In vivo study was performed in BALB/c nude mice. Six weeks old nude mice were divided 4 groups, 10 mice of each group, control, SG135, 5 mg/kg treated, SG135, 20 mg/kg treated and SG135 60 mg/kg treated groups. For the mice of control group were fed saline through out the experimental period. For the mice of three kinds of SG135 treated groups were fed SG at the dose of 5, 20 and 60 mg/kg/day, p.o. three times a week. After medication of SG135 for 12 days, tumor cells, 1×10^7 cells/mouse, were inoculated by s.c. on the flank of mouse. The tumor sizes were measured twice a week. The tumor growth was inhibited in all SG135, 5, 20 and 60 mg/kg/day treated groups, 21.0%, 26.0% and 25.0%, respectively, on day 49 after tumor inoculation when compared with control group. The survival rate were prominently increased in the mice of SG 20 and 60 mg/kg/day treated groups, 150.0% and 200.0%, respectively, on day 120 after tumor inoculation when compared with control group. These data presented that SG135 treatment was most effective in tumor growth inhibition and prominently effective in increase of average survival rate.

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Down-regulation of Sphingosine 1-Phosphate Receptor-1 in intestinal tumorigenesis

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Introduction: The bioactive sphingolipid, Sphingosine 1-Phosphate (S1P) is implicated in the regulation of cellular proliferation, migration, and survival via its G protein-coupled receptors S1P1–5. While animal models of intestinal neoplasia have demonstrated a beneficial effect of dietary sphingolipids in chemoprevention, the role of S1P in colon cancer is still unclear. The purpose of this study was to help define the role of the S1P receptor-ligand system in colon cancer.
Methods: Small intestine specimens of bigenic S1P1+/−Apcmin and S1P1+/+Apcmin mice were compared to determine effect of S1P1 heterozygosity on polyp number. Growth inhibition of RIE-1 cells was assessed using enforced expression of S1P1 receptor by adenoviral vector followed by treatment with S1P. Matched human normal and cancer colon tissue were obtained from surgical specimens.
Differential expression of S1P1 between the tissues was evaluated utilizing western blot analysis and immunohistochemistry.
Results: Bigenic S1P1+/−Apcmin mice revealed a 27% increase in polyp number when compared to control mice. Induced expression of S1P1 in RIE-1 cells caused growth inhibition with treatment of S1P.
Western blot analysis and immunohistochemistry revealed an increased expression of S1P1 in the human normal tissue as compared with tumor tissue.
Conclusions: Our results suggest that S1P1 receptor functions in the intestinal epithelium to inhibit tumorigenesis. Down-regulation of S1P1 in colorectal cancer may have functional consequences in the proliferation and or metastatic spread of cancer. Further evaluation of Sphingosine 1-phosphate receptor-1 is necessary to determine its potential for therapeutic intervention in colon cancer.

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Vitamin E succinate inhibits the in vitro growth of pancreatic cancer cells

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Background: Vitamin E Succinate (VES, α-tocopheryl succinate) is the most potent anti-tumor analog of Vitamin E that selectively induces apoptosis in cancer cells by modulating the expression of Bcl-2 family proteins. Despite its role being studied as a chemopreventive, chemotherapeutic and chemosensitizing agent in various cancers, there are scarce studies of VES in pancreatic cancer. Pancreatic cancer is the number four killer in the US and about 32,000 new cases are reported every year. The five year survival rate is only 5%. In this study, we investigated the effects of VES in three pancreatic cancer cell lines, ASPC-1, COLO-357 and PANC-1. We also assessed the synergistic growth inhibitory effect of VES along with two known cytotoxic drugs, Etoposide and Gemcitabine.
Methods: Cells were treated with varying concentrations (5 μM to 100 μM) of VES alone or in combination with Etoposide or Gemcitabine for different time periods. WST-1 cell proliferation reagent (Roche) was used to determine the cytotoxicity after the treatment. We studied the expression pattern of Bcl-2 family proteins in response to VES in ASPC-1 cells.
Results: VES inhibits the cell proliferation of all the three pancreatic cancer cell lines in a time and dose dependent manner. Our data also demonstrates that VES synergistically inhibits the cell growth in combination with 80 μM etoposide and 0.5 μg/ml Gemcitabine. In ASPC-1 cells, we observed a dose dependent decrease in the expression of Bcl-XL in response to VES.
Conclusion: This study demonstrates that (a) VES inhibits the *in vitro* growth of pancreatic cancer cell lines (b) Vitamin E succinate synergistically inhibits the growth of pancreatic cancer cells in combination with cytotoxic drugs Etoposide or Gemcitabine and (c) VES down-regulates the expression of antiapoptotic protein Bcl-XL in ASPC-1 cells.

