

time of the primary diagnosis of breast cancer might be caused by a more frequent use of mammography. In line with recent data, this small reduction in tumor size does not necessarily translate into improved prognosis.

373

POSTER

Lack of pharmacokinetic interaction between erlotinib, docetaxel and capecitabine in breast cancer patients.

A. Rakhit¹, S. Fettner¹, S. Davis², R. Abbas¹, F. De Rosa², U. Brennschneid², C. Twelves³, J. Baselga⁴. ¹Hoffman-La Roche Inc., Department of Clinical Pharmacology, Nutley, USA; ²F. Hoffmann-La Roche, Basel, Switzerland; ³Beatson Oncology center, Glasgow, Scotland; ⁴Universitat Vall d'Hebron, Barcelona, Spain

Erlotinib (TarcevaTM) is an epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor being developed for the treatment of various solid tumors. This was a multiple ascending-dose safety and tolerability study in metastatic breast cancer patients with additional objective of characterizing the pharmacokinetics (PK) of erlotinib (E), both alone and in combination with docetaxel and capecitabine (D+C). We present here the PK of erlotinib, docetaxel and capecitabine, along with respective active metabolites. Patients were enrolled in three cohorts; Cohort A received 100 mg/day erlotinib for entire 21 day cycle, 825 mg/m² b.i.d. capecitabine for first 14 days of cycle and 60 mg/m² docetaxel i.v. on first day of cycle; Cohort B received same regimen as in Cohort A, but with an increase to 75 mg/m² docetaxel dose level; Cohort C received same regimen as in Cohort B, but with an increase to 1000 mg/m² b.i.d. capecitabine dose level. Erlotinib dosing was delayed until day 2 for the first dosing cycle in order allow for characterization of docetaxel and capecitabine PK in absence of erlotinib. PK sampling for erlotinib was performed on Cycle 1, Day 21 (E alone) and on Cycle 2, Day 1 (E + D + C). PK sampling for docetaxel and capecitabine was performed on Cycle 1, Day 1 (D+C) and on Cycle 2, Day 1 (E+D+C). To date, PK data was available from first two cohorts, both of which were comparable. Mean (± SD) C_{max} for erlotinib in Cohort B was 1,593 (± 481) ng/mL (E alone) and 1,510 (± 480) ng/mL (E+D+C). Mean (± SD) AUC_{0-24hr} of erlotinib in Cohort B was 25,457 (± 11,251) ng.hr/mL (E alone) and 25,445 (± 10,708) ng.hr/mL (E+D+C). Therefore, mean exposure (C_{max}, AUC_{0-24hr}) for erlotinib and its active metabolites (OSI-420 / OSI-413 co-measured) did not appear to change with concomitant administration of docetaxel and capecitabine. Mean (± SD) C_{max} for docetaxel in Cohort B was 2,850 (± 826) ng/mL (D+C) and 2,197 (± 522) ng/mL (E+D+C). Mean (± SD) AUC_{0-24hr} for docetaxel in Cohort B was 3196 (± 830) ng.hr/mL (D+C) and 2,510 (± 1,020) ng.hr/mL (E+D+C). Mean docetaxel half life was unchanged (9.6 hr versus 10.8hr). Therefore, mean PK parameters for docetaxel indicated somewhat lower exposure in the presence of erlotinib. However, these results should be considered inconclusive considering the large interpatient variability and small number of evaluable patients. Mean (± SD) C_{max} for capecitabine in Cohort B was 8,062 (± 6,932) ng/mL (D+C) and 4,975 (± 2,421) ng/mL (E+D+C). Mean (± SD) AUC_{0-24hr} for capecitabine in Cohort B was 5,857 (± 3,401) ng.hr/mL (D+C) and 5,948 (± 2,397) ng.hr/mL (E+D+C). Mean capecitabine half life was also unchanged (0.65hr versus 0.74hr). Mean pharmacokinetic parameters for capecitabine and its metabolites (5-FU and 5'-DFUR) did not appear to change in presence of erlotinib. In conclusion, there was no evidence for any PK interaction between erlotinib, docetaxel and capecitabine (or any metabolites thereof).

