748 ORAL

Thymidylate synthase quantitation of chemosensitivity testing predicts response and survival of patients with liver tumours receiving arterial infusion chemotherapy

M. Kornmann[1], K.H. Link[1], U. Butzer[1], K.D. Danenberg[2], E. Sunelaitis[1], D. Salonga[2], P.V. Danenberg[2], H.G. Beger[1]. [1]*Department of General Surgery, University of Ulm, Ulm, Germany;* [2]*Department of Biochemistry, University of Southern California, Los Angeles, United States*

Purpose: To compare thymidylate synthase (TS) mRNA quantitation and *in vitro* chemosensitivity testing with the clinical outcome of patients with isolated nonresectable liver tumors receiving hepatic arterial infusion (HAI) chemotherapy.

Methods: Tumor tissue was obtained during the implantation of the device for HAI therapy. Intra-tumoral TS levels were determined using a quantitative RT-PCR method with β-actin as internal standard. The *in vitro* sensitivity of cisplatin, epidoxorubicin, 5-fluorouracil, mitomycin C, and mitoxantrone was determined using the human tumor colony-forming assay (HTCA).

Results: Patients which were regarded as sensitive by the combination of both tests (n = 13) were 7.7-fold more likely to respond ($p < 0.005$) than patients which were regarded as *in vitro* resistant by the test combination (n = 11). Moreover, sensitive patients displayed with 32 months (range: 5 to 75 months) a significantly longer median survival than resistant patients with 17 months (range: 3 to 28, $p = 0.003$). Analysis of the Kaplan-Meier curves revealed that sensitive patients have an higher survival probability as determined by the log-rank test ($p = 0.044$).

Conclusion: Intra-tumoral TS mRNA quantitation and chemosensitivity testing using the HTCA may be useful to select patients with liver tumors that profit from hepatic arterial infusion chemotherapy.

749 ORAL

In vitro sequence dependence for the multitargeted antifolate (MTA, LY231514) combined with other anticancer agents

R.M. Schultz[1], J.A. Dempsey[1], L.A. Kraus[2], S.M. Schmid[2], J.A. Calvete[3], A.L. Laws[3]. [1]*Lilly Research Laboratories, Eli Lilly and Co., Indianapolis, IN 46285;* [2]*Southern Research Institute, Birmingham, AL, United States 35255;* [3]*Quintiles, Riccarton Edinburgh, United Kingdom*

Purpose: MTA, a new-generation antifolate, is undergoing broad phase II evaluation as a single agent, and preliminary results show responses in several rumor types, including non-small cell lung (NSCLC) and breast cancer. Clinical trials combining MTA with other active chemotherapy agents are currently underway. *In vitro* studies were conducted to assist in the selection of the appropriate drug combinations or sequences for clinical investigation.

Methods: We investigated drug combination effects on growth inhibition of human NCI-H23 and NCI-H460 NSCLC and ZR-75-1 breast carcinoma cell lines using MTT and neutral red dye uptake assays. Drag interactions were evaluated using CalcuSyn (Chou/Hayball) and Pritchard Shipman analyses.

Results: When the MTA exposure preceded either doxorubicin, taxol, or taxotere by 24 h, synergistic cytotoxic activity was observed. However, the reverse order produced only additive activity. DNA flow cytometry studies indicated that MTA causes a buildup of cells near the G1/S interface after 24 h of incubation. Interaction of MTA with cisplatin or carboplatin was additive regardless of the sequence of adminstration.

Conclusion: These findings suggest that, to obtain maximal minor cytotoxicity, MTA should precede taxanes or doxorubicin when the drags are given in combination chemotherapy protocols.

750 ORAL

A phase I study of sequential gemcitabine and MTA (LY231514) in patients with advanced malignancies

A. Adjei[1], C. Erlichman[1], H. Pitot[1], J. Sloan[1], R. Goldberg[1], P. Peethambaram[1], L. Hanson[1], J. Reid[1], R. Johnson[2]. [1]*Mayo Clinic and Foundation, Rochester, MN;* [2]*Eli Lilly and Company, Indianapolis, IN, United States*

