and 47% - in the third group. Average decreasing of tumor volume in the first group was 17%, in the second group - 44% and in the third group - 47%. The frequency of level 1 and 2 pathological responses was the same in all groups of patients. Level 3 pathological response was observed 2.3 times more often in the third group and 1.3 times - in the second group, compared with the first group without radiomodification.

Conclusion: The proposed regimen of radiation therapy with concurrent radiomodification by arglabin has demonstrated a higher clinical positive effect, increased regression of tumor volume, and more frequent level 3 pathological response. Influence on disease-free and overall survival will be evaluated.

Volume 17 | Supplement 9 | September 2006
doi:10.1093/annonc/mdl205 | 1879
Background: Nodal metastasis is recognized as a powerful prognostic marker in breast carcinoma, but conflicting reports exist for the precise involvement of VEGF-C and VEGF-D in lymphatic invasion and lymph node metastasis. The aim of this study was to determine whether serum VEGF, VEGF-C, VEGF-D levels and VEGF-C/D ratio correlate with lymphatic invasion, lymph node metastasis, CA 15-3, CRP and IL-6 levels in patients with breast carcinoma.

Methods: In this prospective study, the serum levels of VEGF, VEGF-C, VEGF-D, CA 15-3, CRP and IL-6 were determined by ELISA in patients with pretreated breast carcinoma (n=80) and healthy women (n=20). The volume of the tumor was calculated using three-dimensional tumor sizing. Comparison of data between patients and healthy controls; and relationships between circulating factors and clinicopathological variables were analyzed using the Mann-Whitney U or Kruskal-Wallis tests.

Results: The mean age of the patients was 50.7 ± 13.5 years. The mean level of VEGF-C was significantly higher in patients than in healthy controls (p=0.033); however, no statistically significant difference was observed for either serum VEGF and VEGF-D levels. Increased VEG-C levels were detected in patients having smaller volume and low nuclear-grade tumors (p=0.053, p=0.051, respectively). VEGF-D levels were significantly decreased in patients with high IL-6 (p=0.003) and CRP levels (p=0.007). VEGF-D was also decreased in patients having lymph nodes metastasis as compared to patients having negative axillary lymph node (p=0.028). VEGF levels were only elevated in CA 13-3 positive patients (p=0.05). The VEGF-C/VEGF-D ratio was significantly higher in patients with lymph node metastasis than in patients having negative axillary lymph node (p=0.004).

Conclusion: The present study shows positive correlation between serum VEGF-C/VEGF-D ratio and having lymph nodes metastasis; inverse correlation between serum VEGF-D levels and presence of lymph node metastasis; and positive correlation between the IL-6 levels and VEGF-D levels. In conclusion, we can state that serum VEGF-D level and VEGF-C/VEGF-D ratio are reliable parameters to evaluate axillary lymph node metastasis in breast carcinoma.

PREDICTORS OF CRANIAL METASTASIS IN PATIENTS WITH NON-METASTATIC BREAST CANCER RECEIVING POSTOPERATIVE RADIOTHERAPY AND CHEMOTHERapy

Lale Atahan1,2, Ferah Yıldız1, Murat Gurkaynak1, Göknah Özyüz1, Muhtu Hayran2
1Hacettepe University, Faculty of Medicine, Department of Radiation Oncology, Ankara, Turkey, 2Hacettepe University, Faculty of Medicine, Department of Preventive Oncology, Ankara, Turkey

Purpose: We retrospectively assessed the predictive factors of cranial metastasis in patients with non-metastatic breast cancer receiving postoperative radiotherapy and chemotherapy after mastectomy.

Materials and methods: Between January 1994 and December 2002, 957 non-metastatic breast carcinoma patients were analyzed. Chest wall radiotherapy were indicated in case of positive surgical margin, tumor size > 4 cm, skin-fascia invasion. Lymphatic irradiation was applied for more than 3 metastatic axillary lymph nodes, incomplete axillary dissection (<10 lymph nodes), extracapsular extension or perinodal fat tissue invasion. A total dose of 50 Gy was given to chest wall and lymph node regions with 2 Gy daily fractions. Statistical analyses were performed by Kaplan-Meier method, Log-rank test and Cox’s regression analysis.

Results: Median follow up was 55 months. The 5-year overall survival (OS) and disease-free survival (DFS) were 81%, and 65%, respectively. Univariate analysis for OS revealed significance for tumor size (5 cm vs. >5cm, p=0.001), metastatic nodal involvement (0 vs. 1+ vs. 4+ LN, p<0.001), percent positive nodal involvement (metastatic nodes/total nodes removed=100/60 vs. 55% vs.42%, p<0.05), tumor size (0.02), metastatic nodal involvement (0 vs. 1+ vs. 4+ LN, p=0.001), ACC 2002 stage (P<0.001), surgical margin status (negative vs. positive, p=0.05), and hormonal treatment (present vs. absent, p=0.03). DFS had similarly significance for age (540 years vs. ≥40 years, P=0.006), tumor size (0.02), metastatic nodal involvement (P<0.001), percent positive nodal involvement (p<0.001), ACC 2002 stage (P<0.001), and perinodal invasion (present vs. absent, P=0.01). Multivariate analysis revealed significance for tumor size, percent positive nodal involvement, hormonal treatment, and surgical margin status for OS. Age and percent positive nodal involvement were found to be significant for DFS.

Discussion: Percent positive nodal involvement were found to be a significant prognostic factor for survival in all end-points. It seems that more efficient therapeutic approaches are needed for patients with more than 30% axillary nodal metastatic.
a defense mechanism to protect the host from tumor. Recently, a COL18A1 gene polymorphism (D104N) was associated with increased risk of the prostatic adenocarcinoma. Considering that it is unknown whether D104N polymorphism of the COL18A1 gene alters the risk for BC, this was the aim of this study. Genomic DNA from 181 untreated female patients with sporadic breast cancer (SBC) seen in our service and 484 controls were analyzed using the polymerase chain reaction followed by restriction endonuclease digestion with MseI. ELISA for ES was performed in serum samples of all individuals using the commercially assay Accucyte. Statistical significance of the differences between groups was calculated by chi-square or Fischer exact test. Crude odds ratios (ORs) were given within 95% confidence intervals. The frequency of homozygous D104N polymorphism in SBC patients was higher than that found in controls (2.8% vs 0.0%; P = 0.002). Individuals with the NN genotype had an increased risk of disease. No differences in the D104N frequencies were found in patients in accord to clinical and laboratory features. The median value of ES in 118 patients was higher than that found in 158 controls (103.88 vs 98.95 ng/ml; P = 0.001). Similar median values of ES were seen in 4 patients with the NN genotype, in 10 patients with the DN genotype, and in 104 patients with the DD genotype (96.28 ng/ml, 98.69 ng/ml, and 104.83 ng/ml; P = 0.799). No difference in median ES values was also observed in 23 carriers and 135 non-carriers of the 104N allele (107.76 ng/ml vs 88.75 ng/ml; P = 0.55) among controls. In conclusion, our results present, for the first time, preliminary evidence that the D104N variant of the COL18A1 gene is associated with SBC susceptibility. Supported by FAPESP and CNPq.

18TP EXPRESSION OF GROWTH FACTORS AND CHEMOKINE RECEPTORS: NEW INSIGHTS IN THE BIOLOGY OF INFLAMMATORY BREAST CANCER

Nesnihan Cabioglu1, Yun Gong1, Rababi Islami2, Noor Snegiel3, Aysegul Sahin1,
Ana M. Gonzalez-Angulo4, Paolo Morandi2, Corazon Bucana3

1MD Anderson Cancer Center, Department of Pathology, Houston, TX, 2MD Anderson Cancer Center, Department of Breast Medical Oncology, Houston, TX, 3Oncology Hospital, General Surgery, Ankara, Turkey, 4Gazi University, Medical oncology, Ankara, Turkey

Purpose: Recent studies have suggested that chemokine receptors CXCR4 and CCR7 expression correlates with the metastatic potential of breast cancer. Expressions of CXCR4, and CCR7, along with the biomarkers HER2-neu and EGFR were investigated in primary inflammatory breast cancer (IBC) to evaluate their prognostic and therapeutic implications. Experimental design: CXCR4, CCR7, and EGFR were evaluated using paraffin-embedded tissue sections of breast cancers by immunohistochemical staining (IHC). HER2-neu amplification was assessed by FISH and/or IHC. All patients were treated with multidisciplinary management including preoperative chemotherapy based mostly on a regimen including anthracyclines combined with taxanes, surgery, and radiation according to our institutional protocols. Results: Forty-six cases diagnosed with IBC (including two cases with metastatic disease) between 1994 and 2002 were included in the study. The median age was 49 years (range 29-75). CXCR4 was expressed in 39% of cases (18/46), CCR7 expression was found in 26% (12/46). Furthermore, EGFR was highly expressed in 29% of patients (12/42), and HER-2 amplification was 50% (23/46). The median follow-up was 46.5 months (range, 11–127). Five-year disease specific and disease free survival (DFS and DSS, 12/42), and HER-2 amplification was assessed by FISH and/or IHC. All patients were treated mostly on a regimen including anthracyclines combined with taxanes, surgery, and radiation according to our institutional protocols. Multivariate analysis including tumor size, lymph node status and estrogen receptor status were also independent prognostic variables (p<0.05). Regression of tumor volume with chemotherapy was also significant (p>0.05). Multivariate analysis including tumor size, lymph node status and estrogen receptor status were also independent prognostic variables (p<0.05).

190P SERUM YKL-40 LEVELS AS A PROGNOSTIC FACTOR IN PATIENTS WITH LOCALY ADVANCED BREAST CANCER

Deniz Yaman1, Müziüm Gölbahar2, Ugur Coşkun1, İbanu Sancak2,
Niyazi Kamaran2, Can Atalay2

1Gazi University, Medical oncology, Ankara, Turkey, 2Gazi University, Biochemical science, Ankara, Turkey

Background: YKL-40 is a growth factor for connective tissue cells which stimulates migration of endothelial cells. It is also secreted by cancer cells and elevated serum level is associated with poorer prognosis in metastatic breast cancer. In the present study we evaluated the association of serum YKL-40 in locally advanced breast cancer in relation to disease free survival and overall survival. Also the value of serum YKL-40 in monitoring breast cancer patients compared to other prognostic factors was evaluated. Methods: Serum YKL-40 was determined by ELISA in serum obtained from 45 inoperable breast cancer patients before and after neo-adjuvant chemotherapy. The median follow-up time was 46 months (range 10-96). All patients out of two were operated after chemotherapy. There were 21 relapses and 17 patient died.

Results: The median serum YKL-40 concentration was 149.5 µg/ml (range 25–1021.3) in patients with salivary metastases and this was higher than that in patients without metastatic disease (p = 0.44). Serum YKL-40 levels were higher in patients with tumor >2 cm and in patients with node + disease (p = 0.03). Also the tumor volume was found correlated with serum YKL-40 level (r = 0.308, p = 0.039). Regression of tumor volume with chemotherapy was also correlated with serum YKL-40 level decrease (r = 0.485, p = 0.01). Patients with high serum YKL-40 had shorter disease free survival and overall survival but it was not significant (p > 0.05). Multivariate analysis including tumor size, lymph node status and estrogen receptor status were also independent prognostic variables (p < 0.05).

