in comparison to serum HER2/neu positive patients (mean: 31.3 weeks; p=0.018).

Conclusions: Our results indicate that an elevated serum HER2/neu level is a negative predictive factor for bad treatment outcome in terms of progression-free survival. This result, together with the putatively increased anthracycline sensitivity of HER2/neu positive patients, may help for patient selection to a more individualized mode of chemotherapy.

719 POSTER

Biological study of anastrozole in post-menopausal advanced breast cancer (ABC) patients: Effects on bone metabolism and oestrogen suppression

A. Martinetti[1], E. Bajetta[2], R. Buzzoni[2], N. Zilembo[2], L. Ferrari[1], P. Pozzi[2], S.C. Stani[2], L. Catena[2], M. Di Bartolomeo[2], E. Bombardieri[1]. *[1] Nuclear Medicine Unit; [2] Medical Oncology Unit B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy*

Purpose: To study the short term biological effect of anastrozole on serum oestrogens, androgens, 17OH-progesterone (17OH-PGR), gonadotrophins, sex hormone binding globulin (SHBG) and bone metabolism markers.

Methods: 34 consecutive pts with ABC received anastrozole 1 mg/day treatment Blood samples were taken before and at 2, 4, 8 and 12 weeks during treatment to measure serum levels of: oestrogens (E1, E2 and E1-S), androgens (Δ4, DHT, TST, Free TST, DHEA and DHEA-S), 17OH-PGR, SHBG and gonadotrophins. As indicator of bone resorption we measured serum carbossi-terminal telopeptide of type I collagen (ICTP) and the cross-linked N-telopeptide of type I collagen (NTx), and for the osteoblastic activity intact osteocalcin (BGP) and bone alkalyne phosphatase (BAP).

Results: After 2 weeks E_1 and E_1-S levels decreased of an average of 56% (range 23.1–88.8) and 75.8% (range 52.4–87.2) respectively; E_2 decreased of an average of 62% (range 31.4–89.6). No significant changes were detected in androgens and 17OH-PGR. There was a significant increase of gonadotrophins over time ($p = 0.0001$ and $p = 0.0001$ for LH and FSH, respectively), and a significant decrease in SHBG $p = 0.0001$. A progressive significant increase in bone metabolism serum markers was detected in all pts: $p = 0.0394$ for BAP, $p = 0.0156$ for BGP, $p = 0.0021$ for ICTP and $p = 0.0013$ for NTx. In particular, pts with bone metastases had an increase statistically significant of bone resorption markers ($p = 0.0019$ for ICTP and $p = 0.0251$ for NTx) and borderline for bone formation markers. In pts without bone disease BAP, BGP and ICTP remained unchanged, whereas serum NTx significantly increased $p = 0.0186$.

Conclusion: Anastrozole is a selective aromatase inhibitor as it does not modify serum levels of androgens and 17OH-PGR. In our experience no relation was found in the short term period between serum oestrogen suppression and bone metabolism. The evaluation of bone metabolism markers seems to be helpful for the monitoring of bone disease during hormonal treatment.

720 POSTER

Safety and activity of Capecitabine in elderly patients with advanced breast cancer

G. Procopio, E. Bajetta, L. Catena, M. Alù, R. Longarini, N. Zilembo, I. La Torre, M. Platania, S. Della Torre, G. Dognini. *Medical Oncology Unit B, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy*

Purpose: Capecitabine is a selectively tumor activated fluoropyrimidine which is effective in a wide range of solid tumors. This study tested the safety and the activity of Capecitabine in elderly patients (pts) with advanced breast cancer (ABC).

Methods: From May 1999 to March 2001 forty consecutive pts were treated. The first thirty pts were treated using a dosage of 2500 mg/sqm/day b.i.d. for 2 weeks with a week of rest; than to improve the safety profile we are continuing the trial by reducing the dosage (2000 mg/sqm/day). The pts median age was 74 years (range 65–89). Pts could receive one prior chemotherapy and/or 2 hormonal regimens for metastatic disease. A previous therapy containing 5-fluorouracil was allowed but a 12 months withdrawal period was required, starting from the last dosage of the previous treatment. The metastatic sites were liver (19), lung (14), soft tissue (12), bone (9), other (9).