Clinical methodology

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Preliminary results of a accelerated dose escalation phase I trial with a novel anthracycline derivative (RTA-744) in patients with primary brain tumors

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Background: RTA 744 is an anthracycline derivative that was shown in preclinical studies to cross the blood-brain barrier, not be a substrate for p-GP or MRP mediated efflux and improve survival in an orthotopic murine model of glioblastoma. A trial of RTA 744 was initiated at M. D. Anderson Cancer Center in patients with primary, high-grade gliomas.
Methods: RTA 744 is being administered as a 2-hour intravenous infusion on each of the first three days of a 21-day cycle. Dose escalation is proceeding according to an accelerated titration design, with single patient cohorts and 100% dose escalations until evidence of drug-related Grade 2 or greater toxicities are observed. Standard determinants of MTD are being employed. The MTD is being determined first in patients who do not take enzyme-inducing anti-convulsants. Pharmacokinetic samples are being taken at multiple time points on days 1–5 of Cycle 1. Tumor activity is being assessed according to the MacDonald criteria.
Results: As of May, 2006, RTA 744 has been administered to a total of 7 patients (pts) at dose levels of 1.2 (1 pt), 2.4 (3 pts), 4.8 (2 pts), and 9.6 mg/m^2/day (2 pts) (corresponding to 3.6, 7.2, 14.2, and 28.4 mg/m^2/cycle). No Grade $\geqslant$2 drug-related toxicities have been observed at doses of 4.8 mg/m^2 and below; results at 9.6 mg/m^2 have shown the first Grade 2 toxicities (platelets, lymphopenia and elevated SGPT). As a result the 9.6 mg/m^2/day cohort will be expanded and the percent of dose escalation for subsequent cohorts will be reduced. The pharmacokinetic profile indicates dose proportionality, with some accumulation by Day 3. Mean plasma half-life of RTA 744 thus far is approximately 34 hours. Three of the first four patients received at least four cycles, and one of these patients remains on study. Evidence of clinical activity was also seen in the first four patients, including 2 Minor Responses (2.4 mg/m^2) and 1 Stable Disease (1.2 mg/m^2). The most recent patient received a dose 4 times the level at which tumor regression was first documented. MRI results from the two most recently enrolled patients are pending.
Conclusions: RTA 744 is well tolerated up to doses of 9.6 mg/m^2/day, has predictable pharmacokinetics, and shows early evidence of activity. Full results of this trial should be available by the fall of 2006. Based on the activity seen to date, Phase 2 studies of this novel agent in primary and metastatic brain tumors appear warranted.

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Phase II trial of Sequenced Bevacizumab and Erlotinib with Bevacizumab and Chemotherapy for 1st Line Stage IIIB or IV Non-Small Cell Lung Cancer (NSCLC)

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Background: Recent evidence suggests that bevacizumab added to erlotinib increases activity in 2nd line metastatic NSCLC and the addition of bevacizumab to chemotherapy improves survival in 1st line metastatic NSCLC. Bevacizumab plus erlotinib (B+E) has never been tested in 1st line NSCLC. Furthermore, administration of 4 cycles of B+E prior to bevacizumab plus chemotherapy would allow selection of patients who could benefit from consolidation B+E.