MTA, a novel multitargeted antifolate, which inhibits thymidylate synthase, dihydrofolate reductase and glycinamide ribonucleotide formyl transferase, is active in lung, breast, head and neck, pancreas, and colon cancers. Gemcitabine (GEM) is a cytotoxic pyrimidine antimetabolite with broad activity against solid tumors. We have demonstrated sequence-dependent synergistic cytotoxicity between gemcitabine and MTA in the HCT-8 colon cancer cell line. In the first part of our phase I study evaluating GEM administration on days (d) 1 and 8 with MTA on d1, myelosuppression precluded the administration of full GEM doses on d8 in more than 50% of treatment courses. We report here results of an alternate administration schedule of GEM (1000, 1250 mg/m^2) given on d1, d8 and MTA (400, 500, 600 mg/m^2) given on d8, q3wk. Twenty-one patients (15 males, 6 females) have received 55 courses (median, 2; range, 1–7) of treatment. The most common toxicity has been neutropenia, which was dose-limiting at GEM/MTA 1250/600 mg/m^2. Mild to moderate non-hematologic toxicities (NCI CTC grades 1 and 2) include arthralgia, nausea, fatigue, fever, rash and elevated hepatic transaminases. PK studies reveal no effect of GEM on the disposition of MTA. The MTD on this schedule, which is recommended for further clinical testing, is GEM 1250 mg/m^2 given on d1, d8 and MTA 500 mg/m^2 given on d8. To date, 4 partial responses (1 NSCLC, 1 ovarian carcinoma and 2 colorectal carcinoma) have been documented in 17 evaluable patients. Supported by grants from NCI (CA77112; RR00585) and Eli Lilly.

751 ORAL

The cycle-to-cycle variability of docetaxel pharmacokinetics (PK) assessed by population PK analysis

R. Bruno[1], N. Vivier[1], G. Montay[1], M. Klink-Alakl[2], N. Azli[2], P. Fumoleau[3], M. Marty[4]. [1]*Rhone-Poulenc Rorer, Drug Metabolism and Pharmacokinetics, Antony;* [2]*Rhone-Poulenc Rorer, Oncology, Antony;* [3]*Centre Rene Gauducheau, Medical Oncology, Nantes;* [4]*Hopital Saint-Louis, Medical Oncology, Paris, France*

Purpose: To estimate intra-patient cycle-to-cycle variability of docetaxel.

Methods: Docetaxel PK was assessed over 133 cycles (cycles 1 to 5) in 66 patients with breast cancer using a sparse sampling strategy (JCO, 16, 187–196, 1998) in 2 Phase 2 studies. The data were pooled with first cycle data from 547 patients and analyzed according to a previous population PK model (JPB, 24, 153–172, 1996). Inter-patient (IPV) and cycle-to-cycle (CCV) variabilities of docetaxel clearance (CL) were estimated and covariate effects on CL were reassessed (NONMEM program).

Results: CL IPV and CCV were 33.3% and 29.6% respectively, in a basic model with no covariate and 18.1% (NS) and 26.3% in the model incorporating the previously identified 5 covariates: body surface, a1-acid glycoprotein, hepatic function, albumin (ALB) and age. The 5 covariates explained most of IPV which was no longer significant, the only variability left being CCV. When CCV is accounted for, the effects of age and ALB on CL which were previously of low magnitude are no longer significant. Other covariate effects remain of similar magnitude.

Conclusion: Modeling of CCV is essential in population PK analysis. Docetaxel IPV in CL is fully explained by patho-physiological covariates and CCV is low.

752 POSTER

Role of Mdr phenotype in locally advanced breast cancer (LABC) treated with primary chemotherapy (CT1)

B. Coudert, S. Lizard, M. Arnal, Ph. Genne, A. Darut-Jouve, C. Bélichard, L. Arnould, J.M. Riedinger, F. Mayer, C. de Gislain, P. Fargeat. *G.F. Leclerc. 21000 Dijon, France*

Purpose: to determine the role of mdr phenotype in LABC treated with CT1.

Methods: mdr gene expression analysis using semi-quantitative reverse transcription-polymerase chain reaction was performed in 77 LABC diagnosed women undergoing anthracyclin based CT1. Results were expressed by the ratio of mdr/β2 microglobulin used as an internal control and considered positive if > 0.1. Mdr was assessed before and after CT1 (pre or post-CT1 mdr). Stepwise logistic regression or Cox models assessed mdr role in objective response (OR) to CT1 or in disease free (DFS) and global survival (GS).

Results: 43/77 pre-CT1 mdr were positive (mean 0.139 ± 0.126). 47/77 post-CT1 mdr were positive (mean 0.198 ± 0.171). The paired comparison of means was significant ($p < 0.003$). After adjustment on other characteristics, pre = CT1 mdr (positive vs negative) had no role on OR after CT1 while DFS and GS were shorter with positive post-CT1 mdr ($p < 0.05$ for both analysis).

Conclusions: in LABC treated by CT1, positive mdr after CT1 is an independent factor for DFS and GS despite no proven role in OR to CT1. Mdr levels might significantly increase after CT1.

Supported by grants from the G.I.R.E.C., the Ligue contre le Cancer de Bourgogne et de Saône et Loire.