Poster Discussions: Oral

New drugs – Phase I-Pharmacogenetics

53 POSTER DISCUSSION

A phase I study of escalating doses of CCI-779 in combination with 5-fluorouracil and leucovorin in patients with advanced solid tumors

C.J.A. Punt[1], U. Bruntsch[2], A.-R. Hanauske[3], K. Weigang-Köhler[2], M. Peters[1], C. Thielert[4], J. Frisch[4]. [1] *University Medical Center Nijmegen, Medical Oncology, Nijmegen, The Netherlands;* [2] *Klinikum Nürnberg, Med. Klinik 5, Nürnberg, Germany;* [3] *Oncological Out-Patient Clinic, Munich, Germany;* [4] *Wyeth Oncology, Munich, Germany*

Purpose: CCI-779, a novel ester of rapamycin with a unique cytostatic mechanism of action, has shown antitumor activity preclinically and clinically without prolonged immunosuppressive effects when given intermittently. We report the preliminary clinical results of a phase I study with CCI-779 in combination with 5-FU/LV.

Methods: All drugs were administered once weekly IV for 6 weeks (wks) followed by 1 wk of rest: CCI-779 in 30 min (1st cycle starting in wk 2), followed by LV (200 mg/m2) in 1 hr, and 5-FU (2600 mg/m2)in 24 hrs. Pt characteristics: 28 patients (pts) enrolled, preliminary data available for 24 pts (16 male/8 female); median age 57 yrs (34 to 71). PS (ECOG): 0=17 pts, 1=6, 2=1. Prior chemotherapy (CTx): 6 pts; radiotherapy (Rx): 5; CTx+Rx: 4; surgery only: 6; none: 3. Tumor types: 8 colorectal carcinoma (ca), 4 gastric, 3 esophagus, 3 head & neck, 2 cholangio, 4 other.

Results: CCI-779 was administered at the dose levels of 15 (4 pts), 25 (3), 45 (15), and 75 (6) mg/m2. At 75 mg/m2 CCI-779, stomatitis (6/6 pts) requiring dose reductions and/or discontinuations and medical interventions, was dose-limiting. Thus, additional patients were investigated at 45 mg/m2. Of 11 pts for whom preliminary data are available at this dose, 2 toxic deaths (GI perforation) occurred as well as 15 Gr 3 in 9 pts and 4 Gr 4 toxicities (fatigue, dehydration, leucopenia, acute abdomen) in 1 pt, necessitating dose reductions and/or discontinuations in these pts. Various skin toxicities, eg. rash, folliculitis, pruritus, ulceration, and nail changes, as well as stomatitis and asthenia, represent the most prominent toxicities regardless of the dose level tested. Preliminary antitumor activity data showed as best response a CR in a colon ca pt at 15 mg/m2 CCI-779 in wk 42. Ten SD with a maximum duration of 12 months were observed. The median pt duration on study was 9.0 wks (2 to 52 wks).

Conclusion: Clinical efficacy was observed without a clear dose-response relationship, conceivably due to concomitant optimal 5-FU/LV dosing. The safety profiles at the 4 dose levels suggest an overlap of drug toxicities of CCI-779 and 5-FU/LV. The frequency and severity of toxicities and the number of necessary dose reductions and/or discontinuations even at the 45 mg/m2 dose level suggest a narrow therapeutic index for CCI-779 in combination with 5-FU/LV. In the future, other doses and regimens should be explored.

54 POSTER DISCUSSION

A phase I trial of PKC412, an inhibitor of protein kinase C, in combination with bolus 5-Fluorouracil and leucovorin in patients with stage IV colorectal cancer

K. Weigang-Köhler[1], H. Bouterfa[2], U. Bruntsch[3], J. Buekki[4], C. Dutreix[5], G. Greim[6], M. Heike[7], C. Peschel[8]. [1] *Klinikum Nuernberg, 5. Med. Klinik, Nuernberg, Germany;* [2] *Novartis Pharma;* [3] *TU Muenchen, III. Med. Klinik, Muenchen, Germany;* [4] *Johannes Gutenberg-Universität Mainz, I. Med. Klinik, Mainz, Germany*

PKC412, a N-benzoyl-staurosporine, is a derivate of the naturally occurring alkaloid staurosporine and an inhibitor of the protein kinase C (PKC) enzyme family. PKC412 affects deregulated signalling pathways in malignant cells and has antitumor acticity in vitro and in mouse xenografts and antiangiogenic effects.The primary objective of this study was to determine the MTD of PKC412 in combination with 5-Fluorouracil and leucovorin in patients with stage IV CRC and to assess the safety of the combination of PKC412 with 5-FU and leucovorin.

36 patients (median age 64 yrs, 24 m and 8 f) with previously untreated stage IV CRC were included, 33 patients are evaluable for safety and efficacy. 5 - FU (425 mg/m*) was administered on 5 consecutive days as a bolus, preceded by leucovorin (20 mg/m*). Cycles were repeated every 28 days. PKC412 was given p.o. daily starting with cycle 1 for a scheduled period of 6 cycles. Starting dose for PKC412 was 25 mg/day and was escalated in six cohorts to 225 mg/day based on the MCRM estimate of the MTD.

