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

administered at 500 mg (highest safe dose from Part 1) with 5-FU/LV between days 8-12 (cycle I) and days 36-40 (cycle 2). Dose-limiting toxicity (DLT) up to 56 days was defined as the occurrence of drug-related: G3/4 neutrophil or platelet toxicity (>7 days duration); febrile neutropenia; G3/4 skin rash; G3/4 diarrhea, nausea or vomiting (>4 days duration) despite standard supportive measures; significant ocular toxicity; or occurrence of other G3/4 major end organ toxicity. One-hundred and thirty courses have been delivered in Parts 1 (117) and 2 (13), respectively, and DLT has not been observed to date. GI/2 adverse events (AEs) reported included rash, diarrhea, mucositis and neutropenia. G3/4 AEs included neutropenia and G3 diarrhea in 1 pt. No apparent increased frequency or severity of diarrhea or skin toxicity beyond that seen with 5-FU/LV alone was observed. In addition, there was no evidence of cumulative toxicity or emergence of new or unusual toxicity with continued exposure. No significant drug-drug interactions have been observed following preliminary PK analysis of ZD1839 and 5-FU exposure at 250 mg I-ZD1839. At day 56, after two 5-FU/LV courses and 2 wks ZD1839, I complete and 4 partial responses (3 confirmed) have been observed on the I-ZD1839 schedule. Thus, the combination of ZD1839 and 5-FU/LV is feasible and has a manageable safety profile.

"Iressa" is a trade mark of the AstraZeneca group of companies.

60 POSTER DISCUSSION

A phase II study of gemcitabine and oxaliplatin (gemox) in advanced billary adenocarcinoma (ABA). Preliminary results

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Pre-clinical data support an optimal synergistic effect using the sequence gemcitabine followed by oxaliplatin (Faivre S, Cancer Chemother Pharmacol 1999, 44(2):117-23). Based on the results of the gemcitabine oxaliplatin combination in advanced pancreatic adenocarcinoma (Louvet C, Proc Am Clin Oncol 2001; 20), we designed a phase II, to determine activity and tolerance of this combination in ABA. Since July 2000, twenty two eligible patients (pts) received the GEMOX regimen: GEMcitabine 1000 mg/m* in 10mg/m*/mn infusion D1, OXaliplatin 100 mg/m* in 2h infusion D2; treatment was repeated every 2 weeks until progression of disease or limiting toxicity. Eligibility criteria were pathologically-proven biliary adenocarcinoma, PS (ECOG) 0-3, age 18 to 80 yrs, adequate hematological, renal and liver functions, measurable disease, control of pain and jaundice before inclusion, and written informed consent. Pts characteristics: 12 male/10 female; mean age 70 yrs, range 40-80; PS: 0 = 7, 1 = 9, 2 = 5, 3 = 1; 2 Locally Advanced (LA)/20 Metastatic (M); chemotherapy line: 1 = 19, 2 = 2, 3 =1; tumor sites: gallbladder 8, extrahepatic bile ducts 3, ampula of vater 3, intrahepatic bile ducts 7, unknown 1; M tumor sites: liver = 16, lung = 3, distant lymph nodes = 2, peritoneum = 4. Toxicity: 139 cycles were administered (median 5, range 1-18). No NCI CTC grade 4 was observed. Grade 3 (% cycle/% of pts): neutropenia 0.7%/4.8%, thrombocytopenia 0.7%/4.8%, nausea-vomiting and diarrhea 0%/0%; grade 2 alopecia 9.5%, grade 3 peripheral neurotoxicity (specific scale) 4.8% of pts. Overall, 14.3% of pts experienced a grade 3 toxicity. Efficacy: (investigators) 5 PR, 3 SD, 6 PD and 8 to early were observed for a response rate (WHO criteria) of 35.7% (5pts/14).

Conclusion: GEMOX combination is active and well tolerated in ABA. Accrual continues to this study. Updated data with progression free survival and overall survival will be presented at the meeting.

61 POSTER DISCUSSION

Partial duodenopancreatectomy with radical lymphadenectomy in patients with pancreatic carcinoma

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Purpose: Partial duodenopancreatectomy (PD) is the treatment of choice for carcinoma of the pancreatic head and periampullary carcinoma. In contrast the benefit of radical lymphadenectomy in these patients is still discussed controversially.