Conclusions: Our results show that levels of serum YKL-40 might be useful for determination of metastatic status of SN in breast cancer by using intraoperative immunohistochemistry.

190P ELICITATION OF UK HEALTH UTILITIES IN PRIMARY, RECURRENT AND METASTATIC BREAST CANCER

Mel Walker1, Patricia van Hanswijk de Jonge2, Scott Doyle3, Carole Farina4

1Roche Product Ltd, Medical Affairs (Oncoology), Welwyn Garden City, United Kingdom, 2United BioSource Corporation, Outcomes Research, London, United Kingdom

Objectives: The aim of this study was to elicit societal utility scores for primary breast cancer related health states describing early (<5 years post-diagnosis) and later disease free survival (>5 years post-diagnosis), loco-regional recurrence, contra-lateral primary disease and metastatic disease.

Methods: Health state descriptions were developed based upon in-depth exploratory and validation interviews with breast cancer specialists (Medical oncologists n=3, nurses n=3). Following a pilot, participants (UK general public, n=100) assessed their preference for each health state using a Visual Analogue Scale (VAS) and standard gamble (SG) interview.

Results: The study sample was a relatively good match to the characteristics of the general public in England and Wales (ONS, 2001). Mean VAS scores ranged from 69.7 for early disease free survival to 22.5 for metastatic disease. Mean SG utility scores ranged from 0.75 for early disease free survival and for 0.85 later disease free survival, to 0.58 for contra-lateral primary disease and 0.57 for loco-regional recurrence, to 0.48 for metastatic disease (P<0.0001). An ANOVA revealed that SG utility values for the health states were significantly different from each other (F=53.54, P<0.0001) for all the health states with the exception of loco-regional recurrence and contra-lateral primary disease.

Conclusions: Participants could differentiate early and late disease free survival and rated both as resulting in a considerable decrement from full health. In contrast
IMPROVEMENTS IN QUALITY OF LIFE (QOL) ASSOCIATED WITH CAPECTABINE (X) TREATMENT FOR METASTATIC BREAST CANCER (MBC) IN BRAZIL: UPDATED RESULTS FROM A LARGE COHORT OF 1683 PATIENTS (PTS), INCLUDING ANALYSIS AS A FUNCTION OF ECOG PS

Célia Tosseto1, José Segalla2, Ronaldo Ribeiro3, Sérgio Tesseraro4, Sebastião Cabral5, Fábio Franke6, Martha Percardis5, Urias de Paula5, Glaci Moura9, 1Guy’s and St Thomas’ Hospital, Oncology, London, United Kingdom, 2United Carole Cohen5, Una Geary5, Mel Walker5 Beneficência Portuguesa De Santos, Oncology, Santos, Brazil, 8Real City Hospital, Oncology, Birmingham, United Kingdom, 4United BioSource Lucy Brazil1, Edit Remak2, Christopher J. Poole3, Noemi Muszbek4, Celia Tosseto1, José Segalla2, Ronaldo Ribeiro3, Sebastião Cabral5, Fábio Franke6, Martha Percardis5, Urias de Paula5, Glaci Moura9, 1Guy’s and St Thomas’ Hospital, Oncology, London, United Kingdom, 2United Carole Cohen5, Una Geary5, Mel Walker5 Beneficência Portuguesa De Santos, Oncology, Santos, Brazil, 8Real City Hospital, Oncology, Birmingham, United Kingdom, 4United BioSource

BACKGROUND: The oral fluoropyrimidine X (Xeloda®) is highly active and well tolerated as single-agent therapy and extends survival when added to docetaxel in pretreated MBC. (O’Shaughnessy et al. J Clin Oncol 2002). In addition to response rates and survival endpoints, it is important to consider medical resource savings, QoL, and pt preference for oral therapy in pts with metastatic disease.

Methods: QoL was evaluated in women with anthracycline +/- taxane-pretreated MBC while receiving X (baseline before cycle 1, at weeks 7 and 13, and at treatment end) using EORTC QLQ-C30 (v 3.0) and BR-23 questionnaires with repeated measures (generalised estimating equation technique) and SAS (v 9.1) to determine improvement, stabilisation or worsening of QoL scores from week 7 onwards. Each questionnaire item was analysed as a function of pt’s ECOG status before first cycle and the evaluation period.

RESULTS: Baseline characteristics of the 1683 evaluable pts were: median age 54 years (range 22–93), race white/black/other 79%/10%/11%, median EGEC PS 1 (range 0–4). At baseline 86% of pts had ECOG PS 0-3; by the end of treatment 98% of pts had an improvement in ECOG PS. X therapy was also associated with significant improvements in pts’ perception of: physical functioning, constitution and future perspective (p<.0001), role functioning, social function and nausea/vomiting (p<.0008), insomnia, appetite loss and body image (p<.0036).

CONCLUSIONS: Pts treated with X had substantial improvements in almost all functional and symptom QoL domains. These X results, together with other proven clinical outcomes, suggest that early use of X in MBC would be of benefit to pts. Our findings highlight the importance of considering QoL and other measurable benefits of oral treatments alongside well-established clinical measures in pts with MBC.

COST OF MANAGING RECURRENT HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2 (HER2) POSITIVE BREAST CANCER IN WOMEN PREVIOUSLY TREATED FOR EARLY STAGE DISEASE IN THE UK

Lucy Brazil1, Edit Remak2, Christopher J. Poole3, Noemi Muszbek4, Carole Goren5, Una Geary6, Mel Walker7, 1Guy’s and St Thomas’ Hospital, Oncology, London, United Kingdom, 2United BiocSource Corporation, Health Care Analytics Group, London, United Kingdom, 3City Hospital, Oncology, Birmingham, United Kingdom, 4United BiocSource Corporation, Health Care Analytics Group, London, United Kingdom, 5Roche Products Ltd, Health Outcomes, Weiklyin Garden City, United Kingdom

OBJECTIVES: Women with breast tumours expressing HER2 represent a distinct group of patients with poorer prognosis. This study aimed to estimate their monthly treatment costs in the UK, following initial treatment.

Methods: Real costs of treatment are poorly documented, therefore a panel of cancer physicians was asked to complete questionnaires designed to determine patterns of treatment in stage IV disease; follow-up in stage IV disease until disease progression; initial treatment of primary tumour; treatment of local recurrence; treatment of metastatic disease. The average monthly cost of other treatment for recurrence and over and above surgery was £2,252 (±1,773). In metastatic disease, monthly cost of treatment, follow-up, and supportive care was £2,831 (±1,488), £572 (±461), and £2,063 (±1,014), respectively. Duration of end-of-life phase averaged 2 weeks, and cost £2,728 (£823). Therefore, the total estimated cost of treatment for stage IV disease ranged from £23,800 to £46,760. Besides trastuzumab, women with HER2 positive tumours were also reported to consume considerably more resources compared with the average patient populations reported in previous studies.

Conclusion: The additional economic burden associated with HER2 positive patients must be considered when undertaking economic evaluations of treatment interventions in this population.

EXTENDED ADJUVANT LETRozole FOLLOWING FIVE YEARS OF TAMOXIFEN IS COST-EFFECTIVE FROM A BELGIAN HEALTH CARE PAYER’S PERSPECTIVE

Pascal Lecomte1, Martine Bertilié2, Fabrice Branche2, Herman Depypere2, Luc Dirix2, Guy Jerusalem7, Fabienne Liebens5, Patrick Neven3, Robert Pandaens1, Novartis, Regulatory and External Affairs, Vilvoorde, Belgium, 2UCIL, Gynaecology, Brussels, Belgium, 3Erasme, Oncology, Brussels, Belgium, 4Erasme, Gynaecology, Brussels, Belgium, 5LVZ Gent, Gynaecology, Gent, Belgium, 6AZ St.-Augustinus, Oncology, Wilrijk, Belgium, 7CHU Sint-Tiernan, Oncology, Lége, Belgium, 8CHU St-Pierre, Gynaecology, Brussels, Belgium, 9UZ Gasthuisberg, Gynaecology, Leuven, Belgium, 10UZ Gasthuisberg, Oncology, Leuven, Belgium

Background: MA-17 was a randomized placebo-controlled trial of 5 years of letrozole ( Femara®) 2.5 mg/d in 5187 postmenopausal women with early breast cancer, post 5 years of tamoxifen. Due to dose-difference in dose regimens (letrozole [92.8% vs 86.8% at 4 years (p<0.001), HR 0.85 (p<0.001)]) and a similar trend in overall survival [96% vs 93.7% at 4 years (p=0.05), HR 0.76 (p<0.05)], the trial was unblinded early after 2.4 years mean follow-up. Cost-effectiveness of extended letrozole use in Belgium has not been examined previously.

Methods: A published Markov model comparing adjuvant therapies for breast cancer was adapted to evaluate the cost-effectiveness of 5 years extended adjuvant letrozole after five years of tamoxifen in postmenopausal women aged 62 years, 50% node positive, with early breast cancer. Model probabilities were based on patient level data from the MA17 study and the literature. Utility values were derived from published sources and-health care resources used were obtained from a survey among nine Belgian clinicians (oncologists and gynaecologists). Treatment costs were calculated from the Belgian health care payer’s perspective (INAMI/RIZIV). Cost-effectiveness was calculated as the ratio of the difference (letrozole vs. placebo) in expected lifetime costs of breast cancer care to the difference in life years (LYs) and quality-adjusted LYs (QALYs) respectively. Costs, LYs, and QALYs were discounted at 5% annually.

Results: Letrozole therapy was estimated to increase LYS and QALYs per patient by approximately 0.363 and 0.282, respectively. Expected lifetime costs were 5,377€ greater with letrozole vs. placebo (13,797€ vs. 8,404€). The cost per QALY gained with letrozole vs. placebo was 19,063€ which is considered cost-effective. Interestingly, analyses conducted based only on node positive patients and/or considering a shorter duration of letrozole treatment (i.e. 3 years instead of 5 years) also showed that letrozole is cost-effective.

Discussion: Result from the MA17 analysis suggest that 5 years of extended adjuvant letrozole (Femara®) is cost-effective and should be considered in women with early breast cancer, following tamoxifen.

NON-MYELOABLATIVE TRANSPLANTATION FOR BREAST CANCER: RATIONALE FOR TREATMENT GUIDELINES

Marlies E. Van Hoef1, Oncology, Leuven, Belgium

Introduction: In acute leukemia best therapy consist of fast remission-induction, consolidation of complete response and (non-myeloablative)allogeneic transplantation to eradicate residual malignant cells. This therapeutic plan at diagnosis induces highest probability of disease free and overall survival. Herein evaluation of the approach for breast cancer is presented.

