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The farnesyl protein transferase inhibitor (SCH 66336) was subjected to pharmacokinetic evaluation in mice, rats and cynomolgus monkeys and found to possess desirable oral pharmacokinetic properties. In the athymic nude mouse model, a peak serum concentration (Cmax) of 8.8 µM was achieved after an oral dose of 25 mg/kg and persisted at a concentration above its effective bioavailability for 14 hours. The bioavailability was 76% and the half-life after intravenous (IV) administration was 1.4 h. A dose-response study was conducted in the rat wherein plasma levels from 10 to 400 mg/kg were administered. SCH 66336 was orally administered in various doses or IV administration to the cynomolgus monkey at 10 mg/kg. Plasma levels were similar in the mouse and monkeys for the periods evaluated, and were sustained for 12 to 15 h. In human tumor xenograft efficacy studies in the nude mouse, concentrations of SCH 66363 in serum and tumor tissue samples were found to be closely related. These studies indicate that the drug readily reaches the target tissue after oral administration and thus accounts for its potent in vivo tumor activity.

Cellular actions of a farnesyltransferase inhibitor, RPR-115135, in human isogenic colon cancer cell line system. Russo, P., Reinhold, W., Yu, C.-T., Kim, K.-W., Rhee, J.F., and O'Connor, P.M. Laboratory of Molecular Pharmacology, National Cancer Institute, Bethesda, MD 20892, Roussel-Uclaf Rorer S.A. 9403 Vitry sur Seine, France, Department of Experimental Oncology, National Institute for Research on Cancer, Lisbon, Italy.

A non-peptidomimetic farnesyltransferase inhibitor, RPR-115135, was studied in a human colon cancer cell line system. Results showed that RPR-115135 was a potent inhibitor of the farnesyltransferase activity of human colon cancer cells. The IC50 value was determined to be 3.3 µM. The IC50 was lower for the human colon cancer cells than for the parental normal colorectal cells.


Microbial culture broths were screened for apoptosis-inducing agents that are effective against human pancreatic carcinoma cells in vitro. The apoptosis-inducing activity of the polyoxypolyneptide is also involved in the clinical effect of anticancer agents. Apoptosis was assayed by characteristic morphological changes observed in 24 hours. Polyoxypolyneptide, a novel cyclic depsipeptide, was isolated by a bioassay-guided fractionation of the culture broth of Streptomyces sp. Polyoxypolyneptide was extracted with ethyl acetate, purified on silica gel, and recrystallized from acetone or ethyl acetate. Structural determination by 2-D NMR and 1H 1H nuclear magnetic resonance revealed the structure of polyoxypolyneptide to be a novel cyclic hexapeptide containing five hydroxylated amino acids, including the unusual and hitherto unreported amino acid 3-hydroxy-3-methylpyrrole. Polyoxypolyneptide decreased the viability of AsPC-1 cells within 24 hours with an IC50 of 80 nM, though adeninamide, cispilatin, and vinblastine did not. Polyoxypolyneptide also induced nuclear fragmentation and internucleosomal DNA fragmentation in AsPC-1 cells.

Ukraine, a semisynthetic alkaloid of Chelidonium majus, is selectively toxic to malignant cells by causing a metaphase block which results in apoptosis. Panzer, A., Seegers, J.C. Department of Physiology, University of Pretoria, PO Box 2034, Pretoria 0001, South Africa.

Ukrain (3,6-di-O-p-coumaryl-β-D-glucopyranoside) is a semisynthetic compound consisting of the chelidonic alkaloid of Chelidonium majus combined to the thioephosphoryl acid triazide (Austrian Patent No. 354644, Vienna, 1980). Previously, the National Cancer Institute (Maryland, USA) demonstrated Ukrain to have cytolytic activity against human cancer cells in vitro and in vivo (JNCI 68:5178). In this study, the effect of Ukrain was evaluated on two malignant cell lines (human cervical carcinoma, HeLa, and human osteosarcoma carcinoma, WHC05, isolated from a biopsy specimen of squamous osteosarcoma carcinoma) and compared to normal equine lung cells (derived from embryonal and non-embryonal). Flow cytometric analysis of DNA content showed the growth of the equine lung cells to be unaffected by 48 hours exposure to 50µg/mU Ukrain (p=0.167), while the
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growth of the HeLa and WHCOS cells was inhibited to 52.8% and 49.1% of control levels respectively (p<0.0001). Flow cytometry studies showed a dose-dependent increase in G2M cells in both of the malignant cell lines, indicating the equine lung cells did not suffer from cytotoxicity. Morphological studies of the HeLa and WHCOS cells exposed to Uramix, revealed abnormal mitotic spindles and apoptotic cells at concentrations where the equine lung cells remained unaffected. It is concluded that Uramix may be a selective and toxic to malignant cells causing a apoptotic effect which is characterized by abnormal chromosomal distribution, and results in the formation of micronuclei and in apoptosis.