The mean duration of treatment was 3,5 cycles considering all dose levels. At all doses the most frequent reported adverse events were diarrhea, stomatitis/mucositis, nausea, vomiting, pain and headache. Gr 3/4 toxicities suspected to be due to the combination therapy were neutropenia (2 pts Gr 4, 3 pts Gr 3), diarrhea (4 pts Gr 3), stomatitis (2 pts Gr 3), renal/genitourinary complications (2 pts Gr 3), anorexia (1 pt Gr 3), nausea (1 pt Gr 3), vomiting (1 pt Gr 3) and fatigue (1 pt Gr 3). At 225 mg/day, 2 patients were withdrawn from the study due to emesis after first intakes of PKC412. Another patient reduced PKC412 dose from 225 to 150 mg/day after 9 days of treatment due to nausea and diarrhea. No death occurred during the study. DLTs reported were: grade 3 stomatitis/mucositis at 25 mg/day and 50 mg/day, and grade 4 neutropenia at 150 mg/day. The maximum tolerated dose in this population should be regarded as 150-225 mg/day.

Preliminary efficacy showed that among 33 pts, 5PRs, 9 SDs, 10 PDs were reported and 9 pts were not evaluable.

Pharmacokinetic data will be available for presentation at the meeting.

55 POSTER DISCUSSION

Reliable use of Navelbine oral based on pharmacokinetic (PK) bioequivalence

C. Puozzo, P. Variol. *Institut de Recherche Pierre Fabre, Clinical Pharmacokinetics, Castres, France*

Oral chemotherapy should significantly improve patients' quality of life. However, depending on the oral bioavailability the required doses are generally different from i.v. to oral. Since oral administration often generates higher inter-individual variabilities than i.v., suitable pharmacokinetic (PK) dose equivalence may be difficult. Therapeutic use of an oral form should be facilitated if its PK behaviour is very close to the i.v. form and if a reliable dose correspondence exists between both forms.

To compare the PK characteristics of Navelbine oral with Navelbine i.v. a bioequivalence analysis of the blood exposure delivered by each form was carried out. Such a statistical analysis, defined by international regulations, is usually aimed at comparing two pharmaceutical forms and therefore to accurately demonstrate that they have the same PK properties and the same degree of variability on PK parameters of parent compound.

To be bioequivalent, PK parameters of two pharmaceutical forms must present no statistical differences in their mean value and the variability expressed as confidence interval around the mean value must be similar and within the range [0.8 - 1.25] defined in regulatory guidelines.

Through an absolute bioavailability study on 24 patients (any solid tumour) receiving Navelbine oral and Navelbine i.v. in a cross-over design, a bioequivalence analysis was performed by comparing doses at 60 mg/m2 oral versus 25 mg/m2 i.v. and 80 mg/m2 oral versus 30 mg/m2 i.v. The demonstration of Navelbine PK linearity has enabled the comparison at different dose levels. No significant statistical differences were observed in the respective blood exposures. Moreover, the respective confidence intervals [0.87-1.09] and [0.97-1.21] were within the required regulatory range [0.8-1.25], which demonstrated a bioequivalence of blood exposure between oral and i.v. doses.

It was also demonstrated that the haematotoxicity, the main dose limiting toxicity (DLT) of Navelbine, was strongly correlated to blood exposure and therefore showing a pharmacokinetic/pharmacodynamic relationship independent of the administration route.

In conclusion, the equivalence of blood exposure that was demonstrated according to strict criteria of bioequivalence clearly establishes the reliable

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)

S. Mezi[1], F. Primi[1], F. Capoccetti[2], F. Rea[1], O. Schillaci[2]. [1] *University "La Sapienza", Dpt of Experimental Medicine- S.S. Oncology, Rome, Italy;* [2] *University "Tor Vergata", Rome, Italy*

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

R.M. Mader[1], C. Schrolnberger[2], B. Rizovski[1], M. Brunner[2], C. Wenzel[1], G. Locker[1], M. Schmidinger[1], H.G. Eichler[2], M. Mueller[2], G.G. Steger[1]. [1] *Vienna University School of Medicine, Department of Internal Medicine I, Division of Oncology, Vienna, Austria;* [2] *Vienna University School of Medicine, Department of Clinical Pharmacology, Division of Clinical Pharmacokinetics, Vienna, Austria*

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

J. Fahlke[1], K. Ridwelski[3], F. Meyer[1], S. Rudolph[1], U. Kasper[2], H. Lippert[1]. [1] *Otto-von-Guericke University, Surgery, Magdeburg, Germany;* [2] *Otto-von Guericke University, Pathology, Magdeburg, Germany;* [3] *City Hospital, Surgery, Dessau, Germany*

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)

L. Hammond[1], J. Figueroa[2], L. Schwartzberg[3], L. Ochoa[4], M. Hidalgo[4], N. Olivo[1], G. Schwartz[5], L. Smith[1], J. Ochs[6], E. Rowinsky[1]. [1] *Cancer Therapy and Research Center, Institute for Drug Development, San Antonio, USA;* [2] *Arrington Cancer Center, Lubbock, USA;* [3] *Response Oncology Inc, Memphis, USA;* [4] *University of Texas Health Science Center, San Antonio, USA;* [5] *Brooke Army Medical Center, San Antonio, USA;* [6] *AstraZaeneca, Wilmington, DE, USA*

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