Methods: 117 patients with ductal adenocarcinoma of the pancreas who underwent PD between 1988 and 2000 and received either a regional lymphadenectomy (Group A) or an extended radical lymphadenectomy (Group B) were included in survival studies according to Kaplan-Meier. 52 male and 65 female patients with an median age of 62 years were analysed.

Results: Perioperative mortality was 4.3% (5 pat.). The stage distribution according to the UICC was: Stage I: 8 (6.8%), stage II: 23 (19.7%) stage III: 58 (49.6%), Stage IVa+b: 28 (23.9%). Overall 5-year survival rate of these patient was 18%. 5-year survival of curative (R0) resected patients was 23%.

A significant difference could be observed in these group between patients with negative lymph node status (36% 5-year survival) and positive lymph node status (17% 5-year survival). Whether no significant difference could be observed between patients in Group A or B. If only early UICC-tumor stages were compared patients in Group B seemed to have a benefit in survival compared to group A.

Conclusion: The data indicate that extensive retroperitoneal tissue clearance for ductal adenocarcinoma does not improve overall survival compared to regional lymphadenectomy. Patients with early tumor stages might benefit from the extended approach.

62 POSTER DISCUSSION

Intra-arterial hepatic chemotherapy with oxaliplatin combined to intravenous treatment with 5FU + folinic acid in hepatic metastases of colorectal cancer

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Purpose: Due to increase of tumoural exposure to the drugs, intra-arterial hepatic chemotherapy (IAHC) increases response to chemotherapy when fluoropyrimidines (5FU or FUDR) are used. With new drugs such as oxaliplatin and irinotecan the interest of this sometimes difficult way of therapy has been debated. We tried to use one new drug, oxaliplatin, administered intra-arterially in order to increase response rate and to decrease systemic toxicity.

Methods: From May 1999 to January 2001, 23 patients with isolated hepatic metastases of colorectal cancer were included in a phase II study. Patients could have received one previous treatment combining 5FU + folinic acid for their metastatic disease. They should have adequate bone marrow function and adequate liver, cardiac and renal functions. Study protocol: every two weeks the patients received: oxaliplatin 100 mg/m2 IAH 2-hour infusion + FA 200 mg/m2 2-hour infusion i.v. followed by 5FU 400 mg/m2 i.v. bolus followed by 600 mg/m2 as continuous infusion for 22 hours day 1, FA and 5FU were repeated day 2.

Results: 14 men, 19 women, median age: 59 years [44-72]. The median percent of liver involvement was 30% [10-60%]. Median number of cycles was 6 [1-20]. Treatment was stopped in 15 patients (pts): for progressive disease: 2 pts, obstruction of the catheter: 9 pts, other reason: 4 pts. Toxicity was frequent but mild. Grade 3-4 leucopenia: 4 pts, neutropenia: 7 pts, thrombopenia: 1 pt. There was one toxic death due to a neutropenic sepsis. Response rate in 14 evaluable patients (7 too early, 2 less than 4 cycles due to early catheter obstruction): complete response: 1 pt, partial responses: 10 pts, stable disease: 3 pts; objective response rate: 79%. Three patients underwent complete resection of their metastases after response to IAHC. Six-month survival was 86% [66%-95%].

Conclusion: this combined hepatic arterial with oxaliplatin and systemic chemotherapy allowed to observe very high response rate with manageable toxicity.

Lung cancer 1

63 POSTER DISCUSSION

Randomised phase II study of BMS-275291 versus placebo in patients (pts) with stage IIIb or IV non small cell lung cancer (NSCLC) receiving paclitaxel + carboplatin (PC): National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) br.18

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BMS-275291 is a novel matrix metalloprotease inhibitor (MMPI) with broad activity against MMPs but without the dose limiting arthrotoxicity seen with BB2516 (marimastat) and AG3340 (prinomastat). The objective of the phase II study was to determine the incidence of arthrotoxicity and other toxicities, as well as to examine whether the objective response rate for either arm was in keeping with that expected for PC based upon review