374

POSTER

Maximizing internal mammary sentinel lymph node identification

O. Olsha¹, M. Carmon¹, D.B. Odenheimer¹, D. Gimmelreich¹, C. Reinus², D. Hain³. ¹Shaare Zedek Medical Center, Surgery, Jerusalem, Israel; ²Shaare Zedek Medical Center, Pathology, Jerusalem, Israel; ³Shaare Zedek Medical Center, Nuclear Medicine, Jerusalem, Israel

Background: Lymph node mapping has caused renewed interest in the internal mammary nodes in breast cancer. Metastases in these nodes provide important prognostic information both in the presence and in the absence of metastases in axillary lymph nodes. Tracer injection in the dermal lymphatics over the tumor ensures a high rate of identification of the axillary sentinel lymph node (ASLN). Internal mammary sentinel lymph nodes (IMSLNs) are reportedly found in 0% to 35% of patients by conventional mapping methods.

Objective: We carried out a study to test the hypothesis that the addition of a tracer injection into the area of the deep fascia of the breast (near the muscle fascia) would increase the identification rate of IMSLNs.

Methods: Forty-seven consecutive patients with invasive breast cancer, regardless of site, underwent injection of both radioisotope and blue dye in the skin over the tumor and in the deep breast fascia. Pre-operative lymphoscintigraphy and/or intra-operative probe were used to identify the IMSLN. Patients with ductal carcinoma in situ or with known axillary lymph node metastases were excluded.

Results: An IMSLN was identified and biopsied in 24 patients (51%) in 1, 2 or 3 intercostal spaces. For lateral, central and medial lesions the identification rate was 47%, 40% and 75% respectively. A learning curve was evident with an identification rate of 30% for the first 20 patients, and 67% for the next 27 patients. There was 1 instance of metastasis to an IMSLN (2.1%) in a medial lesion. One patient had a small pleural perforation that required no treatment.

Conclusions: The identification rate for IMSLNs with deep fascial injection of tracer was higher than that reported for conventional mapping methods. There is a learning curve, and improvement in the technique of deep fascial injection may maximize identification of the internal mammary sentinel node in the same way that dermal injection ensures maximal ASLN identification. The clinical relevance of this technique in every-day practice has not been established.

375

POSTER

Breast cancer in the elderly - epidemiological characteristics and treatment approach

A. Jovicevic Bekic, Z. Neskovic Konstantinovic, I. Markovic, D. Jovicevic. Institute for Oncology and Radiology of Serbia, Belgrade, Yugoslavia

Background. With the aging of the general population, cancer in the elderly has become increasingly common. It is commonly believed that the diagnosis of cancer in the elderly is delayed for a variety of reasons. Ageing also has an impact on cancer's biology and behavior, with some cancers evolving more slowly and the others becoming more rapidly invasive in older patients. There are also differences in the choice of treatment for elderly patients. The aim of the study was to investigate the epidemiological characteristics and the treatment approach in older breast cancer patients in comparison with younger ones.

Results. In our country, about 50% of cancer cases occur in people aged 65 or over. At the Institute for Oncology and Radiology of Serbia, there were about 1,200 newly registered breast cancer patients the year 2001. About 25% were over 65 years of age. The size of the tumor at diagnosis was on average smaller in younger groups than in older ones, both according to the clinical and pathological TNM. However, there was no significant difference either in the lymph node involvement or in the presence of distant metastases at diagnosis. The share of ductal carcinoma in all breast cancers was lower in elder patients than in younger ones (46 vs. 51%) while the situation was the opposite for lobular carcinoma (34 vs. 25%). However, there were no differences in the tumor grades. Hormonal receptors were more frequently positive in older women. About 80% of patients in both groups underwent surgery. However, there were differences in types of surgical procedures performed. Chemotherapy was 2.5-fold less frequently administered in older women; the difference was significant in each stage of the disease. There was also a significant difference in radiotherapy for each stage of breast cancer.

Conclusion. According to our data, there are some differences in the characteristics of breast cancer between patients over 64 and younger ones. There is a significant difference in the treatment approach for each stage of disease. Two questions remain to be further addressed: is breast cancer in elderly a different disease from breast cancer in younger patients, and, is there a rationale to treat elderly breast cancer patients differently from younger ones.

376

POSTER

Primary chemotherapy with gemcitabine (G), myocet (M) and docetaxel (T): results of a phase I/II trial

P. Schmid¹, K. Krockner², A. Dieing¹, K. Michniewicz², V. Heilmann³, J.U. Blohmer⁴, C. Schulz¹, D. Lueftner¹, D. Elling², K. Possinger¹. ¹Charité Campus Mitte, Humboldt Universität Berlin, Oncology and Hematology, Berlin, Germany; ²Krankenhaus Lichtenberg, Gynecology and Obstetrics, Berlin, Germany; ³Universitätsklinikum Ulm, Gynecology and Obstetrics, Ulm, Germany; ⁴Charité Campus Mitte, Humboldt Universität Berlin, Gynecology and Obstetrics, Berlin, Germany

Introduction: Combinations of anthracyclines, taxanes and gemcitabine are highly effective in breast cancer (BC). Current regimens might be improved by the use of liposomal doxorubicin formulations and by prolonging the

infusion time of gemcitabine. M is as effective as doxorubicin, but provides a lower risk of cardiotoxicity. Prolonged infusion of G can result in higher levels of active metabolites compared to shorter administration. The primary objectives were to determine the optimal doses and the efficacy for G, M and T as primary chemotherapy for locally advanced breast cancer.

