nucleus for 72 hr treatment. Moreover, apicularen A showed potent activity against xenograft tumors of the colon cancer HM7 cells.
From the above results, it is indicated that the mechanism of cytotoxicity of apicularen A in HM7 colon cancer cells are apoptosis through activation of death-receptor pathway and down-regulaion of tubulin synthesis.
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1491 PUBLICATION

The usefulness of continuous administration of hypoxic cytotoxin combined with mild temperature hyperthermia, with reference to the effects on quiescent cell populations in solid tumors

S. Masunaga[1], H. Nagasawa[2], Y. Uto[2], H. Hori[2], M. Suzuki[1], K. Nagata[1], Y. Kinashi[3], K. Ono[1]. *[1]Radiation Oncology Research Laboratory, Research Reactor Institute, Kyoto University, Osaka, Japan; [2]Department of Biological Science and Technology, Faculty of Engineering, University of Tokushima, Tokushima, Japan; [3]Division of Radiation Safety, Research Reactor Institute, Kyoto University, Osaka, Japan*

Purpose: To evaluate the usefulness of continuous administration of hypoxic cytotoxins in terms of targeting acute hypoxia in solid tumors and the significance of combination with mild temperature hyperthermia (MTH) (40ºC, 60 min), we examined the cytotoxic effects of singly or continuously administered tirapazamine (TPZ) or newly-synthesized quinoxaline oxide TX-402 (3-amino-2-quinoxalinecarbonitrile 1,4-dioxide) in combination with or without MTH in vivo. Further, we also analyzed the effects on total (= proliferating (p) + quiescent (Q)) and Q cell populations in solid tumors with our method for selectively detecting the Q cell response.
Materials and Methods: C3H/He mice bearing SCC VII tumors received a continuous administration of 5-bromo-2'-deoxyuridine (BrdU) for 5 days to label all P cells. The tumor-bearing mice then received a single intraperitoneal injection or 24 h continuous subcutaneous infusion of hypoxic cytotoxin, TPZ or TX-402, with or without MTH. On the other hand, to detect the changes in the hypoxic fraction (HF) in the tumors by MTH, another group of mice with or without MTH received a series of test doses of gamma-rays while alive or after tumor clamping. After each treatment, the tumor cells were isolated and incubated with a cytokinesis blocker (= cytochalasin-B), and themicronucleus (MN) frequency in cells without BrdU labeling (= Q cells) was determined using immunofluorescence staining for BrdU. The MN frequency in total tumor cells was determined from the tumors that were not pretreated with BrdU.
Results: The sensitivity to TX-402 was slightly higher than that to TPZ in both total and Q tumor cells. Continuous administration elevated the sensitivity of both total and Q cells, especially total cells. MTH raised the sensitivity of Q cells more remarkably than that of total cells in both single and continuous administrations. It was thought to be probably because of the higher dose distribution of hypoxic cytotoxin in intermediately hypoxic areas derived mainly from chronic hypoxia through MTH.
Conclusion: From the viewpoint of tumor control as a whole including both total and Q tumor cells, the continuous administration of hypoxic cytotoxin combined with MTH may be useful for sensitizing tumor cells in vivo.

1492 PUBLICATION

Pemetrexed combined with gemcitabine and cisplatin: a phase I study in patients with locally advanced or metastatic solid tumors

T. Graefe[1], C. Lübbing[1], C. Bolling[1], E. Yilmaz[1], J. Fleeth[1], F.E. Luedtke[1], S. Müller-Hagen[2], H. Depenbrock[3], U. Ohnmacht[3], A.-R. Hanauske[1]. *[1]AK St. Georg, Hamburg, Germany; [2]Onkologische Gemeinschaftspraxis Hamburg, Hamburg, Germany; [3]Lilly Deutschland GmbH, Bad Homburg, Germany*

