Material and Methods: Plasma and urine concentrations of LC and ALC from eleven patients under carboplatin chemotherapy (1 hr intravenous infusion; AUC dose of 4.8±1.1 mg ml^{-1} min^{-1}) were determined before, during and after treatment using a high performance liquid chromatography method.
Results: Before carboplatin chemotherapy, the plasma concentration (mean±SD) of LC and ALC was 47.8±10.9 and 7.0±1.0 nmol/ml, respectively, and remained constant for the entire period of plasma collection. In contrast, the urinary excretion of LC and ALC, increased significantly during the chemotherapy from 115±105 to 480±348 μmoles/day ($p < 0.01$; One-way repeated measures ANOVA) and from 41±41 to 89±52 μmoles/day ($p < 0.05$) for LC and ALC, respectively. It normalised six days after the end of chemotherapy. Similarly, the renal clearance of LC and ALC increased substantially during the chemotherapy from 1.67±1.43 to 9.05±9.52 ml/min ($p < 0.05$) and from 4.02±4.51 to 7.97±5.05 ml/min (p = not significant) for LC and ALC, respectively, reaching normal values six days after the end of chemotherapy. However, plasma concentration and urinary excretion of glucose, phosphate and nitrogen and the creatinine clearance were not affect by carboplatin treatment indicating no impaired function of the kidney.
Conclusions: Treatment with carboplatin was associated with a marked urinary loss of LC and ALC, most likely due to inhibition of LC (and ALC) reabsorption in the kidney.

1464 POSTER

Enhancement of gemcitabine antitumor effects by pretreatment of S-1, a novel oral derivative of 5-fluorouracil, in pancreatic cancer

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Background: Although Gemcitabine (GEM) has been accepted as a key drug for treatment of pancreatic cancer patients, its efficacy as a single agent remains to be unsatisfied. On the other hand, S-1 is a novel oral derivative of 5-FU prodrug tegafur combined with two modulators, 5-chloro-2, 4-dihydropridine and potassium oxonate, and S-1 has the promising antitumor effect against various malignant tumors including pancreatic cancer. It was recently reported that cellular uptake of GEM was mediated by the equilibrative nucleoside transporter 1 (ENT1) and ENT1 expression was enhanced by TS inhibitor such as 5-fluorouracil (5-FU). In this study, to enhance the effect of GEM by S-1, we evaluated the antitumor effects and treatment schedules of combination therapy with GEM and S-1 in *in vivo* pancreatic cancer model.
Material and Methods: Expression of ENT1 was determined by quantitative RT-PCR. GEM cellular uptake was determined using [3H] GEM. Seven pancreatic cancer cell lines (AsPC1, BxPC3, MiaPaCa-2, PSN1, Panc1, PCI6, and KMP4) were treated *in vitro* with 5-FU either before or following exposure to GEM. Growth inhibitory effects *in vitro* were determined by MTT assay. Human pancreatic cancer xenografts (BALB/c nu/nu mice) were prepared with subcutaneous injection of MiaPaCa-2 cells, and divided into the following six groups (5 mice /group): no treatment; weekly intraperitoneal injections of GEM (240 mg/kg); daily oral administrations of S-1 (10 mg/kg/day) for 5 consecutive days a week; sequential combination treatment with GEM prior to S-1; coadministrations of GEM and S-1; sequential combination treatment with S-1 prior to GEM. The antitumor effects were evaluated with the tumor volume at the day 18.
Results: Significant increases in ENT1 expression and GEM cellular uptake were observed after 5-FU treatment *in vitro* and S-1 treatment *in vivo*. The *in vitro* growth inhibitory effect was significantly greater in the sequential treatment of 5-FU followed by GEM in all cell lines except for Panc1. Furthermore, the significant tumor growth inhibition *in vivo* was observed in the mice treated with S-1 followed by GEM compared with either untreated mice or the mice treated with gemcitabine followed by S-1.
Conclusions: The administration of gemcitabine followed by S-1 provides greater inhibitory effects than the other GEM/ S-1 schedules. These data suggest new effective combination treatment for patients with pancreatic cancer.

1465 POSTER

A heparan-mimetic protects mice from radiation-induced mucositis

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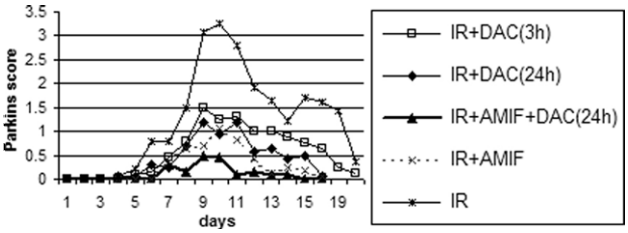
Background: The purpose was to evaluate the effect of RGTA-DAC (ReGeneraTing Agent), a synthetic heparan-mimetic, on radiation-induced mucositis in a murine model and on tumor growth *in vivo* and *in vitro*.
Material and methods: Reagents: RGTA-DAC 1mg/kg for intra-peritoneal (IP) injection; 10 μg/ml in spray solution; 10 μg/ml for *in vitro* assay. Amifostine (Ethyol®) 200 mg/kg for IP injection.
Radiation-induced mucositis: the oral region of C57 black female mice was selectively irradiated with a single dose of 16.5 Gy; mucosal reactions were evaluated daily for 21 days and scored by the Parkins scoring system (Parkins et al, 1983).
Tumor growth: 3×10^6 HEP2 cells (human pharynx cancer cell line) were implanted subcutaneously into nude Balb/c mice. Animals were irradiated with a single dose of 15 Gy selectively to the tumor when tumor diameter reached a mean of 5 mm. The tumor volume was evaluated for 21 days by the formula: length × $width^2/2$ and tumoral response was estimated versus initial volume.
Clonogenic survival: survival fraction of HEP2 cells was evaluated using the Park model; cells were exposed to irradiation (IR) at 0, 2, 4, 6 Gy and to RGTA-DAC 2 h after IR.
Results: Radiation-induced mucositis scored after IR plus RGTA-DAC spray followed by IP injections 3 h after, at day 1 and every 3 days, was significantly lower than after IR alone ($p < 0.001$). A marked decrease of severity and duration of mucositis was observed with administration of RGTA-DAC 3 h after IR ($p = 0.0006$) and 24 h after IR ($p = 0.001$) compared to IR alone. Association of amifostine 10 min before IR with RGTA-DAC 24 h after IR evidenced a major and better protection than RGTA-DAC 3 h or 24 h after IR ($p = 0.002$; $p = 0.001$) and than amifostine 10 min before IR ($p = 0.005$).
Tumor growth: administration of RGTA-DAC IP 3h after IR, then at day 1 and every 3 days didn't evidence significant interference on tumor growth associated (p = NS) or not (p = NS) to IR.
Clonogenic survival: the assay of radio-sensitivity *in vitro* didn't show a significative activity of RGTA-DAC on HEP2 cells clonogenicity (p = NS).



Mucositis

Conclusions: RGTA-DAC demonstrated a protective activity in radiation-induced mucositis in mice, without interference on tumor growth; RGTA-DAC associated with amifostine gave an almost total protection. Further investigations are neeed to understand the selective protective activity on healthy tissues.

1466 POSTER

EGFR and C-KIT/CD117 gene mutational screening and oncoprotein expression in patients with cancer of unknown primary: Implications for molecular pathophysiology and therapy

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Background: Cancer of unknown primary site (CUP) is a heterogeneous group of malignancies that often follow an aggressive clinical course. In order to elucidate its biology, we studied the expression of two transmembrane receptor genes with tyrosine kinase activity, C-KIT/CD117