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PHASE I AND PHARMACOKINETIC STUDY OF TOPOTECAN (T) IN COMBINATION WITH ORAL ETOPOSIDE (E)

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Synergism has been observed *in vitro* and *in vivo* when topoisomerase I inhibitors (e.g. camptothecins) are given before topoisomerase II inhibitors, and antagonism when given simultaneously. The sequence-dependent synergism may be explained by an elevated expression of DNA topoisomerase II enzymes after topoisomerase I inhibition. To exploit this possible advantage, we initiated a phase I/pharmacokinetic study in which T was given by a 30-min i.v. infusion on days 1–5 followed by E given orally on days 6–12. Treatment cycles were repeated at 4-week intervals. To date, 16 patients (7 M/9 F; median age 50 [range 32–60 yrs]) have been enrolled and have received 52 cycles of treatment. Dose levels were T: 0.5, 1.0, and 1.25 mg/m^2/day, and E: 20 and 40 mg twice daily, escalated in an alternating way. Pharmacokinetic studies of topotecan from 12 patients reveal that post-infusion plasma levels decline in a biphasic manner with a terminal half-life t1/2β of 2.1 ± 0.3 h (mean ± SD). Plasma clearance was 14.8 ± 3.1 L/m^2/h (mean ± SD) with a steady-state volume of distribution of 36.9 ± 6.0 L/m^2 (mean ± SD). Dose limiting grade IV neutropenia was observed in 2 of 6 patients at the fourth dose level, i.e. T: 1.25 mg/m^2/day and E: 40 mg twice daily. One patient required hospitalization for neutropenic fever. Anaemia occurred frequently. Non-haematological toxicities were mild and consisted of nausea, vomiting and fatigue. To allow further E dose escalation, T dose will be reduced to 1.0 mg/m^2/day whereby E dosing is prolonged to 40 mg twice daily for 10 days. The observed severe myelosuppression, as opposed to single agent T or E administration, suggests a synergistic cytotoxic effect of this combination of T and E.

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HYDROLYSIS OF IFOSFAMIDE TO CHLOROETHYLAMINE

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We have recently described the formation of Chloroethylamine (CEA) and 1,3-Oxazolidine-2-one (OXAZ) in humans following Ifosfamide (IF) administration†, and have now determined these levels in the plasma of 12 patients, ten of whom received 500 mg oral (o) IF, and two 3 g m^{-2} intravenous (iv) IF. GC-MS was used to measure IF, CEA and OXAZ. Mean CEA/IF peak ratios were 0.072 (o) and 0.49 (iv) and corresponding values for OXAZ/IF 0.011 (o) and 0.029 (iv). As only equimolar quantities of CEA and OXAZ can be formed from isophosphoramide mustard, the relatively high amount of CEA after iv dosing is generated directly by the hydrolysis of IF. This was confirmed by the detection of 2-chloroethyl-3-hydroxypropylamine, its phosphoric acid ester, and CEA, on incubation of IF solution *in vitro* at 37 °C. The rate of formation of CEA was consistent with pseudo-first order reaction kinetics. We conclude that significant hydrolysis of IF occurs, both *in vivo* and in vitro, at 37 °C.

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UPTAKE OF IFOSFAMIDE (IF) AND ITS METABOLITES BY ERYTHROCYTES (E)

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IF is a prodrug requiring activation to isophosphoramide mustard (IPM), but the main site of formation of IPM and its circulating transport form are not certain. We have recently described an instrument (MESED)† allowing the separation and simultaneous analysis of E and plasma(P) fractions, and present the results of such an analysis in two patients receiving an infusion of IF 3 g m^{-2} over 6 hours. Blood was sampled until approx. 24 hrs after the infusion; E and P fractions were separated immediately using MESED; and IF and its metabolites measured with GC-MS. High mean E/P Cmax ratios were seen for IPM (5.94), Carboxyifosfamide (4.28), Ketoifosfamide (2.87) and IF (2.26), and lower ratios for 2- and 3-Dechloroethylifosfamide, Chloroethylamine and 1,3-Oxazolidine-2-one (1.17–1.83). E/P AUC ratios showed a similar trend. Therefore, there is significant uptake of IF and its metabolites, particularly IPM, by E, which may be important in the transfer and delivery of these compounds.