Background: Combining pemetrexed (P, Alimta®) with gemcitabine (G) and cisplatin (Cis) may achieve a synergistic action by combining different mechanisms of action, overlapping spectra of clinical efficacy, and non-overlapping toxicities. The purpose of this study is to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of four different schedules of PGC.
Methods: In the q3w schedule, PGCis was administered on day (d) 1 and G on d8 in a 21d cycle. In addition, the following schedules were studied: A: GP d1 and GCis d15 q 28 days; B: GCis d1 and PCis d15 q 28 days; C: PGC is on d1 q14d. P was administered intravenously (IV) over 10 minutes (min), G IV over 30 min, and Cis IV over 2 hours. Standard pre- and postmedications were used.
Results: In the q3w schedule, 4 of 12 patients (pts) experienced DLTs, dose escalation was stopped in favor of alternative schedules. To date, 12 pts were enrolled into 3 dose levels of A, 22 pts enrolled into 7 dose levels of B, and 4 pts enrolled into 1 dose level of C. Tumor types included: head and neck (8), prostate (4), mesothelioma (4), NSCLC (4), sarcoma (4), stomach (4), kidney (2), esophagus (2) and others (6). 4 DLTs occurred in 4 pts on dose level 3 of schedule A, 2 DLTs in 2 pts on dose level 6 of schedule B and 4 DLTs in 2 pts on dose level 1 of C (MTDs: delay of therapy due to thrombocytopenia in schedule A and fatigue in schedule C). In dose level B, full clinical doses of G and Cis have been reached and further dose escalation of P is ongoing. With a total of 31/64/11 cycles administered so far in schedules A/B/C 4/2/1 pts experienced G3 anemia, 3/4/0 pts experienced G3/4 thrombocytopenia and 9/16/3 pts experienced G3/4 neutropenia. G3/4 non-hematological toxicities included G3 fatigue (6), G3 rash (2), G3 dysphagia (1), G3 syncope (1), G3 elevation of transaminases (1), G3 stomatitis (1) and G3 diarrhea (1). In the q3w schedule 1 partial response (PR) and 7 stable diseases (SD) were observed. For the schedules A, B, and C tumor response is so far evaluable in 7/15/3 pts. 2 pts of schedule A and 6 pts of schedule B achieved a PR, 3/4/2 pts achieved SD.
Conclusion: The PGCis combination is feasible and demonstrates clinical antitumor activity. Tolerability of the combination is influenced by administration sequence. Schedule B appears to offer the best tolerability when compared to the q 3 wk schedule or schedules A and B. Further clinical development of PGCis is promising.

1493 PUBLICATION

New anti-neoplastic agent MK615, extracted from Japanese apricot, Ume, inhibits growth of pancreatic and biliary cancer

T. Sawada[1], T. Okada[1], T. Ohsawa[2], M. Adachi[2], K. Kubota[1]. *[1]Dokkyo University School of Medicine, Second Department of Surgery, Tochigi, Japan; [2]Japan Apricot Co., Ltd., Gunnma, Japan*

Purpose: MK615 is a newly developed anti-cancer agent, extracted from Ume, a japanese apricot. In the present study, inhibitory effect of MK615 to pancreatic and biliary cancer cell lines was investigated.
Methods: Four pancreatic cancer cell lines, MIA, PANC-1, PK-45H, PK-1 and 3 biliary cancer cell ines, HuCCT1, NOZ-W, and OZ were cultured with MK615 at the concentration of (600, 300, 150, 0 μg/ml). After 48 hours of incubation, live cells were counted by MTT assay. Data are presented by % inhibition at each concentration of MK615 to 0 μg/ml, and are shown by (600, 300, 150 μg/ml).
Results: MTT assay revealed that MK615 effectively inhibits the proliferation of all pancreatic and biliary cancer cell lines. For pancreatic cancer cell lines, % inhibitions of MIA, PANC-1, PK-45H, and PK-1 were (28, 6, 0), (68, 9, 3), (46, 9, 0), and (46, 9, 0), respectively. For biliary cancer cell lines, % inhibitions of HuCCT1, NOZ-W, and OZ were (83, 50, 26), (68, 25, 12), and (64, 0.0) respectively.
Conclusion: MK615 effectively inhibits the proliferation of pancreatic and biliary cancer cell lines, especially at the concentration of 600 μg/ml. MK615 should be promising as new anti-neoplastic agent.

1494 PUBLICATION

Pharmacokinetic of a novel cytotoxic agent, ELACYT™ (CP-4055) given according to four different schedules in two phase I studies

E. Raymond[1], S. Dueland[2], M. Lind[3], A. Awada[4], H. Thomas[5], S. Culine[6], N. Tchen[7], A. Yovine[8], W. Sutherland[8], W. Rasch[9]. *[1]Hôpital Saint-Louis, Paris, France; [2]The Norwegain Radium Hospital, Oslo, Norway; [3]The Princess Royal Hospital, Hull, UK; [4]Institute Jules Bordet, Brussels, Belgium; [5]The Royal Surrey County Hospital, Guildford, UK; [6]CRLC Val d'Aurelle Paul-Lamarque, Montpellier, France; [7]Institute Bergonié, Bordeaux, France; [8]CAC, Kremlin-Bicêtre, France; [9]Clavis Pharma, Oslo, Norway*

