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Cisplatin Dose-Response Relationship, Resistance Mechanisms & Optimum Resistance Modulating Strategies in Ovarian (OC) Vs Non-Small Cell Lung Cancer (NSCLC). *David J. Stewart, Simone Dahrouge, Remco Donker. Ottawa Regional Cancer Centre, Ottawa, Ontario, Canada.*

Purpose: To compare cisplatin (Cp) dose-response relationships (DRRs) in OC vs NSCLC & to use DRRs to surmise resistance mechanisms and optimum resistance modulating strategies. Background: We postulated excess resistance factor ('active resistance') would give a shoulder on a dose-response curve (DRC) & factor deficiency ('passive resistance', including resistance due to slow cell division) would give a terminal plateau (Stewart et al. Invest New Drugs 14:115, 1996). Method: We used published response rates in OC & NSCLC to estimate mean% tumor cell kill with varying Cp doses, assuming complete, partial, & minor responses, stable disease & failures represent >99%, 83%, 50%, 13% and 0% mean cell kills, respectively. We used studies with single agent Cp or comparing 2 Cp doses or comparing another drug alone to that drug+Cp. Results were corrected for estimated% cell kill by any concurrent drug. We plotted log% cell survival vs Cp dose/course & dose intensity. DRCs were extrapolated leftwards to the 'Cp dose=0' line. Results: The OC DRC appeared to be steep & to cross the 'Cp dose=0' line near the 100% cell survival point. For NSCLC, the DRC appeared to be flat over the entire Cp dose range studied (50-200 mg/m2/course) & to cross the 'Cp dose=0' line below the 100% cell survival point. Conclusions: If our assumptions are valid, DRCs suggest minimal Cp resistance or low dose active resistance in OC, but passive resistance in NSCLC. Active resistance is analogous to competitive inhibition of drug, & may be inducible with drug exposure. Hence, the optimum initial strategy in OC may be to use Cp at highest tolerable doses by rapid infusion (to achieve high peak levels). Resistance modulating agents should be explored for responding patients who fail to be cured. For the passive resistance in NSCLC, one should define lowest doses giving 'plateau-level' response rates, & should then use this dose at frequent intervals & for as many courses as tolerable, along with drugs with other mechanisms of action.

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Preclinical Synergy of Oxaliplatin (OXA), Topoisomerase I-Inhibitor (topotecan) and 5-Fluorouracil in Sensitive and 5-Fluorouracil Resistant HT29 Cell Line. *M. Taron, C. Plasencia, A. Abad, M. Guillot, C. Martín, A. Barnadas, R. Rosell. Medical Oncology Service and Laboratory of Molecular Biology. Hospital Germans Trias i Pujol. C/Canyet s/n. 08916-Badalona (Barcelona). Spain.*

Topotecan (TPT) and Oxaliplatin (OXA) have demonstrated chemotherapeutic activity in a wide variety of tumors. In our study we have evaluated the potential synergism of TPT, OXA and 5-Fluorouracil (5FU) combination in variants of sensitive and 5FU resistant human colorectal tumor derived cell lines (HT29/HT295FUR). The HT295FUR was obtained in our own laboratory after administration of increasing concentrations of 5FU until a level of 2μM was reached and the doubling times were roughly equivalent to those of HT29. The 5FU resistant cell line showed to be 5-fold resistant to 5FU and proved to be non resistant to TPT or OXA as compared to the parental HT29 cell line (HT29 vs. HT295FUR: 5FU $p < 0,01$; OXA $p = 0,25$; TPT $p = 0,33$). Using this model, we have analyzed cell toxicity in four sequential schedules of administration: OXA → TPT, TPT → OXA, OXA → 5FU, 5FU → OXA. Cell viability was assessed by the MTT-test, and isobologram analysis (Chou and Talalay method) was then performed to determine synergism/antagonism. In all schedules drugs were administered for 24 hours (TPT/5FU) or 4h (OXA). Our results show a highly synergistic effect in all schedules, and being also independent from the 5FU-resistance phenotype, at all levels of fractional survival. (See Combination Index ± SD at IC50 level summarized below; $CI < 1$ indicates synergism, and $CI > 1$ antagonism). In this assay, it has also been demonstrated that the addition of OXA in the OXA → 5FU schedule circumvents the 5FU resistant phenotype of HT295FUR, thus showing the same degree of sensitivity to 5FU than parental cell line.

	OXA → TPT	TPT → OXA	OXA → 5FU	5FU → OXA
HT29	0.77 ± 0.03	0.78 ± 0.07	0.58 ± 0.07	0.40 ± 0.04
HT295FUR	0.65 ± 0.02	0.55 ± 0.007	0.24 ± 0.005	0.47 ± 0.02

In conclusion, OXA/TPT and OXA/5FU combination have shown a highly therapeutic potential in sensitive as well as in 5FU resistant human colorectal tumor derived cell line. These results may be further exploited to promote new schedules of administration for advanced colorectal cancer treatment.

