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THE INFLUENCE OF 5-FLUOROURACIL ON THE APPEARANCE OF ENDOTHELIUM IN SMALL ARTERIES. A SCANNING AND TRANSMISSION ELECTRON MICROSCOPIC STUDY IN RABBITS

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Cardiotoxicity of 5-fluorouracil (5-FU) is mysterious toxic manifestation in treatment of human malignancies. Its possible mechanism might be direct cytotoxic effect on endothelium in cardiac vessels. We tested this hypothesis in experimental study in rabbits. The small arteries after *in vivo* treatment with 5-FU were prepared by perfusion-fixation method. Scanning and transmission electron microscopy evaluation of endothelium was done. We found irreversible cell damage consisting of disruption of endothelium sheet and patchy exposure of subendothelium, frequently observed as location for thrombus formation. Findings support the hypothesis about the thrombogenic effect of 5-FU, secondary to its direct cytotoxic effect on endothelium as pathophysiological mechanism behind 5-FU cardiotoxicity.

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THE PHARMACOKINETICS OF TOPOTECAN (T) AND ITS CARBOXYLATE (C) FORM FOLLOWING SEPARATE INTRAVENOUS ADMINISTRATION TO THE DOG

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In vitro, T undergoes a reversible, pH-dependent hydrolysis of the active lactone form to C. To study the kinetics of this reaction *in vivo*, T and C were separately administered as 30 minute intravenous infusions to female Beagle dogs in a cross-over design. T was also administered orally to the same dogs. After intravenous dosing, T underwent interconversion to C and vice versa. Clearance of T from the body was faster than interconversion to C but clearance of C was slower than interconversion to T. The Vss of T was approximately 9-fold greater than Vss of C. Following oral administration of T, the bioavailability was approximately 50% whether conventional or equations incorporating reversibility were used. After iv administration of T, the amount of T in the dog was much greater than that of C even though their respective plasma concentrations were similar.

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EFFECTS OF KP 735, A NEW PLATINUM-BASED ANTITUMOR AGENT ON CLONOGENIC GROWTH OF FRESHLY EXPLANTED HUMAN TUMORS *IN VITRO*

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Cis-Diammine[(bis(phosphonatomethyl)amino)acetato(2−)−O^1,N^1] platinum (II), (KP 735) is a new platinum-based agent which has shown antitumor activity in established tumor cell lines. We have studied the effects of KP 735 on soft agar colony formation of freshly explanted human tumors *in vitro*. Fifty-three out of 74 specimens (72%) are evaluable. Major tumor subgroups were: breast (9), mesothelioma (7), melanoma (6), kidney (5), carcinoma of unknown primary (6). Using a continuous incubation (21–28 days), concentration-dependent inhibition (colony formation $\leqslant 0.5 \times$ control) was observed with 0/53 specimens inhibited at 0.1 μg/ml, 9/53 (17%) at 1.0 μg/ml and 32/53 (60%) at 10 μg/ml. In a short-term incubation (1 hour), concentration-dependent inhibition was observed with 1/51 specimens (2%) inhibited at 0.1 μg/ml, 3/51 (6%) at 0.4 μg/ml, 6/51 (12%) at 1.0 μg/ml, 15/51 (29%) at 10 μg/ml and 30/51 (59%) at 100 μg/ml. At the highest concentration, KP 735 was more active than vinblastine (12/33 specimens (36%) inhibited, $P = 0.043$ McNemar's test), cisplatin (16/51 (31%), $P = 0.001$) and carboplatin (11/51 (22%), $P = 0.001$). We conclude that KP 735 has antineoplastic activity against freshly explanted human tumor cells *in vitro*. The spectrum of activity includes tumors with known clinical resistance to conventional chemotherapy. Further clinical development of this agent thus seems warranted.