Methods: The three treatment combinations were defined as independent entities and based on European guidelines: treatment related mortality (TRM) of HD-auto-tx is 0-3%. Allogeneic transplants is 2-3 times higher than after allogeneic transplant in first consolidated remission 20%. Adequate prophylaxis for and treatment of graft versus host disease is emerging and can minimize the risk of treatment related mortality.

Discussion: Discussion from the MA17 analysis suggest that 5 years of extended adjuvant letrozole (Femara®) is cost-effective and should be considered in women with early breast cancer, following tamoxifen.
Annals of Oncology

195 RESPONSE OF DOCECTAXE L+ADRIAMYCIN) AND ADRIAMYCIN+CYCLOPHOSPHAMIDE+5-FU (ACF)REGIMEN AS NEOADJUVANT CHEMOTHERAPY FOR LOCALLY ADVANCED BREAST CANCER – A BANGLADESH PERSPECTIVE

Dawooduddin D. Uddin1, Abmatshu H. Hannan2
1Rajshahi medical college hospital, Radiotherapy, Rajshahi, Bangladesh, 2Rajshahi medical college hospital, Surgery, Rajshahi, Bangladesh

Background: The management of LABC which contributes about 80 percent of cases is still questionable. We conducted a phase II trial with the combined Neoadjuvant chemotherapy regimen either with Adriamycin and docetaxel (AT) or Adriamycin,Cyclophosphamide and 5-Fluorouracil (CAF).

Objective: The purpose of the study was to assess the response rate and resectability of primary tumours. The other purposes were to reduce the tumour burden and to limit the number of patients who will require saline wash out before surgery.

Method: Fifty patients of LABC from July 2003 to December 2005 were treated by combination chemotherapy preoperatively either by AT or CAF. We selected doxorubicin 75 mg/m² and docetaxel 75 mg/m² (AT) for 24 patients and doxorubicin is 60 mg/m², cyclophosphamide is 600 mg/m² and 5FU 600 mg/m² (ACF) for 26 patients.

Chemotherapy were given 3 weekly and average 3 cycles were administered for each patient.

Result: In AT regimen, Over all response rate (ORR) is 83% (20patients) with partial response in 12 patients (60%) and complete response in 9 patients (43%) and stable disease in 5 patients (24%). In the patients treated with CAF regimen, 15 patients (62%) underwent surgery. With ACF regimen ORR was 54% (14 patients) where complete response was seen in 11.5% cases and partial response in rate is 37% cases with the stable diseases in 3 patients.

With this regimen, surgical resection rate was 35% with 9 patients.

Conclusion: Neoadjuvant chemotherapy is an active and well tolerated, with no unexpected toxicity.

196 LIPOSOME-ENCAPSULATED DOXORUBICIN PLUS CYCLOPHOSPHAMIDE AS FIRST LINE THERAPY IN METASTATIC BREAST CANCER

Vasilios Heras, Antonios Hatzopoulos, Panagiotis Heras
General Hospital of Naftolon, Internal Medicine, Athens, Greece

Background: The objective of this study is to evaluate the efficacy and toxicity of the liposome- encapsulated doxorubicin (TLC D-99) plus cyclophosphamide (CTX) as first-line treatment of metastatic breast cancer in light of the potential cardioprotective effect of TLC D-99 as compared to conventional doxorubicin.

Furthermore the study is aimed also to understand the role of troponin 1 as a sensitive cardioprotective effect of TLC D-99 as compared to conventional doxorubicin.

Methods: Patients of LABC were included in this study.

Result: From 1990 to 2003, 184 patients were enrolled in 3 consecutive phase II trials of MBC patients undergone 1st line chemotherapy. In addition, 39 (59%) were post-menopausal, 50 (77%) had estrogen receptor positive, and 33 (50%) had progesterone receptor positive.

Conclusion: The majority of patients with breast cancer stage I-II treated with pegfilgrastim once per IV CMF cycle can achieve the threshold of RDI that has been associated with improved survival (85% over all cycles).

197 RELATIVE DOSE INTENSITY OF INTRAVENOUS (IV) CYCLOPHOSPHAMIDE, METHOTREXATE, AND 5-FLOUOROURACIL (CMF) IN PATIENTS WITH STAGE I-III BREAST CANCER RECEIVING PEGFILGRASTIM SUPPORT

Rodolfo Matticci1, Cesare Gridelli2, Javier Castellanos2, Antonio Duque1, Alfredo Falcone1, Marco Mansutti6, Tim Cushway7, Sue Lawrinson8, Rodolfo Mattioli1, Cesare Gridelli2, Javier Castellanos3, Antonio Duque4, Giuseppe Moscati, Oncologia, Avellino, Italy, 3Complejo Hospitalario Universitario Xeral-Cies de Vigo, Oncology, Vigo, Spain, 4Hospital Universitario General Hospital of Nafplion, Internal Medicine, Athens, Greece

Background: The management of LABC which contributes about 80 percent of cases is still questionable. We conducted a phase II trial with the combined Neoadjuvant chemotherapy regimen either with Adriamycin and docetaxel (AT) or Adriamycin, Cyclophosphamide and 5-Fluorouracil (CAF).

Methods: Fifty patients of LABC from July 2003 to December 2005 were treated by combination chemotherapy preoperatively either by AT or CAF. We selected doxorubicin 75 mg/m² and docetaxel 75 mg/m² (AT) for 24 patients and doxorubicin is 60 mg/m², cyclophosphamide is 600 mg/m² and 5FU 600 mg/m² (ACF) for 26 patients.

Chemotherapy were given 3 weekly and average 3 cycles were administered for each patient.

Result: In AT regimen, Over all response rate (ORR) is 83% (20 patients) with partial response in 12 patients (60%) and complete response in 9 patients (43%) and stable disease in 5 patients (24%). In the patients treated with CAF regimen, 15 patients (62%) underwent surgery. With ACF regimen ORR was 54% (14 patients) where complete response was seen in 11.5% cases and partial response in rate is 37% cases with the stable diseases in 3 patients.

With this regimen, surgical resection rate was 35% with 9 patients.

Conclusion: Neoadjuvant chemotherapy is an active and well tolerated, with no unexpected toxicity.

198 WEEKLY CHEMOTHERAPY FOR METASTATIC BREAST CANCER PATIENTS: MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS OF TEN-YEARS EXPERIENCE

Cecilia Nistico1, Federica Cuppone1, Emilio Bria1, Daniela Giannarelli2, Marcella Morello3, Flavia Novelli4, Guido Notoli5, Rossana Pisal,6 Edmondo Terzol7
1Regina Elena Cancer Institute, Medical Oncology, Roma, Italy, 2Regina Elena Cancer Institute, Biostatistics, Roma, Italy, 3Regina Elena Cancer Institute, Pathology, Roma, Italy

Introduction: Weekly administration of chemotherapy represents an emerging option for the treatment optimization of metastatic breast cancer (MBC). Moreover, evidences suggest a intriguing mechanism of action for weekly paclitaxel, which involves pro-apoptotic and anti-angiogenetic pathways. In order to identify clinical and biological prognostic factors for weekly chemotherapy outcome, we performed a multivariate analysis in a 10-years experience of weekly 1 line chemotherapy for MBC patients.

Methods: The original databases of phase II trials of MBC patients undergone 1st line chemotherapy were collected. Clinical and biological co-variables were screened for the eventual relationship with time to progression (TTP) and overall survival (OS) into a Cox model.

Results: From 1990 to 2003, 184 patients were enrolled in 3 consecutive phase II studies, to evaluate activity and tolerability of weekly epirubicin with lonidamine, or vinorelbine or paclitaxel, for 24 weeks. All patients were evaluable for clinical variables, while histological samples were available in only 40 patients. At a median follow-up of 24 months, median TTP was 9 months (95% CI 8.10) and median OS 34 (95% CI 24-42).

Independent variables were: response (HR 2.34, p<0.0001), receptor status (HR 2.42, p=0.01), and stage (HR 2.42, p=0.01). Two variables were selected as independent predictors of survival: response and receptor status.

Conclusion: The preliminary data show that the combination of TLC D-99 plus CTX is active and well tolerated, with no unexpected toxicity.

199 VINORELIN - DOXORUBICIN COMBINATION CHEMOTHERAPY IS AN ACTIVE AND SAFE REGIMEN FOR PATIENTS (PTS) WITH METASTATIC BREAST CANCER (MBC): UPDATED RESULTS OF A LARGE SYRIAN PHASE II TRIAL

Amer Al Chikh Youssef1, Iyad El Shatty2, Rakam El Shatty3, Nadine Haddad4
1Cancer Center of Damascus, Oncology, Damascus, Syrian arab republic, 2Cancer Center of Damascus, Pathology, Damascus, 3Cancer Center of Damascus, Oncology, Damascus, Syria, 4Cancer Center of Damascus, Oncology, Damascus, Syria

Background and Objective: Relapse-free and overall survival in patients with breast cancer treated with CMF is significantly longer in those who receive at least 85% RDI (Bonadonna, 1995). Less than 50% of patients treated with IV CMF achieve ≥85% RDI (Ackland et al, 2001). Severe neutropenia and related complications are a major reason for dose delays and dose reductions (DD/DR). This multicenter, single arm, phase 2 study was designed to evaluate the proportion of patients with breast cancer who achieve ≥85% RDI of IV CMF when pegfilgrastim is administered to support neutrophil recovery.

Methods: Eligible patients had stage I-III breast cancer, no prior chemo- or radiotherapy, and normal blood counts. Patients received cyclophosphamide 600 mg/m², methotrexate 40 mg/m², and 5-fluorouracil 600 mg/m² IV on day 1 and day 8 every 28 days for a total of 6 cycles. Pegfilgrastim was given as a single 6-mg dose on day 8 of each cycle.

Results: Of the 58 patients enrolled, all started the first cycle of chemotherapy and received pegfilgrastim. A total of 50 patients (86%) started all 6 cycles of chemotherapy, and 49 (84%) completed the study. Most of the patients were women (93%) and all were Caucasian. Mean (SD) age was 58 (10.6) years. Disease stage was as follows: stage I, 38%; stage II, 61%; stage III, 2%. In addition, 34 (59%) were pre-menopausal, 50 (86%) were estrogen-receptor positive, and 57 (98%) were undergoing adjuvant therapy. Over all cycles, 48 patients (83% [95% CI, 71%, 91%]) received ≥85% RDI. Of the 10 patients with < 85% RDI, reduced RDI was due to early withdrawal (i.e., failure to complete all 6 cycles) in 8 patients (2 of whom had DD/DR) and solely due to DD/DR in 2 patients who did complete all 6 cycles. Two patients (3%) had febrile neutropenia during the study and 6 patients (10%) had grade 4 neutropenia.

Conclusion: The majority of patients with breast cancer stage I-III treated with pegfilgrastim once per IV CMF cycle can achieve the threshold of RDI that has been associated with improved survival (85% over all cycles).
Background: Vincristine (NovoVinc®) and doxorubicin (A) are active agents in the management of breast cancer. Several international studies reported the definite efficacy of V+A in advanced or in early disease (Blagman; cancer 99, Smith; ASCO 63). Here we report our experience of a large phase II trial with V+A combination in metastatic breast cancer (MBC).