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A Phase I and Pharmacokinetic Study of LY309887 Given Every 3 Weeks with Folic Acid Supplementation. *Sarah Halford, P. Harper, M. Highley, M. Lind, A.H. Calvert, R. Johnson, J. Walling. Eli Lilly, Indianapolis, IN.*

LY309887 is a thiophene derivative of lometrexol, and inhibits glycinamide ribonucleotide formyltransferase (GARFT). It is a specific inhibitor of purine biosynthesis. LY309887 is a more potent inhibitor of GARFT. This occurs by virtue of a greater affinity for the alpha form of the folate receptor. Supplemental folic acid reduces the toxicity of lometrexol in vivo and in patients (pts), and reduces the toxicity of LY309887 in vivo. We report here data from an ongoing phase I study of LY309887 given IV once every 3 weeks, with oral folic acid (5 mg/day) given for 14 days, starting 7 days prior to LY309887. There were 27 pts given 86 courses over 5 dose levels between 2 and 12 mg/m2. Patient characteristics were: age range, 33 to 73, median 55; malignancy, colorectal 9; ovary 4; pancreas 4; other 4; prior chemotherapy 24; prior radiotherapy 6. Doses were escalated in cohorts of 3 pts and dose-limiting toxicity (DLT) was not observed until 12 mg/m2, when the first pt in the cohort expired of septic complications of myelosuppression. The dose for subsequent pts was dropped to 8 mg/m2. The first 3 pts in this cohort did not experience DLT and a total of 9 pts were accrued at this dose level in anticipation that this would be the phase II dose. However, 2 pts had dose-limiting grade 4 neutropenia, and 4 pts developed a slowly reversible neuropathy, characterized by a loss of temperature sensation and burning dysesthesias peri-orally and in the extremities. Two pts had autonomic neuropathy. This dose level was therefore defined as the MTD, with a recommended phase II dose of 6 mg/m2. A minor response was observed in a pt with a right parotid primary. Based on preclinical observations showing improvement in therapeutic index with increased dose of folic acid, an extension to the study was performed to define a MTD using a 25 mg daily dose of folic acid x 14 days. No DLT was observed at 6 mg/m2, and at 8 mg/m2 4 pts were treated. One pt developed pancytopenia and sepsis and expired. Three pts developed neuropathy. LY309887 was cleared rapidly from plasma with an effective terminal elimination half-life of 4 to 6 hours. However, plasma concentrations persist at low levels up to 3 weeks after administration, reflective of a prolonged terminal phase. In conclusion, LY309887 has a long terminal half-life and a toxicity profile characterized by myelosuppression and slowly reversible neuropathy. Neuropathy was not predicted from previous experience with lometrexol, or from preclinical models. The study continues to characterize the safety profile of LY309887 in combination with 25 mg of folic acid.

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Phase I Study of ZD9331 on a 5-Day Short Infusion Schedule Given Every 3 Weeks. *B.C. Goh, M.J. Ratain, D. Bertucci, R. Smith, S. Mani, N.J. Vogelzang, R.L. Schilsky, M. Hutchison, M. Smith, S. Averbuch, E. Douglass. Zeneca Pharmaceuticals, Wilmington, DE.*

ZD9331 is a potent inhibitor of thymidylate synthase (TS) at the folate binding site, differing from 'Tomudex' in that it does not undergo intracellular polyglutamation and therefore may have a different spectrum of activity and toxicity. A qdX5 schedule every 3 weeks was studied in this phase I trial because of the short (6 h) half-life in dogs. Dose escalation followed a 2-stage procedure, with initial doubling of the dose until drug-related toxicity was seen; dose escalation was subsequently guided by a modified Fibonacci series. Sixty-one patients, of which 56 were evaluable, with refractory cancer have been treated at 11 dose levels (0.4 mg/m²/d to 16 mg/m²/d). Myelosuppression was dose-limiting, with grade 4 thrombocytopenia occurring at 4.8 and 7.5 mg/m²/d and febrile neutropenia observed in 1/6 patients at 12 mg/m²/d and 2/8 patients at 16 mg/m²/d. Non dose-limiting neutropenia grade 3 and 4 was observed in 2 other patients at 16 mg/m²/d. Grade 3 erythematous maculopapular rash was observed in 1 patient at 12 mg/m²/d. Other non-hematological toxicities that were not dose-limiting included fatigue, diarrhea, and reversible elevations of transaminases. Pharmacokinetic analysis showed non-linearity, with increased clearance and reduced terminal half-life as doses were increased. This may reflect saturation of tubular reabsorption processes. The mean clearance and terminal half-life of the drug were 6.8 ± 2.4 ml/min and 72.8 ± 27.7 h, respectively. A significant fraction of the drug was cleared within 24 hours, and slow terminal phase accounted for only a small fraction of the drug clearance. Hence steady-state concentrations were reached within 2-3 doses (days). Drug clearance correlated better with estimated GFR than BSA, and further evaluation of the drug will involve fixed dosing. In a multivariate linear regression model, both log of platelet nadir ($r=-0.78$, $p<0.0001$) and log neutrophil nadir ($r=-0.71$, $p<0.001$) correlated with total AUC of ZD9331. AUC correlated better than dose with log nadir neutrophil. A minor response (<50% shrinkage of tumor) was observed in 1 patient with 5-fluorouracil and irinotecan refractory colorectal cancer treated at 12 mg/m²/d. Two patients with colorectal cancer treated at 6 mg/m²/d had stable disease for more than 6 months. In conclusion, the recommended dose for ZD9331 on this schedule is in the range of 12 to 16 mg/m², based on which a fixed dose of 25 mg/day is undergoing evaluation presently. Neutropenia and thrombocytopenia were dose-limiting, and efficacy studies in colorectal cancer are indicated.
'Tomudex' is a trade mark, the property of Zeneca Ltd.