Results: Toxicity according to NCI-CTC Bethesda was: *grade 3–4* diarrhea (10%), *grade 3* vomiting (7%), *grade 2* (10%) and *grade 1* (26%) hand-foot syndrome, *grade 2–3* asthenia (13%), *grade 2* stomatitis (7%). One patient died for gastrointestinal toxicity and one patient developed deep venous thrombosis. The objective responses were 11/31 (35%), 3% complete remission, stabilizations of disease were 9/31 (29%), and progressions 11/31 (35%). The median time to progression was 6 months.

Conclusions: These results suggest that Capecitabine is safe and active in elderly pts with advanced breast cancer.

The Authors would like to thank the Italian Trials in Medical Oncology (I.T.M.O.) for its editorial assistance.

721 POSTER

Paclitaxel-ifosfamide for anthracycline-resistant advanced breast cancer

P. Kellokumpu-Lehtinen[1], A. Lantto[2], R. Kokko[3], I. Elomaa[4], R. Järvenpää[1], C. Blomqvist[5]. *[1] Tampere University Hospital, Tampere, Finland; [2] Vaasa Central Hospital, Vaasa, Finland; [3] Central Finland Hospital, Jyväskylä, Finland; [4] Turku University Central Hospital, Turku, Finland; [5] Academic Hospital, Uppsala, Sweden*

The combination of paclitaxel 135mg/m2 as a 3 hour infusion on day 1 and ifosfamide 1.7 g/m2 as a 4 hour infusion on days 2 to 4 every 22 days was given to patients (pts) with advanced breast cancer resistant to anthracyline containing regimen or patients relapsed after antracycline containing adjuvant chemotherapy. Pts had to have measurable or evaluable progressive metastases or local disease, and only one regimen for metastatic disease. Thirty one pts with a median age of 49 years (range, 30-69) entered the study. Nine (29%) had lung and seventeen (55%) liver metastases (mts), nineteen (61%) bone mts. Only seven (23%) had lymph node mts and four (13%) skin mts. Median of 7 cycles (range 1-18) were delivered. Responses were evaluated according to WHO guidelines and side effect according to NCI criteria. A panel of oncologist and one radiologist reviewed all responses. At baseline only three patients (10%) were free of the adverse consequenses of the prior therapy. During the treatment severe toxicities (grade >3) included nausea 3%, vomiting 3%, pulmonary 3%, neuromotor 3%, asthenia/fatigue 7%, pain 7%, neutropenia 90%, thrombocytopenia 10%, anaemia 10%, infection 7%, while alopecia was universal. Three complete responses (10%), 10 partial responses (32%), 8 (32%) stable disease and 8 progressive disease (26%) were documented. Median survival and progression free survivals after beginning of treatment were 19.3 months and 6.1 months, respectively.

Conclusion: Combination of paclitaxel and ifosfamide seems to be a promising regimen (objective response rate of 42% and a median survival time of 19 months) with acceptable side effects in advanced breast cancer patients relapsed after antracycline based adjuvant treatment or resistant to antracycline treatment.

722 POSTER

Salvage treatment with irinotecan and gemcitabine in breast cancer patients pretreated with taxanes and anthracyclines: a multicenter phase II study

S. Agelaki, A. Alexopoulos, C. Kouroussis, G. Ardavanis, N. Malamos, S. Kakolyris, K. Kalbakis, N. Androulakis, A. Pallis, V. Georgoulias. *The Greek Cooperative Group for Breast Cancer*

Purpose: A multicenter phase II study was conducted to evaluate the efficacy and toxicity of the irinotecan (I) - gemcitabine (G) combination in women with disease progression after initial chemotherapy for metastatic breast cancer.

Patients and Methods: Thirty-six breast cancer patients pretreated with regimens including taxanes and anthracyclines received G 1200 mg/m2 on day 1 and day 8 and I 300 mg/m2 on day 8, every 3 weeks. The median age was 58 years and the performance status (WHO) was 0-1 in 26 (72%) patients and 2 in 10 (28%). Nineteen patients had received one, and 17 two or more prior chemotherapy regimens.

Results: All patients were evaluable for toxicity and 28 for response. One-hundred forty treatment cycles were administered with a median of 3.5 cycles/patient. Complete remission was recorded in one (4%) patient and partial response in 5 (18%) for an overall response rate of 22% (95% CI: 6.23% - 36.63%). Nine (32%) patients had stable disease and 13 (46%) progressed. Responses were observed at all metastatic sites with a median duration of response of 5.5 months (range, 2.5 to 6.5), and a median time to progression of 7.5 months (range, 4.5 to 15.5). The median survival was 9 months (range, 1 to 13) and the one-year survival rate 37%. Grade 3 neutropenia occurred in 7 (19%) and grade 4 in 6 (17%) patients. Neutropenia was associated with fever in 3 (9%) patients without toxic deaths. Grade 3 thrombocytopenia developed in 4 (11%) patients and grade 4 in 1 (3%). Non-hematologic toxicity was mild with grade 2-3 diarrhea reported in 6 (17%) patients and grade 2-3 asthenia in 13 (35%).

