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

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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

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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

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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

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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