Patients and methods: Eligible pts had confirmed MBC, WHO PS ≤2, measurable disease, adequate bone marrow, renal and liver functions. Prior neo/adjuvant chemotherapy was allowed. Pts received V: 25 mg/m² on d1 & d8, plus A: 50 mg/m² on d1. Chemonaive pts received a total of 6 cycles, anthracycin pre-treated pts received 4 cycles. Cycles were repeated q3w. Pts were evaluated every 3 cycles for response and every cycle for toxicity.

Results: 54 pts were enrolled: 27 pts (50%) chemonaive, and 27 pts (50%) had received neoadjuvant (2pts) or adjuvant (25pts) chemotherapy. Median age: 44 years (range 25 to 70), WHO PS 0-1. The main sites of metastasis were liver in 14 pts (25.9%), lung in 15 pts (24.1%), bone in 11 pts (20.4%), and skin in 4 pts (7.4%). Median number of metastatic sites per patient: 2. All pts were evaluable for efficacy and safety. 45 pts with achieved clinical objective responses (ORR:83%) including 2 CR and 9 PR.

Conclusion: Result of our study are similar to the international data and confirm that V+A combination in metastatic breast cancer (MBC) is a highly active and safe regimen for MBC pts.

### Table 1: Chemonaive vs. Non chemonaive

<table>
<thead>
<tr>
<th></th>
<th>Chemonaive</th>
<th>Non chemonaive</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>77.8%</td>
<td>88.8%</td>
</tr>
<tr>
<td>TTP (months)</td>
<td>21.7</td>
<td>10</td>
</tr>
<tr>
<td>OS (months)</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
</tbody>
</table>

### Table 2: DOXETAXEL(D) AND GEMCITABINE(G) FOLLOWED BY LIPOSOMAL DOXORUBICIN(LD) AS FIRST-LINE SEQUENTIAL THERAPY IN METASTATIC BREAST CANCER: SAFETY RESULTS IN ONGOING GALICIAN STUDY

Silvia Antonio, Jesus Garcia Mata, Manuel Ramos, Juan F. Cuenca, Lourdes Calvo, Jesus Garcia Gomez, Ana Gonzalez, Diana Doipo, Eva Perez

C. H. U. Juan Canalejo, Oncology, A Coruña, Spain; C. H. U. D. Ourense, Oncology, Ourense, Spain; C. Centro Oncologico De Galicia, Oncology, A Coruña, Spain; C. H. U. Santiago, Oncology, A Coruña, Spain

Purpose: To evaluate activity and toxicity of the bieweekly combination of D and G followed by LD (EoLon®) as first-line therapy of MBC. Patients and methods: To date, twelve patients have been enrolled in the study. All pts had MBC erb-2 negative, age < 75 years, measurable lesion, ECOG ≤ 2, normal haematological and biochemical tests, no prior chemotherapy for MBC, left ventricular ejection fraction (LVEF) >50% and the informed consent was given in all the cases. Patients received D 65 mg/m² and G 1.650 mg/m², both in 1 h infusion, day 1 every 14 days for a minimum of four cycles up to a maximum of six followed by LD 25 mg/m² day 1 every 21 days, up to 4 cycles. Toxicity was evaluated every cycle and response at the end of DG and LD.

Results: For this safety analysis, median age of the population was 49.5 years (37–65); and ECOG was 0–1 for all the pts. Post-menopausal status was in 75% of pts. Prior adjuvant chemotherapy was given in 75% (with anthracycin in 67% of pts and taxane in 25%). Seven of pts received adyuvant radiotherapy. Median recurrence-free interval was 2.5 years. More than two distant metastatic sites were present in 67% of pts and dominant disease included pleuro-pulmonary (5 pts), liver (2 pts), bone (1 pt) and soft tissue (4 pts). A total of 305 cycles were administered and the median of number of cycles were 5 for DG sequence and 4 for LP treatment. On February 2006, all pts were evaluable for safety and ten pts for efficacy (two pts are still ongoing). Median relative dose intensity was 92% for D, 95% for G and 100% for LP. After sequence, none progression was observed and overall response rate (ORR) was 25%. At the end of sequence, the ORR reached 60% with none complete response nor disease progression. The safety profile showed good tolerability. No G4 toxicity was found. G3 neutropenia was observed only in 12% of DG of cycles and in 2% of LD cycles. Fatigue G2-G3 was observed in 22% of cycles. Only 4 pts progressed after median follow-up of 11 months, without deaths.

Conclusion: In this subset of patients with MBC, the sequence DG followed by LD provides a promising response rate, particularly after LD treatment, and acceptable safety profile with low toxicity.
Conclusion: In this group of MBC patients, with a high percentage of visceral disease was 1 CR, 16 PR, 17 SD, 12 PD (remission rate 34.5%; 95% CI: 22%–46%). Activity diarrhea (3.6%), mucositis (2%), hand-foot syndrome (9.3%). In 51 assessable there disease: soft tissues 7 pts (13%), bone 9 pts (16%), visceral 39 pts (71%); prior treatment for advanced disease were treated with capecitabine 2000 mg/m²/day for 14 consecutive days, every 3 weeks. At least 1 complete cycle was required for substantial anti-tumor activity, with little myelosuppression.

Background: Capecitabine (Xeloda) is an oral fluoropyrimidine active against MBC. Our purpose was to evaluate its efficacy and safety in our daily clinical practice. Method and Materials: Patients with measurable or evaluable MBC, KI ≥ 40%, adequate bone marrow, liver and renal functions, prior adjuvant chemotherapy or prior treatment for advanced disease were treated with capecitabine 2000 mg/m²/day p.o., for 14 consecutive days, every 3 weeks. At least 1 complete cycle was required for evaluable results. Results: From Sep 02 to Dec 05, 55 patients with MBC received 359 cycles (median cycle/patient 4.5, range 1-19). Median age 64 yr (range 32-83); predominant site of disease: soft tissues 7 pts (13%), bone 9 pts (16%), visceral 39 pts (71%); prior chemotherapy: adjuvant 22 pts (40%), metastatic 16 (29%). Grade 3-4 toxicities: NCI CTC version 3.0: pts) = anemia (2%), asthenia (2%), anorexia 3.5%, vomiting (3.6%), diarrhea (3.6%), mucositis (2%), hand-foot syndrome (9.5%). In 51 assessable there was I CR, 16 PR, 17 SD, 12 PD (remission rate 34.5%: 95% CI 22%–46%). Activity was not related to site of disease or prior chemotherapy. Median relative dose intensity received was 79.2% (range 58%–112%). Median time to disease progression and survival time were 25.6 wks (95% CI 13.8–37.4) and 68 wks (95% CI 38.5–92.2), respectively. Conclusion: In this group of MBC patients, with a high percentage of visceral disease and exposed to prior chemotherapy, capecitabine was an effective and well tolerated treatment.

ACTIVITY OF FIRST OR SECOND-LINE CAPECITABINE IN METASTATIC BREAST CANCER (MBC). A RETROSPECTIVE ANALYSIS OF ITS APPLICATION IN THE CLINIC

Maria Luque, Paula Jimenez, Yolanda Fernandez, Emilio Esteban, Jose Maria Busa, Marta Capelan, Beatriz Llorrente, Joaquina Frn, Noemí Villanueva Hospital Universitario Central de Asturias, Clinical Oncology, Oviedo, Spain

Background: Capecitabine is an oral fluoropyrimidine active against MBC. The clinical activity of first or second-line capecitabine in advanced breast cancer patients has been already demonstrated. Our experience with this treatment is described in this study.

Method and Materials: From Sep 02 to Dec 05, 55 patients with MBC received 359 cycles (median cycle/patient 4.5, range 1-19). Median age 64 yr (range 32-83); predominant site of disease: soft tissues 7 pts (13%), bone 9 pts (16%), visceral 39 pts (71%); prior chemotherapy: adjuvant 22 pts (40%), metastatic 16 (29%). Grade 3-4 toxicities: NCI CTC version 3.0: pts) = anemia (2%), asthenia (2%), anorexia 3.5%, vomiting (3.6%), diarrhea (3.6%), mucositis (2%), hand-foot syndrome (9.5%). In 51 assessable there was I CR, 16 PR, 17 SD, 12 PD (remission rate 34.5%: 95% CI 22%–46%). Activity was not related to site of disease or prior chemotherapy. Median relative dose intensity received was 79.2% (range 58%–112%). Median time to disease progression and survival time were 25.6 wks (95% CI 13.8–37.4) and 68 wks (95% CI 38.5–92.2), respectively. Conclusion: In this group of MBC patients, with a high percentage of visceral disease and exposed to prior chemotherapy, capecitabine was an effective and well tolerated treatment.

PEGYLATED LIPOSOMAL DOXORUBICIN (PEG-LD) AND PACITAXEL IN PATIENTS WITH METASTATIC BREAST CARCINOMA: A PHASE II STUDY

Vita Leonardi, Valentina Palmisano, Alessio Pepe, Antonella Usset, Giuseppina Savio, Agata Laudani, Caterina Calabria, Giacomo Rondello, Gianluca Marrone, Elia Agostoni Oncologic Hospital “M.Ascali” ARNAS Civico, Oncologic Department, Palermo, Italy

Introduction: Systemic chemotherapy has saved the life of many patients with cancer, but the maximum efficacy of cytotoxic agents is severely limited by their adverse effects. PEG-LD has the advantage of delivering the active anthracycline directly to the tumor site while exposing the patient to a lesser degree of doxorubicin-associated toxicity. More recently, a regimen in which Paclitaxel is infused weekly over 1 hour produced substantial anti-tumor activity, with little myelosuppression.

Materials and Methods: We designed a phase II trial to study the efficacy and toxicity of Peg-LD 10 mg/m² administered weekly in metastatic breast cancer patients with high cardiologic risk. All patients were pretreated with Pyridoxine 500 mg/daily per os and Desmatasono 8 mg i.v. before each chemotherapy administration to prevent the palmar-plantar erythrodysesthesia (PPE). To date, 25 pts have been recruited, 22 pts (88%) evaluable for efficacy and 25 pts (100%) for toxicity. Adjuvant chemotherapy had been administered in 21 pts (anthracycline-based in 14 pts); 17 pts (68%) had two or more sites of disease. Efficacy: Overall, 3 CR, 13 PR have been recorded with an overall response rate of 68.1%. 5 NC and 2 PD had been registered. Toxicity: Toxicity was generally manageable; the only grade 3.4 side effects recorded were: PPE 12%, mucositis 4%, leukopenia 16%, AST/ALT 4%. No cardiotoxicity, no neurotoxicity was seen. Conclusions: The weekly Paclitaxel and Peg-LD appears to be a well tolerated and effective approach in metastatic breast cancer patients with high cardiologic risk. This phase II study will continue to accrue patients until 40 pts are enrolled.