Conclusions: The combination of CPT-11 with gemcitabine is an active and well tolerated regimen in the treatment of metastatic breast cancer patients pretreated with taxanes and anthracyclines.

723 POSTER

'Faslodex' (ICI 182,780) 250 mg shows consistent pharmacokinetic profile when given as either a one x 5-ml intra-muscular (i.m) injection or two x 2.5-ml injections in postmenopausal (PM) women with advanced breast cancer (ABC)

J.F.R. Robertson[1], M. Harrison[2]. [1] *Nottingham City Hospital, Unit of Surgery, Nottingham, UK;* [2] *Astra Zeneca Pharmaceuticals, Macclesfield, UK*

Faslodex (ICI 182,780)(FAS), is a novel estrogen receptor downregulator that has no estrogen agonist activity. FAS is administered as 250 mg i.m injection once monthly. In the North American based FAS trials, differences in clinical practice preferences led to FAS 250 mg being given as 2 x 2.5 ml injections as opposed to 1 x 5 ml dose in Europe/Rest of World based trials. Given the differences in dose administration within the FAS breast cancer trial programme, it was therefore considered important to compare the PK of FAS when given as either 1 x 5 ml dose or 2 x 2.5 ml dose.

Here we report the PK findings of an open, randomized multicentre, parallel-group trial in PM women with ABC. Patients (n=38) were randomly assigned to either a single dose of FAS, as 1 x 5-ml injection (n = 20) or 2 x 2.5-ml injections (n = 18). Blood samples for PK analysis were taken at various time points up to 28 days after treatment. Tolerability assessments were also made. PK parameters included AUC0-28days, C28 days, Cmax and tmax. Safety follow-up continued until 8 weeks after the injection was given.

The geometric mean AUC0-28days blood levels were 106.8 ng.day.ml and 105.5 ng.day.ml for 1 x 5 ml and 2 x 2.5 ml respectively. The ratio of the geometric means of 1.01 (95% CI 0.68*1.51) showed there was no significant difference in AUC between the two dose regimens (p=0.94). The geometric means of C28 days, and Cmax and the median of tmax were similar in both treatment groups. Both treatment regimens were well tolerated, with there being no major differences in adverse events. The data from this study were in line with AUC0-28 days data from an earlier study involving postmenopausal women with primary breast cancer, where based on 22 women receiving FAS 250 mg (1 x 5 ml), the geometric mean AUC0-28 day was 116.5 ng.day.ml.

In conclusion, there was no significant difference in PK and adverse events between 1 x 5-ml injection and 2 x 2.5-ml injections of FAS. Based on these PK findings, the dosing regimen employed with FAS in the clinical setting would not be expected to impact on the clinical outcome indicating that the 250 mg dose of FAS may be administered as either 1 x 5-ml injection or 2 x 2.5-ml injections. Additionally the single-dose PK findings in two trials using FAS 250 mg (1 x 5 ml) demonstrate the consistency of FAS PK between trials.

724 POSTER

Cardiac safety of herceptin(R) in combination with epirubicin plus cyclophosphamide: interim results of a phase II study in patients with metastatic breast cancer

M. Untch[1], G. Schaller[2], F. Jaenicke[3], W. Jonat[4], H.-J. Lueck[5]. [1] *Clin Grosshadern, Muenchen, Germany;* [2] *Univ Hosp Benjamin Franklin, Berlin, Germany;* [3] *Univ Hosp Eppendorf, Hamburg, Germany;* [4] *Univ Hosp of Kiel, Kiel, Germany;* [5] *Med Univ Hannover, Hannover, Germany*