#2184 Silymarin decreases prostate specific antigen (PSA) expression concentration in prostate cancer xenografts, reduction of cell growth, induction of neuroendocrine differentiation, and perturbations in cell cycle in human prostate carcinoma cells LNCaP, Agarwal, R., and Zi, X. Department of Dermatology, Case Western Reserve University, Cleveland, OH 44106.

Prostate Cancer (PCa) is the most common non-skin cancer and second leading cause of cancer deaths in US men. One approach to control PCa is chemotherapeutic intervention. Recently, we showed that Silymarin alters PSA expression in prostate cancer xenografts. Our studies suggest that Silymarin might be useful as a chemotherapeutic agent for the treatment of prostate cancer.


SU101 is a signal-transducing inhibitor that is currently in clinical trials, appears to inhibit tumor cell growth via two distinct mechanisms: 1) the parent compound inhibits PDGF-R signal transduction, and 2) its major metabolite (SU1002) inhibits pyrimidine biosynthesis. In vivo efficacy of SU101 was examined in tumor xenograft bearing rats (C6) and human lung tumor (Calu-6) cells. Both tumor models, parenteral (IP) administration of SU101 significantly inhibited tumor growth; in contrast, oral administration of SU101 inhibited the growth of rat C6 tumors, but not human Calu-6 tumors. In the C6 model, the efficacy of SU101 administered orally was completely reversed by coadministration of uridine, while efficacy following IP administration was not affected. Thus, SU101 accounted for the anti-tumor efficacy following IP administration, while SU1002 accounted for the temporary efficacy following oral administration. Parenteral administration of SU101 to mice bearing C6 tumors resulted in detectable levels of SU101 in both brain and tumor, while oral administration of SU1002 in detectable levels was found in only SU1002 in the plasma. Oral administration of SU101 in rats resulted in the complete conversion to SU1002, and prevented progression in the human tumor model but not the rat tumor model. These results suggest that the parent compound of SU101 is required to achieve efficacy in the treatment of human cancers.


KF25706 (UCS1006-S15) is a novel derivative of radicicol, an inhibitor of multiple signal transduction pathways. KF25706 inhibited tyrosine kinase activity in v-src transformed rat fibroblast cells and EGF phosphorylation in K-ras transformed rat epithelial cells, with IC50 values of 120 and 100M respectively, after 48 hr exposure. KF25706 also inhibited the growth of both cell lines with IC50's of 22 and 8M respectively, after 12 hr exposure. KF25706 also inhibited the growth of human breast cell lines with IC50's ranging from 15M to 150M, and rapidly depleted the oncogenic tyrosine kinase p185 erb-b2 from SK-BR-3 cells. The multiple activities of KF25706 may stem from the drug's interaction with the hsp90 chaperone family, which was assessed by the drug's ability to compete for chaperone binding with the known hsp90-binding agent, geldanamycin. More importantly, KF25706 showed significant in vivo growth-inhibitory activity against ER (+) human breast cancer MCF-7 cells xenografts, following a 5 day continuous daily intraperitoneal injections at a dose of 100mg/kg. KF25706 was also shown to possess anti-tumor activity against ER (+) human breast carcinoma MCF-7 cells xenografts following the same treatment schedule. The compound exhibited no liver or no renal toxicity, as assessed by serum GPTase and, and very mild myelitis, as-determined by peripheral blood cell line. These results indicated that KF25706 with its novel mechanism(s) of action is a candidate drug for further preclinical study.

CLINICAL RESEARCH 7: Phase I Clinical Trials

#2187 Phase I/II and pharmacology study of pacitaxel (P) plus or -1,2-dihydroxypropane (D) in treatment of patients (PTS) with metastatic breast cancer (MBC). Kii U., Ehrlicher, S., Hilger, R., Bouquet, D., Oberhoff, C., Chazard, M., Ben Harstrick, A. and Seebor, S. Dept. of Internal Medicine (Cancer Research) German Cancer Center, University of Essen, Germany.