206 WEEKLY PACITAXEL AND TRASTUZUMAB AS FIRST-LINE CHEMOTHERAPY IN PATIENTS WITH HER-2 POSITIVE METASTATIC BREAST CANCER

Jin-Soo Kim1, Hyo-Suk Han1, Seok-Ah Im1, Do-youn Oh1, Won-Shik Han2, Se-Hoon Lee1, Dong-Wan Kim1, Tae-You Kim1, Dong-Young Noh2, Yung-Jue Bang3
1Seoul National University Hospital, Internal Medicine, Seoul, Republic of Korea, 2Seoul National University Hospital, Surgery, Seoul, Republic of Korea

Background: The clinical efficacy and favorable safety profile of trastuzumab in HER-2 positive metastatic breast cancer (MBC) have been demonstrated when administered as monotherapy and in combination with chemotherapy. Weekly paclitaxel is effective and well tolerated in patients with MBC. We evaluated the efficacy and safety of weekly paclitaxel and trastuzumab in women with HER2 positive MBC as a first line chemotherapy. Patients and methods: Patients with HER-2 over-expression defined as 3+ using IHC or amplification using fluorescence in-situ hybridization (FISH) were eligible. From Feb 2004 to Apr 2006, 30 patients with HER-2/neu positive MBC were enrolled (Median age 47.5 years, 20 patients: relapsed, 10 patients: initially stage IV). Treatment consisted of weekly paclitaxel; given by one-hour infusion at a dose of 80 mg/m² immediately followed by trastuzumab, 4 mg/kg as a loading dose and 2 mg/kg i.v. given over 30min, thereafter weekly. Results: Patients received a median of 15 weekly infusions (range, 3 to 39 infusions). 27 patients completed at least 8 weeks of combined treatment. Three patients (10.0%) achieved complete response, 19 patients (63.3%) partial response, and 5 patients (16.7%) stable disease. The response rate (CR + PR) was 73.3%. The median follow-up duration was 202 days (range 71 to 762 days). The median duration of response, time to progression and overall survival was not reached. Five patients positively progressed after a median of 7.4 months. One year projected progression free survival was 59.8%. Therapy was tolerated well, the grade 3/4 toxicities were leukopenia (6.7%), neutropenia (16.7%), neurotoxicity (6.7%). Onycholysis grade 2 was recorded in two patients. No symptomatic cardiac toxicity was observed. Conclusion: The combination of weekly paclitaxel and trastuzumab is well tolerated and effective regimen for patients with HER-2 positive MBC as 1st line chemotherapy.
majority of pts experienced skin rashes: Grade (GR) 1/2 (50%); GR 3/4 (6%). Other GR 3/4 non-hematological toxicities included: fatigue (12.5%); nausea (6.3%); vomiting (6%); anemia (6.3%); ALT elevation (6.3%); neutropenia (6.3%); grade 2–4 neurotoxicity (5%); neuropathy (6.3%) and peripheral neuropathy (6.3%). One pt experienced reversible GR 3/4 elevation of liver transaminases. The most significant hematological toxicity was febrile neutropenia (FN 19%).

Conclusions: PEM and GEM were generally well tolerated with the exception of FN. This regimen showed no clinical activity in the dose and schedule tested. This study did not meet the predefined criteria to proceed with additional accrual.

208 SEQUENTIAL DOXORUBICIN PLUS VINORELBINE (AV) FOLLOWED BY DOXETAXEL PLUS CARBOPLATIN (DC) AS NEOADJUVANT CHEMOTHERAPY FOR ADVANCED BREAST CANCER PATIENTS

Maria Santelias1, Susana de la Cruz1, Jesús Javier Solà2, José Manuel Aranda1, Laura Espert1, Cristina Garrido1, Fernando Martínez-Peguera1, Gerardo Zornoza1, Oscar Fernández-Hidalgo1, Yago Nieto1
1Clinica Universitaria de Navarra, Clinical Oncology, Pamplona, Spain, 2Clinica Universitaria de Navarra, Anatomicopathology, Pamplona, Spain, 3Clinica Universitaria de Navarra, Radiology, Pamplona, Spain, 4Clinica Universitaria de Navarra, Breast Disease Unit, Pamplona, Spain

Background: We aimed to determine the feasibility of a novel sequential AV - DC treatment as preoperative treatment for advanced BC.

Methods: Patients (pts) with chemotherapy-naive BC who were deemed candidates for preoperative chemotherapy were eligible. The regimens were as follows: C(40–75 mg/m2) on day 1 and V210 mg/m2 on days 1 and 8 every three weeks, followed by 4 cycles of D(15 mg/m2) and C(50 mg/m2) every 23 days. Five patients received ramsuth (6 mg/kg) × 4 doses concurrently with DC in the neoadjuvant setting. Surgery was performed after either 4 or 8 cycles in 19 and 13 pts, respectively.

Results: 32 pts were enrolled between 8/2001 and 8/2005. Median age was 48 (26–79) years. Tumor characteristics were ER status 90%, PR status 68%, C-erbB2 status 18%. Dose modifications were performed in 7 pts (22%); in 6 cases due to myelosuppression, 1 due to peripheral neuropathy.

Conclusion: This regimen is feasible, well tolerated and active in the preoperative setting when compared with other sequential regimens for advanced breast cancer.

209 CAPECITABINE MONOTHERAPY IN PRE-TREATED PATIENTS WITH METASTATIC BREAST CANCER

Constantine Gennatas1, Vasili P. Michalaki1, John Psychogios1, Christos E. Koraklis1
1University of Athens, Areteion Hospital, Medical Oncology Clinic, Department of Surgery, Athens, Greece, 2University of Athens, Areteion Hospital, Department of Pathology, Athens, Greece

Background: The optimal management of patients with metastatic breast cancer (MBC), whose diseases have failed to respond to anthracycline and taxane, represents a significant challenge. Many of these women remain candidates for cytotoxic chemotherapy, and several treatment options exist. Capecitabine, a selectively tumour-targeting agent that has been proven to be effective when used alone for metastatic breast cancer, is a feasible treatment option for pre-treated MBC patients.

Patients and methods: Forty-two patients (age 36–75, median 55), with MBC, who had been previously treated with anthracycline and taxane, received oral capecitabine monotherapy 1,000 mg/m2 twice daily, days 1–14, every 3 weeks until progressive disease. Clinical response was evaluated every 3 cycles and all patients were evaluable for toxicity.

Results: Among the 42 evaluable patients, 14 patients (33%) achieved an objective response, including 2 (4.7%) complete responses. With a median follow-up duration of 18 months the median time to progression was 4.5 months and the median overall survival was 14.5 months. The most common adverse events were hematological toxicity 16%, hand-foot syndrome 12%, asthenia 10%, diarrhea 9.5%, vomiting 7% and mucositis 2.4%. Toxicities (following dose reductions if needed) were in generally manageable by most patients. There were no treatment-related deaths.

Conclusion: Capecitabine monotherapy is effective and well tolerated for MBC patients who had previously been treated with anthracycline and taxane. This agent was also demonstrated to have a favourable safety profile, with a low incidence of treatment-related grade 3/4 adverse events. However, elderly patients, patients with impaired renal function or patients receiving warfarin need special attention.

210 AN PHASE II TRIAL OF DOXETAXEL AND CISPLATIN AS FIRST-LINE THERAPY FOR ANTHRACYLINE-NAIVE METASTATIC BREAST CANCER PATIENTS

Wen-chen Shih1, Hsien-Kun Chang1, Jen-shih Chen2, Yung-chang Lin1
1Chang Gung Memorial Hospital, Division of Hematology-Oncology, Taipei, Taiwan

Background: The combination of docetaxel and cisplatin has shown promising activity in anthracycline-pre-treated patients with advanced breast cancer, but with substantial toxicity. However, the efficacy and safety in anthracycline-naive pts has not been evaluated.

Methods: Between Oct 2003 and Jun 2006, we enrolled 39 pts with metastatic breast cancer. None had prior chemotherapy for metastatic disease or prior exposure to adjuvant anthracyclines based regimen. Eligibility criteria included: histologically proven metastatic cancer; WHO PS 0–2; adequate hematological, hepatic, and renal function. Docetaxel 70 mg/m2 and cisplatin 50 mg/m2 were administered every 3 weeks until progression, unacceptable toxicity, patient’s request to withdraw from the study or up to maximal 9 cycles. Tumor response (RECIST) was assessed every three cycles. Toxicity was evaluated by NCI Common Terminology Criteria II.

Results: One pt was withdrawn from toxicity (hepatitis B flare up). Thirty-eight patients who received at least 3 cycles and had a complete tumor assessment were evaluable. Median age was 50 years old (range, 28–63); 51% had ECOG PS 0; 49% PS 1. 77% PS 2; 17% had visceral organ involved. A total of 275 cycles (range, 3–9) were administered. There were 2 complete responses, 29 partial responses (overall response rate 31/8% vs). 5 pts had stable disease, and 2 had disease progression. Grade 3–4 toxicities included: diarrhea 10%, nausea/vomiting 10%, fatigue 2.5%, mucositis 5%, sensory neuropathy 5%, hand-foot syndrome 5% and neutropenia 74%. 5 pts developed febrile neutropenia (12.8%). No severe renal or ototoxicity was observed. The median follow-up period was 18 months. The median time to progression was 12.6 months, while the median survival has yet to be reached. Conclusion: Taxotere plus cisplatin is a well-tolerated and active regimen in the first-line treatment of metastatic breast cancer. The study supports the rationale for TP as a non-anthracycline based regimen for future adjuvant chemotherapy.

211 CAPECITABINE AND CISPLATIN COMBINATION IS AN ACTIVE AND WELL-TOLERATED DOUBLET IN THE TREATMENT OF METASTATIC BREAST CANCER PROGRESSING AFTER ANTHRACYLINE AND TAXANE

Nuray Yildirim Ozdemir1, Huseyn ABALI2, Benna Oksuzoglu3, Burcin Budakoglu4, Dogan Urcuo1, Tunc Goller1, Nurullah Zer4, Anikara Namure Stavrosi5, Medikal Onkoloji Klinigi6, Kırık, Ankara, Turkey

Background: Capecitabine (C) and cisplatin (P) are active agents against metastatic breast cancer. Predichelistic data is present and previous phase one data for the combination was available. We aimed to investigate the activity of CP in patients with metastatic breast cancer who had recurred after anthracycline and taxane.

Patients and methods: Sixteen consecutive patients, median age 36 years (Min-max: 20–55), were enrolled onto the study. Case records were evaluated retrospectively. C 2×1000 mg/m2 on days 1-14, P 50 mg/m2 on day 1 every 21 days was given up to 6 cycles. In case of no toxicity in the presence of disease control, C single agent was continued until intolerable toxicity or disease progression. Response was evaluated according to RECIST and toxicity according to CTG.