The monoclonal antibody Herceptin" (H) is indicated for treatment of HER2-positive metastatic breast cancer (MBC), as monotherapy or in combination with Taxol. Previous trials have shown that the concomitant use of an anthracycline (A)-containing regimen (doxorubicin (D)) plus cyclophosphamide (C)) together with H is associated with an increased risk of cardiotoxicity as compared to DC alone. Epirubicin (E) is considered to have less cardiotoxic potential than D. This phase II study was designed to compare the incidence of cardiotoxic events in patients treated with EC plus H, versus patients treated with EC alone. Dose-limiting cardiotoxicity was defined as (a) a decrease of left ventricular ejection fraction (LVEF) of more than 10% points from the screening value and below 50%, or (b) acute coronary syndrome including MI, cardiopulmonary resuscitation, congestive heart failure or severe rhythm disturbances. Patients with HER2-positive disease would all receive EC+H. A control arm of HER2-negative patients would receive EC alone. The dose of E for the first 25 HER2-positive patients was 60mg/m2. Providing dose-limiting cardiotoxicity was not encountered, after completing 6 cycles of ECH, the dose of E would be escalated to 90mg/m2 for a second cohort. Subsequently, the number of patients in both active and control arms would increase to 100. All patients would have prospective cardiac monitoring using echocardiography and results would be reviewed by an independent cardiac review board.

Here we report the results of cardiac assessments in the first cohort of HER2-positive patients treated with 60 mg/m2 E, dose of C plus H (2mg/kg/week maintenance). Data are available for 25 patients. Baseline values for LVEF were in the range 57 to 82%. Four patients discontinued before reaching the sixth cycle of ECH for non-cardiac reasons. Five patients experienced non-serious cardiac disorders which did not coincide with changes in LVEF. An asymptomatic decrease of LVEF of more than 5% points was observed in 12 patients and 5 patients had an increase of more than 5% points. 8 patients experienced asymptomatic decreases of more than 10% points, and for 5 patients the decrease was transient. No dose-limiting cardiotoxic event was observed and LVEF values did not fall below 50% in any patient. Therefore, the Steering Committee has recommended dose escalation to 90mg/m2 E.

Radiotherapy and radiobiology

725 POSTER

Activity-Based Costing in radiotherapy: the costs of activities

Y. Lievens[1], K. Kesteloot[2], W. Van den Bogaert[1]. [1] *University Hospital, Radiotherapy, Leuven, Belgium;* [2] *Catholic University, Centre for Health Services and Nursing Research, Leuven, Belgium*

Purpose: to analyse the costs of the different activities within the Leuven radiotherapy process.

Materials and methods: an Activity-Based Costing model was developed for the calculation of radiotherapy costs in the Leuven radiotherapy department. Resource costs (wage, equipment, space, material and overhead costs) were collected for the year 1999, as well as data on that year's productivity. The resource costs were allocated to the final radiotherapy products based on the activity consumption necessary to produce the products. The activities of the radiotherapy department were defined as 30 treatment related activities and as care related and non-care related support activities. For this overview the treatment related activities were aggregated into 11 major activities and 4 activity groups (administration, treatment preparation and delivery and quality control).

Results: In 1999 the global resource costs of treatment related activities of the Leuven radiotherapy department amounted to 3.253.986 Euro. Wage, equipment, space, material and overhead costs accounted for respectively 45%, 25%, 23%, 4% and 3% of these global costs. The costs incurred by the different activity groups were 210 240 Euro, 1 008 625 Euro, 1 751 580 Euro and 283 540 Euro for administration, treatment preparation, treatment delivery and quality control respectively. Within treatment preparation simulation and planning roughly consumed the same amount of resource costs; i.e. 364 560 Euro and 324 760 Euro.

Conclusion: Wage and equipment consume a large proportion of the treatment related radiotherapy costs. Activities within the radiotherapy process that intensively employ staff and equipment are therefore most expensive, as has been shown in our data where radiotherapy delivery, simulation and planning turn out to be the three biggest resource consumers in radiotherapy. Treatment delivery is by nature a repetitive process, which explains that its costs by far outweigh the costs of other activities, even of the very complex ones, provided they only occur once or twice within the radiotherapy process.

726 POSTER

Radiotherapy compared to extracorporeal shockwave therapy for supraspinatus tendinitis - randomised prospective single-blind trial with two-sample parallel group design

M.W. Gross[1], A. Sattler[2], J. Schmitt[2], R. Hildebrandt[2], H.H. Mueller[3], M. Haake[2], R. Engenhart-Cabillic[1]. [1] *Radiotherapy and Radiooncology, University of Marburg, Marburg, Germany;* [2] *Orthopedics, University of Marburg, Marburg, Germany;* [3] *Epidemiology, University of Marburg, Marburg, Germany*

Aim: In the case of supraspinatus tendinitis conservative therapy delivering either antiinflammatoric drugs or low-dose irradiation is the treatment of