Background: ELACYT™ (CP-4055, Ara-C-5′-elaidic acid ester) is a novel cytotoxic agent which has shown wide spectrum of preclinical antitumour activity in solid tumours. ELACYT™ is based on the Lipid Vector Technology and has a different cellular uptake compared to Ara-C. We report pharmacokinetic (PK) results from two European phase I studies, exploring a daily x 5 schedule (sch) and weekly and biweekly sch.
Methodology: Using standard dose-finding design, patients (pts) with solid tumours received CP-4055 as a 30min infusion, daily x q3 week (w), over a 30–200 mg/m^2/infusion dose range in Study 1, and as a 2h infusion in Study 2 according to 3 sch: Days (D)1, 8 q3w (sch A); D1, 15 q4w (sch B); D1, 8, 15 q4w (sch C) over a dose range 100 to 800 mg/m^2/infusion. PK was assessed on D1 and D4 (Study 1 only) of cycle 1. Samples were taken at: 0:00, 0:15, 0:30, 0:35, 0:45, 1:00, 1:30, 2:00, 2:30, 4:30, 7:30, 10:30, 24:30h in Study 1; 0:00, 1:00, 2:00, 2:05, 2:15, 2:30, 3:00, 4:00, 6:00, 9:00, 24:00h in Study 2. CP-4055, Ara-C and Ara-U were qualified.
Results: As of May 2005, 61 pts (Study 1:24, Study 2: 37) with a variety of malignancies were evaluable for PK at D1 and 24 pts at D4. Accrual is ongoing in Study 2. Results from 56 pts are presented. *PK over all dose levels*: Interpatient variability of CP-4055, Ara-C and Ara-U was generally

low. CP-4055 and Ara-C plasma concentration decreased rapidly after end of infusion. Plasma concentration of Ara-U was several fold higher than for Ara-C. $t_{1/2}$ Study 1; CP-4055: 0.34h (0.26–0.40), Ara-C: 0.55h (0.38–0.63), Ara-U: 6.73h (5.69–8.38). Study 2: $t_{1/2}$ in same ranges. $C_{max}$of CP-4055 and Ara-C were higher after 30min infusion than after 2h infusion at similar doses.

Conclusion: The plasma concentration and AUC of CP-4055 and Ara-U are broadly linear with increasing doses of CP-4055, independent of the CP-4055 infusion time. The PK parameters display relatively low interpatient variation.

Table 1: PK parameters (mean±standard deviation) at D1 for selected dose levels only.

	Study 1 (30 min)			Study 2 (2h)		
	30 mg/m^2	100 mg/m^2	200 mg/m^2	320 mg/m^2	480 mg/m^2	800 mg/m^2
N(pts)	3	3	6	3	3	1
C_{max} (µg/mL)						
CP-4055	3.3±0.4	11.2±3.3	32.4±6.9	19.9±1.2	40.7±13.2	89.4
Ara-C	0.045±0.005	0.76±0.5	0.64±0.2	0.47±0.08	0.89±0.5	1.2
Ara-U	0.41±0.04	1.6±0.2	3.1±0.5	4.3±0.6	7.3±1.5	15.0
$AUC_{0-\infty}$ (µg-h/mL)						
CP-4055	2.1±0.5	7.2±3.3	23.3±6.0	35.9±6.6	72.3±10.0	164.0
Ara-C	0.054±0.002	0.43±0.2	0.74±0.2	1.0±0.2	2.1±1.0	3.4
Ara-U	3.8±0.7	17.3±4.7	30.0±12.1	40.3±7.9	99.5±32.5	110.5

1495 PUBLICATION

Pharmacokinetics (PK) of AMG 706 on CYP3A activity using oral midazolam and the bioavailability of solid formulations in patients (pts) with advanced solid tumors: results of two phase 1 substudies

L. Yan[1], S. Wong[1], M. Ingram[1], M. Parson[2], M. Mulay[2], A. Van Vugt[2], M. Dinolfo[2], L. Rosen[2]. *[1]Amgen Inc., Thousand Oaks, CA, USA; [2]John Wayne Cancer Institute, Santa Monica, CA, USA*

Background: AMG 706 is a potent, oral, multi-kinase inhibitor with both anti-angiogenic and direct antitumor activity achieved by selective targeting VEGF, PDGF, RET, and c-Kit receptors. In vitro, AMG 706 inhibits CYP3A4, 2D6, 2C8, 2C9, and 2C19 (IC_{50} range: 2.0–11.7 µM). Early results from a phase 1 trial of AMG 706 in pts with advanced solid tumors indicated that AMG 706 dosed once daily (QD) provides sustained exposure with no evidence of accumulation or metabolic induction (Rosen ASCO 2005). During this study, the formulation of AMG 706 was changed from capsule to tablet.

