82% (9/11) cell lines, including 4 primary and 7 commercial cell lines, after 4 days treatment ($p < 0.001$). The cell death resulted from suppression of PAX8 was profound in GBM harboring mutant p53 (mtp53), whilst it was delayed in U87MG, which has wtp53.
Conclusion: The current study represents the first extensive analysis of the expression of PAX2, 5, and 8 and their phosphorylated proteins in gliomas. Our results showed that it is possible to induce a potent cytocidal effect by silencing PAX8 expression in a significant proportion of GBMs. PAX8 serves a pro-survival function in GBM, and therefore a potential therapeutic target in GBM.

336 POSTER

Combination of proapoptotic gene and cisplatin for the treatment of resistant SCLC xenografts in nude mice

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Background: Small cell lung cancer (SCLC) metastasizes at an early stage, and most cases relapse and become resistant to current therapies. A systemic therapeutic approach with higher specificity and efficacy is needed.
Materials and Methods: Lipids: DPEPC, DPPC, and DSPE-PEG2000 were used to make a stable liposome formulation to encapsulate the plasmid. Plasmids: an activity-enhanced human telomerase reverse transcriptase promoter (hTRpG) was used to drive bik (Bcl-2 interacting killer) or luciferase gene. CMV promoter was used as comparison in the similar constructions. Cells: human SCLC cell lines H69, H82, H466, H345 (ATCC) and human normal bronchial epithelium cells were used in vitro and in vivo studies. Nude mice were used in the efficacy studies. The main method was to use liposome delivered tumor-specific proapoptotic gene combined with chemotherapy for systemic treatment of human SCLC xenografts in nude mice.
Results: The transfection efficiency of the liposome formulation in human SCLC cell lines was equivalent to Fu-gene 6. The hTRp-driven luc specifically expressed in human SCLC cell lines but not in the normal cells, the RLU in the cancer cells was 5- to 20-fold higher than that in normal cells ($p < 0.002$). The liposome delivered hTRp-bik could significantly sensitize the chemo-resistant human SCLC cell lines for cisplatin treatment (by increasing the response [%killing] by >5-fold, $p < 0.004$). In nude mice bearing orthotopic human SCLC, the reporter gene expression after IV injections of the liposome delivered hTRp-luc was significantly higher in tumor but not in other organs compared with the same formulation delivering CMV-luc. The combination therapy of liposome delivered hTRp-bik and cisplatin in human SCLC xenografts in nude mice was 2- to 4-fold higher than the chemotherapy alone ($P < 0.01$).
Conclusions: The nonviral gene delivery system is capable for the systemic gene delivery in animal. The combination strategy presented above is significantly more effective than the optimal chemotherapy alone in the resistant human SCLC xenografts models. The survival genes of Bcl-2 family may be used as targets for sensitizing the resistant SCLC.

337 POSTER

Long-term suppression of tumor growth by intermittent administration of oblimersen sodium in combination therapy with taxanes and kinase inhibitors