Patients and Methods: Patients with histologically confirmed, locally advanced BC were treated with M and T on d1 and G as 4h infusion on d4 every 3 weeks. Patients with an objective response received a maximum of 6 cycles. Treatment was discontinued in case of stable disease or progression after the 2nd cycle. All patients received G-CSF. For the phase I part doses were assigned at registration. Starting dose was G 350mg/m², M 50mg/m² and T 60mg/m². The maximum tolerated dose (MTD) was used for all patients within the phase II part.

Results: 39 pts have been enrolled (Stage: T2 24pts, T3 4pts, T4 11pts, inflammatory BC 7pts. Pretreatment Nodal Status: N0 13 pts, N1/2 26 pts). Currently, 37 pts and 32 patients are evaluable for toxicity and efficacy, respectively. Dose-limiting toxicities were observed in 3/3 pts at G 400mg/m², M 60mg/m² and T 75mg/m² consisting of grade 3 diarrhea and infection in 2 pts and grade 3 stomatitis in 1 pt. The MTD was G 350mg/m², M 60mg/m² and T 75mg/m². Preliminary clinical response data: 2/32 pts with CR, 21/32 pts with PR, 8/32 pts with NC and 1 pt with PD accounting for an overall response rate of 71%. Pathologic response data are pending. Hematological toxicity was moderate (grade 3/4 leucopenia in 23% of courses, thrombocytopenia in 2%, anemia in 2%). Predominant non-hematological toxicities were stomatitis (grade 2 in 26% of courses, grade 3 in 7%), asthenia (grade 2 12%) and nausea (grade 2/3 14%). Other non-hematological toxicities were mild (<10% grade 2/3, except for alopecia). No grade 4 non-hematological toxicity was observed.

Conclusions: GMT is a well tolerated and effective combination. The MTD is G 350 mg/m², M 60 mg/m² and T 75 mg/m². The phase II part of the trial is still ongoing.

377

POSTER

A double marker RT-PCR approach for the detection of disseminating breast cancer cells in peripheral blood

R. Salaman, E. Hennessy, V. Uhlmann, C. Curren, D. Courtney. *Department of Surgery, University College Hospital Galway, Galway, Ireland*

The detection of disseminated cancer cells in peripheral blood of in breast cancer patients may help to predict disease recurrence and potential metastasis. Cytokeratin 19 (CK19) is commonly used marker for the detection of occult epithelial cells in blood. Mammaglobin 1 (MG1) expression is limited to mammary epithelium and is over-expressed in 95% of primary breast tumours. Our aim was to determine whether the use of two markers (Cytokeratin19 and Mammaglobin 1) for the detection of metastatic breast cancer cell using quantitative RT-PCR improves specificity as well as sensitivity of the RT-PCR assay. In several spiking experiments, breast cancer cells (ZR-75) were added to 5ml of human peripheral blood of a healthy donor. After epithelial immunomagnetic enrichment, total RNA was extracted using a silica-based extraction kit. RNA specific primers for MG1 and CK19 were designed to amplify these genes in a single-enzyme RT-PCR. cDNA amplicons were visualised in 2% agarose gel. All samples were analysed using Real-time quantitative TaqMan RT-PCR for both CK19 and MG1 primers. We demonstrated similar sensitivity levels for CK19 and MG1 using solution phase RT-PCR. We also showed improved specificity using MG1 as a second breast specific marker. Using quantitative RT-PCR we demonstrated increased sensitivity compared to solution phase RT-PCR. Real-time quantitative RT-PCR is faster, less laborious and sensitive method for detecting occult metastatic breast cancer cell in peripheral blood. Combined markers are the way in the future for the detection of tissue-specific tumour cells.

378

POSTER

Serum levels of matrix metalloproteinase 2 and 9 in patients with breast cancer.