Methods: In 2 substudies conducted concurrently in 12 pts, the relative bioavailability of a capsule and tablet formulation of AMG 706 (substudy 1) and the in vivo effect of AMG 706 on CYP3A activity, using oral midazolam as a probe (substudy 2) was evaluated. On day 1, pts received midazolam 2 mg alone. On day 2, pts were randomized (1:1) to receive 100 mg AMG 706 as either a tablet or capsule. After a 1–3 day washout period, pts received 100 mg AMG 706 of the alternate formulation. Subsequently, pts received AMG 706 125 mg QD. On day 21, pts received concomitant midazolam within 5 minutes of consuming AMG 706. Serial 24-hr PK blood collections were drawn for both substudies 1 and 2. Pts fasted for at least 8 hrs before and 2 hrs after dosing on each PK collection day.

Results: Mean (range) age of this cohort was 61.3 yrs (36–90 yrs). In substudy 1, similar plasma concentrations between the tablet and capsule formulation were observed. The estimate geometric mean ratio (tablet:capsule) was 1.02 for AUC and 1.23 for C_{max}. In substudy 2, maximum serum concentrations of midazolam were observed 0.25 to 1 hr after the dose. There was a slightly increased systemic exposure to the second dose of oral midazolam given concomitantly with AMG 706 125 mg. The point estimate (90% CL) for the geometric mean ratio of midazolam serum AUC when midazolam was administrated together with AMG 706 125 mg vs midazolam alone was 1.82 (1.50, 2.22).

Conclusions: The relative bioavailability study (substudy 1) indicated that the PK profiles of the new tablet formulation are comparable to those generated by the capsule formation. In the midazolam study (substudy 2), AMG 706 was found to be a weak inhibitor of CYP3A in humans; therefore, clinically significant interactions of AMG 706 with drugs that are CYP3A substrates are generally not expected.

1496 PUBLICATION

Phase 1 study to determine tolerability and pharmacokinetics (PK) of D0/NDR/02, a novel nanoparticle paclitaxel in patients with locally advanced or metastatic breast cancer (MBC)

P.P. Bapsy[1], D. Raghunadharao[2], A. Majumdar[3], S. Ganguly[3], D. Khattar[4], R. Mukherjee[5], S.K. Mishra[3]. *[1]Kidwai Memorial Institute of Oncology, Medical Oncology, Bangalore, India; [2]Nizams Institute of Medical Sciences, Medical Oncology, Hyderabad, India; [3]Dabur Research Foundation, Clinical Research and Medical Services, Ghaziabad, India; [4]Dabur Research Foundation, Novel Drug Delivery Systems, Ghaziabad, India; [5]Dabur Research Foundation, Research and Development, Ghaziabad, India*

Background: Conventional paclitaxel is formulated in cremophor, which is known to be associated with hypersensitivity reactions and non-linear pharmacokinetics [PK]. DO/NDR/02 is a novel, cremophor free, polymeric, nanoparticle formulation of paclitaxel. A phase I dose escalation study was designed to determine the maximum tolerated dose (MTD) and the safety profile of the formulation in patients with locally advanced or metastatic [MBC] who had failed on anthracyclines or taxanes. The secondary objectives included evaluation of PK and preliminary assessment of efficacy.

Method: DO/NDR/02 was administered in 3-weekly cycles as a one-hour infusion, without premedication, in doses ranging from 135 to 375 mg/m^2, for a maximum of six cycles. Serial blood samples were collected for PK analysis during cycles 1 and 2 and paclitaxel concentrations were determined using a validated HPLC method. The toxicities were graded using NCI CTC version 2.0.

Results: Twenty-five patients who had received prior therapy with either anthracyclines or Taxanes were treated at various dose levels up to 375 mg/m^2. Hypersensitivity reactions were not observed in any patient. The major hematological toxicities have been grade 4 neutropenia (3 out of 123 cycles) two of which occurred at the highest dose of 375 mg/m^2. There was only one incidence of febrile neutropenia at the highest dose. The major non-hematological toxicities were grade 3 infection without neutropenia (n = 1) seen at 135 mg/m^2 and grade 3 diarrhea (n = 2) at 300 and 375 mg/m^2 respectively and grade 3 neuropathy (n = 1 at 300 mg/m^2). The maximum tolerated dose (MTD) was determined to be 375 mg/m^{2}and the dose one level below that (300 mg/m^2) was selected as the recommended phase II dose. Objective responses (OR) were seen in 5 out of 25 (24%) patients. There was no response noted in taxane failed patients. PK analysis showed a linear correlation between the mean AUC and dose, up to 375 mg/m^2.

Conclusions: DO/NDR/02 may be safely administered without any premedications, to a higher dose than cremophor paclitaxel. It has also shown a linear PK profile and encouraging clinical activity in advanced breast cancers. A phase II study to further establish its safety and efficacy is presently being conducted in patients with anthracycline failed MBC.