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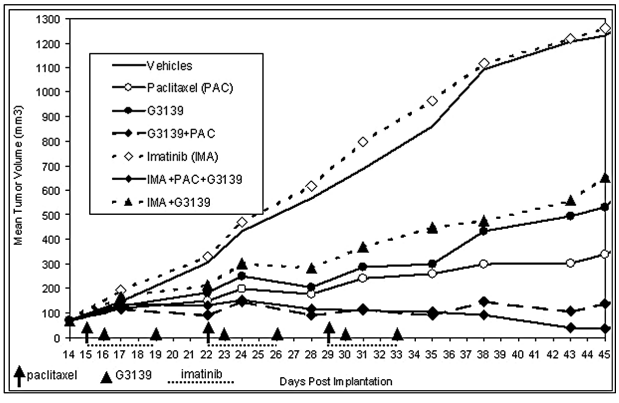
Background: Periodic dosing of the Bcl-2-targeted antisense oligonucleotide oblimersen sodium (G3139, Genasense®) has been shown to be as efficacious as or more efficacious than daily dosing against xenograft tumor models both as monotherapy and in combination with other agents. These results are highly consistent with the analysis of tumor sections taken from animals treated with fluorescently labeled oligonucleotide (FAM-G3139 or G4243). In these studies, intermittent dosing caused greater oligonucleotide uptake into xenograft tumor tissues, even when the total oligonucleotide dose was held constant or reduced by a periodic administration schedule. Finally, G3139 has been shown to increase the efficacy of other antitumor agents with distinct mechanisms of action, such as paclitaxel, DTIC, and kinase inhibitors gefitinib and erlotinib.
Materials and Methods: Xenograft tumors (A375 melanoma, A549 NSCLC, H460 NSCLC, HT29 colon carcinoma) grown in C.B-17/SCID mice were used to evaluate antitumor efficacy. G3139 was administered intravenously (i.v.) via bolus injections at levels ranging from 2.5 mg/kg/day daily to 20 mg/kg twice a week. Kinase inhibitors (erlotinib, imatinib, sunitinib, sorafenib) or temozolomide were administered orally (p.o.) daily. Taxanes (paclitaxel and paclitaxel albumin nanoparticles) were administered once a week i.v. Weight loss was used as a marker of overall toxicity.
Results: Intravenous administration of G3139 as infrequently as twice a week, in triplet combinations with a taxane and a kinase inhibitor was more efficacious than any doublet combination therapy. This result was most striking for imatinib in the A549 model, where single agent imatinib alone has no detectable activity at doses as high as 100 mg/kg/day. Weight loss was dependent on dosing schedules and drug sequencing. Highly effective therapeutic regimens were identified that were well tolerated and that could be administered repeatedly to completely suppress xenograft tumor growth. Growth delay and life span results will be presented.



A549 NSCLC treated with imatinib + paclitaxel + G3139.

Conclusions: G3139 does not require continuous administration to significantly inhibit tumor growth. On the basis of the preclinical efficacy of G3139 administered periodically via either subcutaneous bolus injections or short intravenous infusions, periodic dosing regimens will be incorporated into clinical trials combining oblimersen sodium with other agents such as alkylators, taxanes and kinase inhibitors.

338 POSTER

Carcinoma of the Ampulla of Vater with CIMP+ after treatment with pegylated liposomal based formulation of Ras siRNA combined with vinorelbine-tartrate exhibited inhibition of Raf/MEK/ERK, PI3K/AKT, DNA methylation and re-expression of tumor suppressor genes inducing type I, II, III PCD

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Background: Activated Ras signaling pathway due to mutations is common in carcinoma of the ampulla of Vater(CAV) causing upregulation of DNA and DNMT1 which leads to inactivation of tumor suppressor genes with subsequent chemoresistance due to inhibition of programmed cell death.
Materials and Methods: We treated chemoresistant CAV characterised by Ras codon 12 point mutations which activated the Ras/DNMT1/DNA methylation pathway with pegylated liposomal double stranded short interfering RNAs (siRNA) of synthetic 21 nucleotides specific to Ras combined with vinorelbine.
Results: Post-treatment, we observed Ras gene silencing after recognition of cognate mRNA through hydrogen bonding of the complementary short interfering RNA sequence leading to inhibition of DNA MeTase, DNMT1, Raf/MEK/ERK, PI3K/AKT, Wnt, p44/42 MAPK, cyclin D1, FGF-8, FGFR3, TGF-b, cyclin E-CDK2, RFC1, IL-8 and VEGF-R3 leading to reduced vessel density as assessed by CD31. Angiogenesis and lymphangiogenesis was inhibited. The complete degradation of Ras mRNA after the siRNA mediated RNA interference (RNAi) led to upregulation and re-expression due to epigenetic inactivation of PTEN, RB1, small GTPase RhoB, Par-4, GADD153, p16INK4a/p19Arf, p27Kip1, Skp2, thrombospondin-1, PKC-ä, CKIp21, HIC-1, p15, RARB, p53-MDM2, CHK2, RASSF2A, pcdc-25c and ATM. Vinorelbine-tartrate depolymerized microtubules at G2/M of tumor and endothelial cells and inhibited by phosphorylation the expression of anti-apoptotic and metastatic oncogenes bcl-2, bcl-xL, bcl-w and bcl-G, while it downregulated mcl-1, cIAP1, CAP2, XIAP, bfl-1/A1. Furthermore, vinorelbine upregulated 15-PGDH, ARHI, ICAD, Omi, Diablo, cyt-c, procaspase 7, bax, bak, bok, bad, bid, bcl-xs, bin, krk, Mtd, Nip3,