Results: Estrogen receptor (ER), progesteron receptor (PR) and C-erbB2 were positive in 46.6%, 60.0%, 61.5%, respectively. ER status, PR status and C-erbB2 status were unknown in 1, 1 and 3 patients. In 12 patients with assigned histological grade, 33.3% had grade 3, 38.3% grade 2 and 38.3% grade 1 disease. All received anthracycline and taxane. Of all, 81.2% received CP combination beyond 3 cycles. The best response to CP was as follows: Complete remission (CR) in 2 (12.5%), partial remission (PR) in 8 (50.0%), stable disease (SD) in 2 (12.5%) and progressive disease in 4 (25%). Grade 3 neutropenia was observed in 3 (18.8%), and grade 3 hand and foot syndrome in 1 (6.3%). Median time to progression was 4.9 months (95% CI 2.0–7.7) and median overall survival 10.6 months (95% CI 6.4–10.8). Conclusion: CP combination appears to be active and well-tolerated in the treatment of breast cancer relaps after anthracycline and taxane. However, patient number is small and we continue to enrol more patients.

212 METRONOMIC CYCLOPHOSPHAMIDE-ETOPOSIDE CHEMOTHERAPY AND SERUM VEGF LEVEL IN METASTATIC BREAST CANCER PATIENTS

Mehrun Arik1, Hakim Bozok1, Berka Macan2, Mustafa Ozdogan3, Muğan Timur1, Mustafa Yıldız1, Mustafa Samur1, Burhan Savas1
1Akdeniz University Medical Faculty, Medical Oncology Department, Antalya, Turkey, 2Akdeniz University Medical Faculty, Department of Internal Medicine, Antalya, Turkey, 3Akdeniz University Medical Faculty, Department of Biochemistry, Antalya, Turkey, 4Pamukkale University Medical Faculty, Medical Oncology Department, Denizli, Turkey

Background: The role of vascular endothelial growth factor in the angiogenic regulation of tumors has already been defined by the previous research. Our aim was to...
Annals of Oncology

determine the feasibility of metronomic oral cyclophosphamide-etoposide chemotherapy and to assess the relation of serum VEGF (vascular endothelial growth factor) levels with the efficacy of this regimen.

Patients and methods: We enrolled metastatic breast cancer patients progressing after anthracycline, taxane and capecitabine containing regimens. Oral cyclophosphamide-etoposide metronomic chemotherapy (cyclophosphamide 50 mg daily, etoposide 50 mg twice daily on days 1–5 every 3 weeks) was started. Serum VEGF levels were tested before the first cycle and after the second cycle of chemotherapy by ELISA. Kaplan-Meier and Cox regression analyses were used for the survival analysis.

Results: A total of eight patients were enrolled. Overall survival (OS) and progression survival (PFS) figures were 29.4 and 18.9 months respectively. After the second cycle of chemotherapy, high serum VEGF level was found to be inversely related with the progression free survival (P=0.042, HR=1.03). The serum VEGF level decreased after the second cycle of metronomic chemotherapy (P=0.03). Median: 495 pg/ml versus 346 pg/ml. There was no grade 3-4 toxicity.

Conclusion: Metronomic cyclophosphamide-etoposide chemotherapy was found to be effective and minimally toxic. It decreased the serum VEGF level and this could be an indirect indicator of inhibition of the angiogenesis. Although the study population was very small and highly selected, the results of survival and toxicity analyses warrants further research.

NANOPARTICLE ALBUMIN-BIND (NAB) PACLITAXEL (P) IN COMBINATION WITH BEVACIZUMAB (B) WITH AND WITHOUT Goserelin (G) IN PATIENTS WITH REFRACTORY BREAST CANCER

Gilberto Lopez, Christopher Lobo, Orlando Silva, Stefan Gluck

Brannon Breast Cancer Institute; Sylvester Comprehensive Cancer Center, Division of Hematology/Oncology, Miami, FL

Background: Nab-P improves outcomes when compared against single agent cremophor-based P, as does the addition of bevacizumab or gemcitabine to the same agent. There are no available data regarding combinations of Nab-P with B and/or G. Ongoing investigational efforts are evaluating various doubles with these agents, but not all 3 together. All drugs are available for the treatment of breast cancer.

Methods: Review of single-institution experience, evaluating safety and preliminary evidence of activity with the use of Nab-P with B and with and without G in heavily pretreated her2neu-negative metastatic breast cancer patients. Assessment of response was undertaken by the investigators independently of treating physician. RECIST criteria were used. Three patients received Nab-P and B at the following doses: Nab-P 100 mg/m2, B 10 mg/kg every 3 weeks, and 3 patients received all 3 drugs as follows: Nab-P 100 mg/m2, G 1,000 mg/m2, B 10 mg/kg every 2 weeks.

Results: Six women have been evaluated. Median age was 51 (range 34–69). Two patients had hormone-receptor positive disease and 4 had ER/PR/Her2neu-negative cancer. Prior number of regimens was 3 (range 2–7). Five patients had been treated with a taxane: one received paclitaxel and docetaxel, and 4 docetaxel only. A median of 5 cycles have been administered (range 1–9). First-cycle grade 3/4 toxicity was seen in only one patient who had a baseline grade 2 thrombocytopenia that progressed to grade 3. The thrombocytopenia resolved without requiring transfusion and without any hemorrhagic complication. Another patient developed grade 2 peripheral neuropathy. Two patients are not yet assessable for response. At time of first evaluation 1 patient had progressive disease (Nab-P, B, G), in the second group, 2 patients had stable disease (one received Nab-P, B, G; the other Nab-P, B; both had 3 prior lines of therapy), and 1 had a partial response (Nab-P, B, G; 2 prior therapies, including docetaxel).

Conclusion: These very preliminary data suggest that Nab-P in combination with B with and without G is a safe regimen and formal Phase I/II trials are being developed at the University of Miami to confirm its safety and clinical activity.

TOREMIFENE IN THE CONSERVATIVE TREATMENT OF GYNAECOMASTIA

Sergey Azatyan, Natalia Zaliznyak

Ukraine, Kiev, UKRAINE

Surgery is a standard treatment of nodes forms of gynaecomastia, however, in certain cases, surgery is impossible or a patients refuses an operation. The anti-estrogen tamoxifen can be administered for the conservative treatment of the proliferative phase of gynaecomastia since aromatazine inhibitors are not suitable in such cases. Because of the cancerogenic hepatopotic effects of tamoxifen and a better safety profile of toremifene, the latter drug was selected for anti-estrogen therapy. 29 patients having refused surgery were included in the study. All patients underwent aspiration biopsy during the examination in order to rule out cancer. Monotherapy with toremifene in the dose of 20 mg/day was administered. The drug was administered for 2 months in 20 patients and for 4 months in 9 patients. Complete reduction of pain syndrome was noticed in 24 patients (83%), partial reduction - in 4 patients (14%), and no effect was found in 1 patient (3%). X-Ray investigation showed full regress of neoplasm in 19 patients (65.5%) and partial (from 25 to 50% reduction) - in 6 patients (21%), whereas no objective effect of the treatment was found in 4 patients (13.5%) (although one such patient reported an alleviation of pain symptoms). In 9 patients (31%), clinically satisfactory regress of neoplasm (50 to 70%) with a lack of pain syndrome was noticed in 2 months following the beginning of the treatment. The treatment of such patients was prolonged to 4 months, which resulted in a complete regression of neoplasia in three of those patients. No adverse effects were noticed in patients taking toremifene. Toremifene has shown high efficacy in the conservative treatment of the proliferative phase of gynaecomastia and thus may be administered in patients rejecting surgery or in patients with contraindications for an operation.

THE COMPARATIVE EFFICIENCY OF COMBINATIONS OF TAMOXIFENE AND TOREMIFENE IN PREMENOPAUSAL PATIENTS WITH DISSEMINATED BREAST CANCER

Rasim Zeynalov, Ilgar Musayev, Sevindzh Giyasbeyli, Nailya Dadashdeva, Dzhavid Gasanzade, Nadzir Ahadova

Azerbaijan Oncological Research Center, oncology, Baku, Azerbaijan

The aim of the research was comparative study of efficiency of combinations of Tamoxifene and Toremifene in premenopausal patients with disseminated breast cancer. 76 patients with disseminated breast cancer, not selected by receptor status were enrolled in this clinical trial. All patients were randomized in 2 groups by the method of hormonal therapy. First group patients (n=36) received combination of Tamoxifene at an oral dose of 20 mg daily + Goserelin at a dose of 3.6 mg, subcutaneous injection is given once every 28 days. The patients of second group (n=40) were treated with combination of Toremifene at an oral dose of 60 mg daily + Goserelin at a dose of 3.6 mg, subcutaneous injection is given once every 28 days. In both groups the treatment continued until manifestation of disease progression. The criteria of estimation of therapy efficiency were an objective response, a median remission duration. All patients were monitored no less than 3 years. In the first group 36.1% patients had an objective response, in the second group - 47.5% patients. Median remission duration was 16.2 and 25.7 months, accordingly. Combination of Toremifene with Goserelin reliably exceeded in efficiency the combination of Tamoxifene with Goserelin. Received data gives reason to recommend combination of Toremifene with Goserelin as a first line hormonal therapy in premenopausal women with disseminated breast cancer.

THE EFFICIENCY OF TAMOXIFENE AND TOREMIFENE IN POSTMENOPAUSAL PATIENTS WITH BREAST CANCER ASSOCIATED WITH LIVER METASTASIS

Rasim Zeynalov, Ilgar Musayev, Sevindzh Giyasbeyli, Nailya Dadashdeva, Dzhavid Gasanzade, Nadzir Ahadova

Azerbaijan Oncological Research Center, oncology, Baku, Azerbaijan

Historically, the endocrine therapy is more effective in patients with breast cancer associated with metastasis in bones and soft tissues. Visceral metastases, especially metastasis in a liver, are treated more hardly. Detoxicational dysfunction of the liver, affected with metastatic tumor restricts use of aggressive chemotherapy. Application to clinical practice the second generation antiestrogen Toremifene, demonstrated in some randomized trials advantages over Tamoxifene, gives possibility for researchers to hope for the improvement of the results of hormonal therapy in patients with this pathology. The aim of research was comparative study of efficiency of combinations of Tamoxifene, standard and high doses of Toremifene in postmenopausal patients with breast cancer, associated with metastasis in a liver. 73 postmenopausal patients with breast cancer associated with liver metastasis, not selected by receptor status were enrolled in this clinical trial. All patients were randomized in 3 groups. In the first group (n=24) hormonal therapy was administered with Tamoxifene at a dose of 20 mg daily, in the second group (n=26) patients received Toremifene at a dose of 60 mg daily; in the third group (n=23) the treatment was administered with high doses of Toremifene at a dose 240 mg daily. In all groups the treatment continued until a disease progression. The efficiency of treatment was determined by following criteria: an objective response, a toxic manifestation and duration of remission. In the first group 12,5% patients had an objective response, in the second group 23,1% patients, in the third group - 34,8% patients. Median remission time was 3,8, 7,1 and 10,5 months accordingly. Side effects in all groups were not significant, did not require specific correction and delay of the treatment. The escalation of Toremifene doses didn’t lead to significant worsening of toxic profile of hormonal therapy. Received data convincingly indicated about advantages of Toremifene in standard and high dose compared to Tamoxifene. It gives reason to recommend Toremifene for wide use as hormonal therapy in postmenopausal patients with breast cancer, associated with liver metastasis.