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EFFECTS OF KP 1220, A NEW PLATINUM COMPOUND, ON COLONY FORMING UNITS FROM FRESHLY EXPLANTED HUMAN TUMORS *IN VITRO*

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Dichloro(5, 7, 8, 10, 11, 13, 14, 16-octahydro [1, 4, 7, 10] tetraoxacyclohexadecino- [13, 12-b: 14, 15-b′] dipyridine-N^1, N^{20}) platinum (II), (KP 1220) is a platinum analog reacting with nucleophilic sites on DNA, causing intra- and interstrand crosslinks as well as DNA-protein crosslinks. This agent has shown antitumor activity in established tumor cell lines. We have studied the effect of KP1220 on *in vitro* soft agar colony formation of 77 freshly obtained human tumors using a capillary cloning system. Major tumor subgroups were: 13 melanoma, 10 mesothelioma, 9 renal, 7 breast, 6 non-small cell lung, 6 ovary, and 6 carcinoma of unknown primary. Final concentrations were 0.1, 1.0, 10.0 μg/ml for continuous exposure (21–28 days) and 0.1, 0.4 (equimolar to cisplatin), 0.48 (equimolar to carboplatin), 1.0, 10.0 μg/ml for short-term (1 hour) exposure. Using a continuous exposure, 52/77 specimens (68%) showed evaluable colony formation in controls. KP 1220 inhibited tumor colony formation in a concentration-dependent manner with 2/52 specimens (4%) inhibited at 0.1 μg/ml, 12/52 (23%) at 1.0. μg/ml and 36/52 (69%) at 10.0 μg/ml. Using a short-term exposure, 49/77 specimens (64%) were evaluable. Again, concentration-dependent inhibition of tumor colony formation was observed with 1/47 specimens (2%) inhibited at 0.1 μg/ml, 9/49 (18%) at 0.4 μg/ml, 16/48 (33%) at 1.0 μg/ml and 35/49 (71%) at 10 μg/ml. At concentrations $\geqslant 1$ μg/ml, KP 1220 was as active as other clinically used antineoplastic agents. We conclude that KP 1220 has antitumor activity. Further clinical development of these agents should be considered.

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EVALUATION OF TOPOTECAN AGAINST THE SK-MES HUMAN LUNG CARCINOMA XENOGRAFT

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Topotecan, a promising topoisomerase I inhibitor being developed as an anticancer agent, was evaluated vs the SK-MES human lung tumor xenograft in nude mice. Topotecan (4 mg/kg; daily × 5) was tested as a single agent, and in combination with navelbine or gemcitabine. Topotecan alone was quite effective vs SK-MES, causing 75% tumor growth inhibition, with greater than 50% tumor shrinkage in several mice. Neither gemcitabine (3 mg/kg; daily × 5) nor navelbine (2 mg/kg; daily × 5) as a single agent was active in this model. Addition of gemcitabine or navelbine to the topotecan regimen did not improve the efficacy of topotecan given alone. Also, each combination resulted in a number of drug-related deaths in mice, without improving the efficacy of topotecan. In conclusion, topotecan demonstrated excellent activity as a single agent against the SK-MES human lung tumor xenograft. The data suggest that topotecan may have potential as an antineoplastic agent in patients with lung cancer.

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EXPRESSION OF LUNG RESISTANCE-RELATED PROTEIN (LRP) IN LUNG CANCER

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Expression of LRP seems to be of prognostic relevance in advanced ovarian cancer and acute myeloid leukemia. In this study we evaluated the expression of LRP in lung tumor samples derived from patients and its relation to survival, tumor differentiation, TNM classification and histology. Immunohistochemical staining (IH) was performed on 42 frozen lung tumor tissue samples using the mouse monoclonal antibody LRP-56 (IgG2b) directed to the 110 kD protein. LRP expression was calculated as the percentage of tumor cells which stained with the antibody. As cut-off point for Kaplan-Meier curves we took 10% LRP expression; comparisons of survival curves were performed by Mantel-Cox