dose equivalence between Navelbine oral and Navelbine i.v. It shall allow to use both forms with the confidence of achieving, at the respective doses, the same blood exposure.

56 POSTER DISCUSSION

Detection of resistance to anthracyclines(A)-based neoadjuvant chemotherapy (NACT) in locally advanced (LABC) and inflammatory breast cancer (IBC)with tc-99m sestamibi scintimammography (SM)

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Purpose: Tc-99m sestamibi is recognized as transporter substrate by MDR and MRP, member of ATP-binding cassette transport proteins that confer resistance to an overlapping array of structurally and functionally unrelated chemotherapics. The aim of this study was to evaluate SM role in predicting the response of LABC and IBC to NACT and in vivo detecting intrinsic and acquired chemioresist tumors.

Methods:SM was performed before (1° scan) and after 4 fixed courses (2°scan) of NACT, unless clinically progressive disease, in 21 LABCs (dose intensive EC-EPI 120 mg/m2 and CTX 600 mg/m2 every two weeks plus G-CSF)and in 3 IBCs (Doxo 50 mg/m2 day 1 and VRL 25 mg/m2 days 1-8 of 21 days cycle). Tracer uptake in the lesions was calculate by tumor-to-normal breast ratio (TBR) early (E) and delayed (D) images;by dividing D-TBR by the E-TBR a retention index (RI) was determined. Tumors with a low RI (<0.56) were consider resistant.

Results:5 LABCs and 2 IBCs had a low RI in both scan (intrinsically resistent tumors) showed a stable disease (SD) or progressive disease (P). 9 tumors with the 1°RI high but the 2° one low (acquired resistive tumors) had 7 partial responses (PR) and 2 SD. In the 7 patients with an high RI in pre NACT imaging and no tumor detectable in the 2° SM there were 3 pathological complete responses(14,28%)and 4 PR. The 3° IBC showed a clinically CR and had both the 1°and the 2° RI high.

Conclusion:SM may be a noninvasive methods to identify tumors in which MDR/MRP are expressed and functional.SM before treatment can select rapidly effluxing tumors with the potentiality or predicting a lack of response in patients treated by A and cross-resistance related drugs. 2° SM is useful for singling out tumors that became resistant during treatment in which MDR-related drugs would have to be avoid in adjuvant setting.

57 POSTER DISCUSSION

Penetration of capecitabine and its metabolites into malignant and healthy tissue from patients with advanced breast cancer

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Purpose: Capecitabine is an oral prodrug of 5-fluorouracil (FU). Since FU concentrations reached in malignant lesions are an important determinant of efficacy, we investigated the intratumoral transcapillary transfer of capecitabine and its metabolites in vivo in patients with breast cancer.

Methods: 10 Patients with skin metastases from breast cancer received a daily dose of 2500 mg/m2 capecitabine administered orally in two divided doses for 2 weeks followed by a 1-week rest period. To evaluate the transcapillary transfer of capecitabine, microdialysis probes were inserted into a cutaneous metastasis and subcutaneous connective tissue of capecitabine naive patients. Capecitabine and its metabolites 5'-deoxy-5-fluorocytidine (DFCR), 5'-deoxy-5-fluorouridine (DFUR), and FU were analyzed in plasma and tissue by capillary electrophoresis.

Results: After peroral administration of capecitabine, high concentrations of the metabolites DFCR and DFUR (mean cmax: 5.9 μg/ml and 3.8 μg/ml, respectively) were observed in plasma, whereas FU rarely exceeded 0.5 μg/ml plasma. Capecitabine and its metabolites equilibrated within minutes between plasma and tissue. Considering tissue exposure, no significant differences between healthy and malignant tissue were observed. Distribution into tissue and metabolism did not change under daily exposure to capecitabine.

Conclusion: Capecitabine and its metabolites easily penetrated malignant and healthy tissue. FU was present in low concentrations in plasma and tissue thus explaining the moderate side-effects observed on this regimen. Under daily therapy with capecitabine, there was no evidence of acquired drug tolerance, which may be attributed to pharmacokinetic phenomena.

Gastro intestinal tract tumours

58 POSTER DISCUSSION

Immunhistochemistry of lymph nodes in pancreatic carcinoma

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Introduction: The prognosis of pancreatic carcinoma is still poor despite radical surgical procedures because of locally recurrent tumor growth or early occurrence of metastases. The early infiltration in neighboring lymph nodes significantly shortens survival time. The aim of the study was to determine the incidence of early tumor cell dissemination in lymph nodes, which were classified tumor-free with conventional histopathology at the time of surgical intervetion using immunohistochemistry.

Methodology: Twenty five patients with a pancreas-associated adenocarcinoma (15 ductal carcinomas of the head of the pancreas, 10 carcinomas of the papilla of Vater) without metastases and histopathologicly tumor-free lymph nodes (N0) were enrolled in the study. Each patient underwent radical resection (R0). As control, 81 excised lymph nodes obtained from patients with chronic pancreatitis were compared. All lymph nodes were investigated for cytokeratin expression using an antiepithelial monoclonal antibody against cytokeratin (AE 1/AE3). Detection of cytokeratin-positive cells in the lymph nodes was defined as disseminated tumor cells.

Results: In total, 229 resected lymph nodes from patients with pancreas-associated adenocarcinoma were investigated, which had been classified tumor-free with conventional histopathology. Overall, 55 of 229 lymph nodes (27.1%) showed disseminated tumor cells. In each patient with adenocarcinoma of the pancreatic head, disseminated tumor cells were detected in at least one lymph node whereas in no patient with carcinoma of the papilla of Vater, tumor cell dissemination in the lymph nodes was found. Similarly, there was no detection of cytokeratin-positive cells in the control group.

Conclusion: The results suggest that the ductal carcinoma of the head of the pancreas generates early, clinically not detectable lymph node metastases explaining partly worse outcome of this tumor compared with the carcinoma of the papilla of Vater (mean survival, 14 versus 48 months, resp.; $P<0.05$). The frequent occurrence of disseminated tumor cells in patients with ductal pancreatic carcinoma of early stage (pT1-3N0M0) may indicate the need for novel neoadjuvant treatment protocols.

59 POSTER DISCUSSION

Epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), ZD1839 ('Iressa'), in combination with 5-fluorouracil (5-FU) and leucovorin (LV), in advanced colorectal cancer (ACRC)

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In preclinical studies ZD1839 ('Iressa'), an orally active, selective EGFR-TKI that blocks signal transduction pathways involved in the proliferation and survival of cancer cells, has been shown to have additive/superadditive antitumor activity in combination with chemotherapeutic agents, including 5-FU. Twenty-three chemotherapy naive patients (pts) (except for 5-FU/LV >6 months earlier) with aCRC were enrolled in this two-part safety and pharmacokinetic (PK) profiling study that involved escalated intermittent (I) and continuous (C) schedules of ZD1839 plus 5-FU/LV (370/20 mg/m2 daily x5, respectively). In Part 1, 17 pts were randomized to I-ZD1839 plus 5-FU/LV on either schedule (A): ZD1839 between days 1-14, 5-FU/LV between days 8-12 (cycle 1) and days 36-40 (cycle 2); or schedule (B): 5-FU/LV between days 1-5 (cycle I) and days 29-33 (cycle 2) plus ZD1839 between days 22-35. I-ZD1839 was dose-escalated (250/400/500 mg) in cohorts of 6 pts. In Part 2, in the 5 pts enrolled to date, C-ZD1839 was