WHICH OF POSTMENOPAUSAL METASTATIC BREAST CANCER PATIENTS SHOULD BE TREATED WITH FULVESTRANT IN 3RD LINE HORMONAL TREATMENT?

Jelena Zdrobenja, Agnieszka I. Jageljo-Gruszfeld, Malgorzata Czerniawka, Jovana Grzankowska-Skuja

Zośa naświa z Warminsko-Mazurskim Centrum Onkologi, Chemotherapy Department, Olsztyn, Poland

Background: Fulvestrant (F) is an estrogen receptor antagonist with no agonist effects. Actually F was used in postmenopausal breast cancer pts after failure of TAM and AI treatment. Unfortunately only 50% of pts derived an advantage from F therapy.

Patients and methods: We conducted a retrospective analysis of pts treated with F in our center from March 2005 to April 2006. Fulvestrant 250 mg was given as a single 5 mL intramuscular injection, once-monthly until disease progression. Tumor response was assessed every 2-3 months using RECIST criteria. Time to progression (TTP) was defined from start of treatment until PD. Median age is 59 years (range 51–77 years). All had received one (88%) or two lines (22%) prior endocrine treatment for advanced disease and 88% had received adjuvant endocrine treatment (Tam): 88% of pts received prior chemotherapy as adjuvant (67%) or metastatic setting (55%).

Results: F was well tolerated and we observed no WHO-III/IV toxicity. The clinical benefit rate is 55%. Median of TTS - 6.8 months. Data suggest that median of TTP in group of pts, who did not receive chemotherapy in metastatic setting is sustained (7 vs 3 months). In the group of pts, who were previously treated with chemotherapy (excluded adjuvant) clinical benefit from F was not observed.

Conclusion: F 250 mg has demonstrable efficacy and a good tolerability profile in hormone-dependent postmenopausal patients with metastatic breast cancer. 55% of patients gained clinical benefit from F treatment. Our data suggest that F should be used in pts, who did not receive chemotherapy as metastatic setting.

218 CLODRONATE POSSIBILITIES IN COMPLEX THERAPY OF ADVANCED BREAST CANCER WITH BONE METASTASES AND WITHOUT THEM

B. Monakhov, K. Yerzhinov, Kh. Tumabayezya, Z. Khabibulina
Kazakh National Medical University, Oncological, Akmaty, Kazakhstan

Aim: To study therapeutic and preventive possibilities of Clodronate (Bonefos®) among breast cancer patients with and without bone metastases.

Patients and methods: We analyzed data of 412 advanced breast cancer patients with bone metastases and without them during 5 years. Median age was 54 years (range 38–71 years). All patients undergone mastectomy, received standard regimens of chemotherapy; 80% of patients received hormonal therapy. Clodronate was used according to a conventional method during 2 years. 258 patients with intensive pain and bone metastases were divided into 2 groups: 1st group of 133 patients was treated with clodronate, in 2nd (control) group of 125 patients no clodronate was used. Preventive effect of clodronate was studied in 154 patients with no pain and no bone metastases. 3rd group of 75 patients received clodronate from the date of diagnosis, and 4th group of 79 patients received no bisphosphonates.

Results: In 1st group treated with clodronate, a number of bedridden patients decreased in 2.6 times; a number of patients, able to fulfill easy and sitting work, increased in 2.2 times. In patients of 2nd group, not treated with clodronate, pain intensity had a tendency to increase, and performance status worsened considerably. Median survival time was 29 months in 1st group and 21 months in 2nd group (p<0.005). At 36 months of observation overall survival in 1st group was 60% compared to only 42% in 2nd group. Among patients with no bone metastases at inclusion, new bone metastases during 5 years of observation were revealed in 9.3% of patients in 3rd group and in 26.9% of 4th group (p<0.005), and overall survival was accordingly 85% vs. 78%.

Conclusion: clodronate considerably decreases pain, improves performance status, and overall survival of patients with bone metastases.

219 BISPHOSPHONATES AND JAW OSTEONECROSIS IN PATIENTS WITH ADVANCED BREAST CANCER

Giuseppina Saniga1, Lorenzo Preda2, Roberto Bruschi2, Maria Cossu Rocca1, Laura Adamoli1, Elena Verri1, Gilda Ascione1, Aron Goldhirsch1, Franco Nole`1
1European Institute of Oncology, Department of Medicine, Unit for Medical Care, Milan, Italy, 2European Institute of Oncology, Division of Radiology, Milan, Italy

Background: In last years, several cases of mandibular necrosis associated with long-term use of bisphosphonates have been reported. The estimated incidence varies from 1% up to 6.7%.

Patients and methods: We conducted an observational study with the objectives to determine the incidence of jaw osteonecrosis in breast cancer pts under bisphosphonate treatment and to identify subjects at higher risk of developing this complication evaluating preclinical signs, in particular radiological modifications. We considered two groups of pts. All the pts complaining of odontostomatological symptoms underwent maxillary CT scan and maxillo-surgeon clinical examination. Asymptomatic pts were asked to perform a standard orthopantomography (OPT).

Results: From February 2005 to October 2005, we observed five pts with jaw bone necrosis. Diagnosis was radiological and clinical. In two patients a confirmatory biopsy was performed. In the same time interval, OPTs were collected from 76 asymptomatic pts. Three OPT’s revealed radiological features of suspicous jaw necrosis. Maxillary CT and/or MRI confirmed the presence of an osteolytic area with signs of periosteal reaction. All the three pts were referred to maxillo-surgeon and two underwent mandibular biopsy, but histopathological results were not conclusive.

Conclusions: In our experience, the incidence of jaw bone necrosis in breast cancer patients associated with the use of bisphosphonates seems to be higher than in other reports (6%). We observed radiological features of suspicous necrosis in 3 out of 76 asymptomatic pts. We do not know how these findings should be considered. Therefore, performing standard OPT is a simple procedure, and may allow identification of peridontal conditions that in some way can predispose to the development of this uncommon event.

220 MALE BREAST CANCER – A REVIEW OF 56 CASES FROM INDIA

Kulltan Rathheesun1, Geetha Narayanan1, Jayaprakash Madhavan2, Parameswaran B1, Rajan B1
1Regional cancer centre, Division of breast cancer, Thiruvananthapuram, India, 2Regional cancer centre, Radiation Oncology, Thiruvananthapuram, India

Breast cancer in men is uncommon and constitutes only 1% of all breast cancers. Aim: To study the clinical profile and treatment outcome in male patients with breast cancer.

Material and methods: Fifty six men with carcinoma of the breast seen at our institute during the period 1985 and 2002 form the subjects of our study. The case records of these patients were studied in detail with regard to the clinical presentation, treatment and follow up data obtained.

Results: The median age at diagnosis was 61 years (range 31-94 yrs). The right and left breast were equally affected. The TNM status was T1 in 3, T2 in 1, T3 in 5 and T4 in 27, N1 in 24, N2 in 2 and Nx in 7, M1 in 6 patients. Fifty three patients had infiltrating duct carcinoma, and 1 patient each had mucinous, medullary and lobular carcinoma. Fifty three patients underwent surgery (Simple mastectomy(SM):9, SM+axillary clearance:17, Radical mastectomy:12, Modified Radical Mastectomy:6 and lumpectomy: 9). Post operatively, 40 patients received radiotherapy to the primary site with a median dose of 40Gy. 11 chemotherapy and 29 received tamoxifen. The median survival of the series is 36 months. Twelve patients survived more than 5 years.

221 CNS METASTASIS IN BREAST CANCER, A CASE OF PROLONGED RESPONSE TO LETROZOLE

Giuseppe Valmache1, Renzo Epiri2, Alessandro Pastorini1, Claudia Pedrotti1,
Davide Leni2, Massimo Pfiego2
1E.Morelli Hospital AOIV, Internal Medicine and Hematology, Sondalo (Sondrio, Italy), 2E.Morelli Hospital AOIV, Neuroradiology, Sondalo (Sondrio), Italy

Background: Breast cancer is the second most common cause of CNS metastases. These results in progressive neurologic disability and the prognosis is poor. Only few trials have explored the use of chemotherapy in this setting. The intact blood-brain barrier (BBB) precludes the entry of most chemotherapeutic agents. However the BBB is frequently disfunctional in presence of brain metastasis. Tamoxifen achieves high concentration in the CNS and is active against metastasis. Aromatase inhibitors act primarily at extratumoral sites and so their ability to cross the BBB is not important for their pharmacological activity.

Case report: In January 05, a 66 year old woman came to our attention for a ductal infiltrating carcinoma of the right breast (G2, ER +, PGH+, HER2 +) with multiple metastasis pleural, hepatic and bones. After chemical pleurodesis she underwent F aromatase. In May 05 she was hospitalized for headache and worsening of general condition. A CT scan of the brain revealed multiple cerebellar lesions (right cerebellar lobe with mass effect and dislocation of fourth ventriculus and in paravermian site) and multiple brain lesions. Chemotherapy was discontinued and an AI (Letrozole) was started. Two months later (June 05) the PS ECOG was 1. A new brain CT revealed: reduction in number and size of metastasis, reduction of the compression on fourth ventriculus. In November 05, at thoracic-abdominal-brain CT: stability of visceral disease, further reduction of cerebral lesions (max 1 cm). Last CT follow-up was on December 06: left frontal brain. Revision of letterature: We found only one report (Madhup R. et all) about a confirmatory biopsy was performed. In the same time interval, OPTs were collected from 76 asymptomatic pts. Three OPT’s revealed radiological features of suspicous jaw necrosis. Maxillary CT and/or MRI confirmed the presence of an osteolytic area with signs of periosteal reaction. All the three pts were referred to maxillo-surgeon and two underwent mandibular biopsy, but histopathological results were not conclusive.

Conclusions: In our experience, the incidence of jaw bone necrosis in breast cancer patients associated with the use of bisphosphonates seems to be higher than in other reports (6%). We observed radiological features of suspicous necrosis in 3 out of 76 asymptomatic pts. We do not know how these findings should be considered. Therefore, performing standard OPT is a simple procedure, and may allow identification of peridontal conditions that in some way can predispose to the development of this uncommon event.