5-FU is the classic example of a cycle specific-5 phase dependent drug with short half life. Therefore conventional bolus injection may not be the most effective schedule. Recent phase II studies demonstrate high efficacy for a weekly schedule of 24-hour infusion 5-FU/LV (Wilke, Ann. 7:15-8, 1996) as well as for the continuous infusion of 5-FU (Rejzor Oncol. 7:807-19, 1996) in intensively pretreated pts. With MBC, UFT may be an administration of long term low dose oral 5-FU with the same pharmacological profile as a continuous infusion (Tashiro, Jpn. J. Clin. Oncol. 24:211-24). Within this ongoing phase I/II study UFT, which is composed of 1,2-dihydroxypropane (D)-5-FU (torafu) administered orally to 5-FU/LV and in combination with P. So far 17 pts were treated as a part of an phase II/III protocol in order to determine the safety, activity and pharmacology of this combination. After standard pretreatment all pts received oral 175mg/m2 3i.d. on day 1 at all dose levels (d). UFT was administered in combination with 50mg/dL of LV in three divided doses for 14 days. D: d1: 300mg/dL, d2: 400mg/dL, d3: 500mg/dL, d4: 600mg/dL. The cyclerepeated every 21 days. So far within Phase I 17 pts entered the trial: the 6 pts d1; 3 pts d2, 3 pts d3, 4 pts d4. All excluded pts have had prior CTX for MBC. Ti toxicity was neutropenia 68% WHO grade II/III. No febrile neutropenia, xerostomia, myalgia WHO grade I and II were seen but not d2 when pts had myelotoxicity grade III. Even at d4 we did not see any dose related gastrointestinal toxicity. 10 pts are evaluable for response: PR: 4, SD, 4. UFT will be followed in the ongoing phase II. Furthermore, we determined that plasma levels in 6 more pts planned to be treated at d4 giving a plan phase I/II first cycle and in combination with UFT/LV during the second cycle in show pharmacokinetic interactions of the drug combination. To confirm to combination of P and oral UFT/LV seems to be a safe, convenient and regimen for pts with pretreated MBC.

#2188 Dose-finding study of Docetaxel (Taxotere®) and Vinorelbin (Vinobeste) D1 and D8 as 1st-line chemotherapy for metastatic breast (MBC). Bonneterre, J., Oublier, C., Bonneterre, M., Mart, M., Saussengue, M., Centre Oscar Lambret, Lille, Hôpital Saint Louis, Paris, Roines Rhône-Poulenc Rorer, Montargues, France.

Taxotere® (TXT) has shown very high activity as a single-agent che for MBC. Vinorelbine® (NVS) has also shown significant activity in the first line treatment. Thus, we decided to perform a dose-finding study combining NVS 1st-line chemotherapy for MBC. Eligible patients (pts) had histology specific or not. pts had standard first line therapy and/or adjuvant chemotherapy allowed if >12 months disease free (radiosensitization and/or adjuvant chemotherapy allowed if <12 months before accrual). PS 1, age <= 75, normal hematological, hepatic functions and signed informed consent. NVS 20 mg/m² administration D1 and D8 and TXT at D8 in escalated doses.

<table>
<thead>
<tr>
<th>TXT Dose Level</th>
<th>No pts</th>
<th>Evol. cycles</th>
<th>Grade 4 events</th>
<th>Febrile neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg/m²</td>
<td>6</td>
<td>48</td>
<td>52%</td>
<td>5%</td>
</tr>
<tr>
<td>75 mg/m²</td>
<td>6</td>
<td>48</td>
<td>37%</td>
<td>17%</td>
</tr>
</tbody>
</table>

"Febrile neutropenia at first cycle requiring antibiotics and/or hospitalization"

Although the MTD was not formally reached (9/9 pts presented a grade 3 leukopenia after the 2nd cycle), we decided to evaluate the safety/efficacy profile of this 2-drug combination at dose level 75 mg/m² TXT in 75 cm².

#2189 Phase I study of a weekly schedule of CPT-11, FA and 5-FU in advanced colorectal cancer. Vanhoefer, U., Hartmann, Ch.H., Ackterherr, W., Wilke, H. and Seebor, S. University Hospital, Robert Rossie Clinic, 13125 Berlin, Rhone-Poulenc Rorer, 50029 New York.

A weekly schedule of CPT-11, FA and 5-FU was evaluated in patients with advanced colorectal cancer as first line chemotherapy. Treatment was weekly therapy x 4 cycles, all with FA 600mg/m² and fixed doses of 5-FU (mg/m²), 90 mg/m² and FA (mg/m², 2 h Int). Dose of 5-FU in mg/m², 90 mg/m² and 5-FU (mg/m², 2 h Int). Dose of 5-FU in mg/m², 90 mg/m² and 5-FU (mg/m², 2 h Int). Dose of 5-FU in mg/m², 90 mg/m² and 5-FU (mg/m², 2 h Int).