† *Clin Biochem*; 27:195–196 (1994).

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TOXICITY OF 13-CIS-RETINOIC ACID, IFN-α AND SIMULTANEOUS RADIOTHERAPY IN ADVANCED SQUAMOUS CELL CARCINOMAS

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We evaluated prospectively feasibility and toxicity of a combined treatment using 13-cis-retinoic acid (RA) and interferon-α (IFN) together with simultaneous radiotherapy (IR) in pts. with advanced squamous cell carcinomas (SCC). Treated were 20 pts. (12 female/8 male) with a median age of 53.8 yrs. Tumor type was: 9× cervical cancer, 4× head and neck cancer, 6× NSCLC, 1× esophageal cancer). Treatment schedule consisted out of RA (0.5 mg/kg body weight p.os daily), IFN-α (3.0 Mill. IU s.c. 3 ×/week) and concomitant irradiation (50–70 GY in 2.0 GY daily fractions (ICRU) in 5–7 weeks). Sytemic treatment was administered for 12 wks.

Toxicity was graduated according to the WHO-toxicity score. Overall toxicity was moderate. Skin toxicity and mucositis (WHO I–III) were the main side effects observed and occurred in 20–50% of cases depending on the individual tumor type. Hematological toxicity was moderate and did not exceed WHO grade II. Dose reduction was necessary in 6 cases due to mucositis and skin toxicity (WHO II–III). We observed one case of major lung toxicity (pneumonitis WHO IV) together with rapid tumor progression in a female patient with NSCLC.

The combination of RA and IFN has proven to be effective in advanced SCC. The addition of simultaneous IR has both a preclinical and clinical rationale. We conclude that such a kind of treatment is feasible and suggest further evaluation of this combination in phase-I/II-trials.

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PHARMACOKINETICS OF 5,10-METHYLENETETRA-HYDROFOLATE IN PATIENTS WITH ADVANCED COLORECTAL CANCER

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Conversion of 5-fluorouracil to FdUMP and subsequent formation of a ternary complex of FdUMP, thymidylate synthase (TS) and 5,10-methylene-tetrahydrofolate (CH_2FH_4) results in TS inhibition. CH_2FH_4 is difficult to use clinically due to instability in contact with oxygen but can be used when reconstituted and injected under oxygen free conditions for which convenient devices are now available. 15 patients with advanced colorectal cancer received i.v. push injections of 100 mg (n = 8) or 200 mg (n = 7) CH_2FH_4, followed 20 minutes later by a rapid injection of 5-FU. Blood samples were collected before and 5, 10, 15, 20, 30, 40, 50 and 60 minutes after CH_2FH_4 injection. Plasma drug concentrations were analysed by HPLC and area under the curve calculated according to the trapezoidal rule. Peak plasma concentration achieved after 5 min. was 18.6 ± 1.3 μmol/l and 43.3 ± 2.6 μmol/l after 100 and 200 mg CH_2FH_4 respectively. Mean alfa phase $t_{1/2}$ was 8.9 ± 0.5 min for the two doses, while mean beta $t^{1/2}$ was 42 ± 2 min. for the 100 mg dose and 120 ± 3 min for the 200 mg dose. Mean AUC was 263 ± 12 and 1088 ± 37 μmol/l/h after 100 and 200 mg CH_2FH_4 respectively. Intravenous injection of CH_2FH_4 increase plasma levels of this active cofactor for TS inhibition and might be an option for increasing therapeutic results of 5-fluorouracil treatment.