221 CNS METASTASIS IN BREAST CANCER, A CASE OF PROLONGED RESPONSE TO LETROZOLE
Efficacy and safety of liposomal cytarabine (DepoCyt®) in patients with leptomeningeal metastasis (LM) associated with stage III/IV breast cancer (BC)

Lucia Gonzalez-Cortijo, Javier Hermedo

As systemic therapies for cancer have improved and patients live longer, the incidence of metastatic disease in the central nervous system (CNS) has increased. Approximately 5–8% of patients with solid tumours (mainly melanoma, breast, lung) develop LM, which has a severe impact on the prognosis and quality of life of affected patients. The drugs most commonly used, intrathecal (IT) methotrexate and cytarabine, are cell cycle phase-specific agents with short half-lives within the cerebrospinal fluid (CSF), requiring intermittent injections 2–3x a week. Liposomal cytarabine (DepoCyt®, DeCy) is a sustained-release formulation for IT injection that maintains therapeutic concentrations in the CSF for 2 weeks, offering the advantages of fewer injections and potentially greater efficacy than conventional IT therapies. The two patients reported here, aged 29 (A) and 54 (B) years, had concurrent systemic and CNS relapse of advanced BC and were treated with systemic chemotherapy (A: capecitabine + trastuzumab; B: epirubicin + vinorelbine) as well as DeCy q4 weeks x 6 (Patient A received additional DeCy q4 weeks x 2), with prophylactic desmamethasone 4 mg TID. Patient A had a complete neurological response to DeCy that persisted to the time of reporting (Nov 05–Apr 06), and an improved Karnofsky score, without side effects. Patient B had a partial neurological response to DeCy, without side effects, but the disease course was complicated by placement of a shunt for hydrocephalus. The feasibility, efficacy, safety and tolerability of DeCy in the treatment of LM associated with advanced BC are highlighted by these cases. This agent should be considered in patients who develop this distressing complication.

Subsequent outcome in metastatic breast cancer (MBC) patients (pts) surviving >5 years

Eliśbia Senieus-Koneńska1, Piotr Winczura2, Renata Zaucha2, Barbara Radecka1

Purpose: Breast cancer is the most common cancer in women with 20-85% of distinct metastasizes. The metastasis in five years and 10% metastatic disease at diagnosis. The prognostic factors for prediction of further prognosis.

Methods: Twenty patients with metastatic breast cancer without prior therapies who were candidate for epirubicin (E) and docetaxel (D) (E 75 mg/m², D 75 mg/m², I.V, 1q 2 weeks x 6) were included. A: age 29, B: age 54 years, had concurrent systemic and CNS relapse of advanced BC and were treated with systemic chemotherapy (A: capecitabine + trastuzumab; B: epirubicin + vinorelbine) as well as DeCy q4 weeks x 6 (Patient A received additional DeCy q4 weeks x 2), with prophylactic desmamethasone 4 mg TID. Patient A had a complete neurological response to DeCy that persisted to the time of reporting (Nov 05–Apr 06), and an improved Karnofsky score, without side effects. Patient B had a partial neurological response to DeCy, without side effects, but the disease course was complicated by placement of a shunt for hydrocephalus. The feasibility, efficacy, safety and tolerability of DeCy in the treatment of LM associated with advanced BC are highlighted by these cases. This agent should be considered in patients who develop this distressing complication.
Since the first report of radiographically occult DIH metastases of positive for estrogen receptor. The patient died 15 days after admission by acute were normal. Hepatic biopsy revealed diffuse intrasinusoidal metastatic carcinoma Computed tomografic scan, magnetic resonance of abdomen and hepatic ultrasound carcinoma of the breast. Laboratory profile detect AST, 650 U/L; ALT, 499 U/L; total presentation of metastatic disease, involving a poor prognosis. We report a case of a 51-year-old patient with hormone receptor (ER+/PR-) breast cancer who was admitted to the hospital with abdominal pain, jaundice, and fever. Physical examination revealed a mass in the right upper quadrant of the abdomen. Laboratory tests revealed elevated liver enzymes, including aspartate transaminase (AST) and alanine transaminase (ALT). Imaging studies, including computed tomography (CT) scan and magnetic resonance imaging (MRI), showed a mass in the liver, consistent with metastatic disease. The patient underwent a hepatic biopsy, which confirmed the presence of breast cancer metastases. The case highlighted the importance of considering breast cancer as a cause of hepatic failure, even in the absence of radiographic evidence of metastases.

Introduction and Objectives: The most important prognostic factor in breast cancer (BC) is axillary lymph node involvement, followed by tumor size. The main non-morphological prognostic factor is hormone receptor expression. Overexpression of the Her-2/neu oncogene is increasingly gaining importance as a prognostic factor. Various clinical studies indicate that patients with ER+/PR- BC have a different phenotype possibly resistant to tamoxifen therapy. Materials and methods: Sixty-eight patients with BC (41% premenopausal, 34% postmenopausal), median age 52 (range, 27-80) were studied. At the time of diagnosis, 34 (44%) of these patients presented axillary involvement (13% with more than 4 lymph nodes involved), 76% infiltrating ductal carcinoma, and 10% lobular carcinoma. At the time of the analysis, 34 patients (50%) presented distant metastasis (15 visceral disease and 19 bone-lymph node disease). Her-2/neu overexpression was determined by immunohistochemistry and FISH. Results: Among the 68 patients analyzed, 48 (70%) expressed ER+ and 39 (57.4%) PR+, 37 patients (54.4%) were ER+/PR- and 8 (12%), ER+/PR+. Of the patients with ER+/ PR-, 24.3% overexpressed Her-2/neu versus 30% of those with ER+/PR+. No age-related differences were found between the two groups. Conclusions: Despite the small sample size, a greater tendency toward overexpression of Her-2/neu overexpression appears to exist among patients with the ER+/PR+ phenotype, possibly explaining hormone-dependent differences in both groups. At the present time, more patients are being analyzed to obtain data on the prognostic value of hormone receptor expression.
**CLINICAL SIGNIFICANCE OF CIRCULATING TUMOR CELL (CTC) DETECTED BY RT-PCR FOR SNP2 IN PERIPHERAL BLOOD OF METASTATIC BREAST CANCER PATIENTS**

Elvira del Barco1, Carola Delgado1, Lorenia Betiko2, M. Angeles Nava-Rodriguez3, Manuel Sanchez-Martín4, César A. Rodriguez2, Arnalía Gómez-Bernal1, Germán Martin1, Juan J. Cruz-Hernandez1, Isidro Sánchez-García1

1University Hospital of Salamanca, Medical Oncology Service, Salamanca, Spain, 2University of Salamanca, Department of Medicine, Salamanca, Spain, 3Instituto Biología Molecular y Celular del Cáncer (IBMCC), Centro de Investigación Biomolecular Apliadas, CSIC/University of Salamanca, Spain

Background: Loss of expression of the E-cadherin cell-cell adhesion molecule is important in carcinoma development and progression. The zinc-finger transcription factor SNAI-2 repress endogenous E-cadherin expression, suggesting a potential in vivo molecular marker of CTCs and disseminated carcinomas.

Methods: In a prospective study, we analyzed the expression of SNAI-2 in peripheral blood by reverse transcription polymerase chain reaction (RT-PCR) in 70 metastatic breast cancer patients before initiation the therapy (first line or new line). We have correlated these data with clinical factor and progression-free survival (PFS) and overall survival (OS).

Results: The mean follow-up time was 76 weeks (w). Thirty-six patients (51.4%) expressed SNAI-2.

Postmenopausal: 44.4% vs 38.8 premenopausal (p=0.495); RE +/-: 50% vs 55.3% (p=0.39); R0 vs R1-2: 76.6% in HER2+ (p=0.304); 63.3% in HER2-. Patients that expressed SNAI-2 had a worse prognosis than patients that not expressed: median PFS was 14,14 w (95% IC: 9,78-19,51) vs 23,78 w (95% IC: 16,84-36,59), respectively (p=0.038, log rank). Cox multivariate analysis showed that, of all the variables in the statistical model, SNAI2 expression in peripheral blood was a significant predictor of progression and survival: hazard ratio for progression: RR= 0.319, 95% IC: 0.199-0.508, p=0.016.

Conclusion: These results indicate that SNAI2 expression in peripheral blood could serve as a biomarker of CTCs in metastatic breast cancer and is an independent predictor of progression-free survival in this patients.

**Epidemiology and Patterns of Care for Carcinoma Breast at a Community Hospital in Southern India**

Sambasivasai Kuruparthi1, Manthym Kumaranarayanan Reddy2, PV Ramasubramaniam1, Y Matheeswaraswathi1, AV Lakshmi1, BV Pranindra3

1SV Venkateswara Institute of Medical Sciences, Oncology, Tirupati, India, 2SV Venkateswara Institute of Medical Sciences, Pathology, Tirupati, India, 3SV Medical College, General Surgery, Tirupati, India

Background: Breast cancer incidence in India is on rise, particularly in urban women. Access to comprehensive cancer centers and affordability are not uniform. We report epidemiological, clinical and survival patterns at community level in Southern India.

Methods: All breast cancer patients treated at this hospital from 2000 to 2004 were included. TNM stages for staging and IHC to assess the receptor status were used. Breast conservation surgery (BCS) or Modified radical mastectomy (MRM) was done for operable breast cancer, followed by adjuvant chemotherapy to patients with pt>1 cm or positive node or ER negative status; Radiotherapy was advised to patients after BCS, or pt size > 5 cm, or >4 positive nodes or stage IIIB disease. Chemotherapy was more toxic. ER positive tumors had better survival.

Results: During the period of follow up, relapses and metastases have arisen at 10 years (9%). Thus, the duration of relapse-free survival essentially depend on the factor of preoperative cryoablation of tumor. By using of cryoablation and tumor and cryoablation in a complex with cryoautovaccine, the relapse-free survival of patients with BC significantly increased. In control group relapses have arisen at 8 women (14%). In group with application of cryoablation during the period of supervision relapses have arisen in 2 cases (6%). In group where cryoablation of tumor has been combined with cryoautovaccine (21 women), relapses have not arisen on any patient. The revealed distinctions are significant (p<0.05).

Conclusion: The application of cryoablation with the subsequent cryoautovaccination significantly reduces the development of metastases and relapses after operation (0% vs 14%), p<0.05.
**SELECTIVE SENTINEL LYMPHADENECTOMY AFTER NEOADJUVANT CHEMOTHERAPY FOR PRIMARY BREAST CANCER: EFFECT OF CLINICAL PRESENTATION OF NODE, EVALUATION OF MITOMYCIN C, 5-FLUOROURACIL, AND FOLINIC ACID IN METASTATIC BREAST CANCER PATIENTS WITH IMPAIRED LIVER FUNCTION**

Samir S. Eid, Al-Gezawy SM, Moharram, Samir Shaheta, Hoda Hasan

*Faculty of Medicine, Clinical oncology, Assiut, Egypt*

**Purpose:** To prove the efficacy and safety of the combination of mitomycin-C with 5-fluouracil (5-FU) and folinic acid in patients with metastatic breast cancer and severely impaired liver function.

**Patients and methods:** Between May 2004 and Jul 2005, 40 breast cancer patients with visceral metastases and severely impaired liver function were enrolled in this trial. The chemotherapy regimen consisted of: 100 mg/m^2^ folinic acid (FA) and 400 mg/m^2^ 5-fluorouracil (5-FU) given i.v. o'er 2 h for 5 days plus 3 mg/m^2^ mitomycin C (MMC) given i.v. on days 3-5. The cycles were repeated every 21 days until progression or severe toxicity.

**Results:** Eight patients (20%) achieved a partial remission (PR). Fifteen patients (37.5%) had stable disease (SD), nine of them maintained SD for more than 5 months.

**Conclusion:** Use of new chemotherapeutic agents affected the overall survival in metastatic breast cancer. All the patients with good performance status should be favored to receive treatment.