R. Salaman, C. Curren, V. Uhlmann, D. Courtney. *Department of Surgery, University College Hospital Galway, Galway, Ireland*

The Matrix Metalloproteinases MMPs are a large family of proteolytic enzymes, which are involved in the degradation of many different components of the extracellular matrix. MMPs have been reported to be associated with invasive and metastatic behaviours of human malignant tumours. Enhanced expression of matrix metalloproteinases-2 (MMP-2) has been reported to be associated with increased metastatic potential in various tumours and aggressiveness in breast cancer. This study was designed

with the aim to elucidate the possible relationship between the preoperative circulating MMP-2, MMP-9 and breast cancer. Eighty consecutive patients with invasive breast cancer undergoing surgery were prospectively included and evaluated. Venous blood samples were collected before surgery. Sera were obtained by centrifugation, and stored at -80° C until assayed. The control group consisted of 20 patients with benign breast disease (10 with fibrocystic disease and 10 with fibroadenoma). Serum concentrations of MMP-2 and MMP-9 were measured by the ELISA technique. The data on the primary tumour, age, grade and TNM staging were reviewed and recorded. The mean value of serum MMP-2 and MMP-9 in patients with breast cancer were 241.65± 65.668 ng/ml and 1185.00± 773.37 ng/ml respectively and the difference was significant from the control group. Furthermore, there were significantly higher serum levels of MMP-9 in the patients with more advanced primary tumour staging and in the patients with more advanced lymph node status. In multivariate analysis, TNM staging appeared as independent factor and patients with more advanced TNM staging were shown to have higher serum MMP-2 and MMP-9 Levels. Thus preoperative serum metalloproteinases level might reflect the severity of invasive breast cancer and deserve further evaluation with postoperative serum levels.

379

POSTER

Male breast cancer - review of 93 patients

N. Costa¹, D. Pereira¹, G. Rocha², C. Costa², C. Coutinho¹, C. Azevedo¹.

¹ Portuguese Institute of Oncology, Medical Oncology, Porto, Portugal;

² Portuguese Institute of Oncology, Internal Medicine, Porto, Portugal

Background: Male breast cancer (MBC) is a rare disease with similarities to breast cancer in women. The clinical and pathologic features of MBC, the prevalence of known risk factors, prognostic factors, treatments, and survival, were studied.

Material and methods: Retrospective analysis of 93 patients with MBC admitted and treated at the Portuguese Institute of Oncology, Oporto, Portugal, in a 28-year period (1974 and 2002). Clinical data were obtained from each patient's record. Information regarding macroscopic and microscopic characteristics of the lesion were obtained from the pathologist original report. Patients who died of non-cancer-related causes were censored at last follow-up. Overall and disease-specific survival, were calculated using the Kaplan-Meier method, and univariate comparisons of survival were performed using the log-rank test. A *p* value of 0.05 or less was considered significant.

Results: The mean follow-up time was 58 months (±47), 10 patients (11%) abandoned follow-up. Median age at diagnosis was 65 years (34-94). Most patients came from rural areas, working in the primary sector, and were in contact with known risk products for cancer. Family history of oncology disease was positive in 23 patients (25%), and 11 (12%) have family breast cancer. In our population 78 patients (85%) present a breast nodule, 39 in a subareolar location (42%), and 63 with firm consistency (69%). The mean interval time between first symptom and diagnosis was 19 months (±25). The most frequent histopathologic type of MBC was invasive ductal carcinoma, representing 65% of the cases. Lobular carcinoma, rarely described, was present in 2 of our patients. Node dissection was performed only in 59 patients (64%), metastization involvement in 39 of them (66%). Histologic grade, according the WHO classification modified by Bloom and Richardson, was mainly grade II (26 patients, 28%). Hormonal receptors were analyzed in 68 patients, 38 (56%) were simultaneously positive for estrogen and progesterone receptors. Primary treatment was surgery in 72 patients (78%). Adjuvant treatment was performed in 63 patients (68%), being radiotherapy (RT) in 52 patients (57%), chemotherapy (CTX) in 12 patients (13%), and hormonal (HT) in 38 patients (41%). Five and ten years overall survival (OS) was 69% and 51%, respectively. Twenty patients (22%), recurred, predominantly with bone and lung metastasis. The mean time for the first recurrence was 42 months (±38). Five and ten years disease-free survival (DFS) was 80% and 53%, respectively. The OS and DFS were not statistically influenced by survival comparisons regarding age, tumour size, lymph node metastization, stage at diagnosis, grade of differentiation, and hormonal receptors.

Conclusions: Our results are similar to the available literature. We observed a long mean time to diagnosis, but it did not influence OS. Treatment changes, with emphasis in the adjuvant setting to RT, CTX and HT, probably contribute to the better outcome achieved.