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Lipidic nanoparticle CPT-11 in a bioluminescent orthotopic pancreas cancer model FREE

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Abstract

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Efforts to treat pancreas cancer have been hampered by a lack of effective therapeutic options as well as predictive preclinical models. We hypothesized that nanoparticle agents encapsulating potent cytotoxic compounds may be useful against pancreatic cancer; and that antibody-targeted versions directed against EGFR may further increase efficacy against EGFR-overexpressing pancreatic cancers. We applied a liposome-based drug loading and stabilization technique to generate nanoliposomal CPT-11, a novel lipidic nanoparticle agent containing the prodrug CPT-11 (irinotecan) that has entered clinical trials. In addition, Fab' fragments of C225 were conjugated to nanoliposomal CPT-11 to generate EGFR-targeted immunoliposomal CPT-11.

Another objective of this study was to develop a bioluminescent-based orthotopic xenograft model of pancreas cancer with EGFR-overexpression to test this therapeutic approach. COLO357, a human pancreatic cell line, was passaged multiple times in vivo to generate the sub-line L3.6pl. This cell line was subsequently modified by lentiviral transduction to generate a firefly luciferase-expressing cell line, L3.6pl-T. L3.6pl-T cells were injected, during surgery, directly into the pancreas of a nude mouse to generate a tumor xenograft. Following ip administration of luciferin, animals were immediately imaged using a Xenogen IVIS 100 bioluminescent imager, and subsequently imaged at weekly intervals. Tumor burden was quantified by measuring luminescence. The signal was quantified by defining regions of interest (ROIs) and measuring photons/sec/str.

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Agents evaluated in this model included EGFR-targeted immunoliposomal CPT-11, nanoliposomal CPT-11, free drug or vehicle control. All treatments were administered i.v. by tail vein beginning at 7

days post- tumor implantation and continued weekly for a total of three treatments. Both nanoliposomal CPT-11 and immunoliposomal CPT-11 showed potent antitumor activity, including durable tumor regressions, and were markedly superior to the equivalent dose of free drug. While both nanoparticle constructs were highly potent, the immunoliposome agent appeared to provide more prolonged duration of responses than the non-targeted version. Systemic toxicity was not observed with any treatment.

We conclude that nanoparticle-mediated delivery of CPT-11 via nanoliposomal CPT-11 or anti-EGFR immunoliposomal CPT-11 greatly enhances antitumor efficacy in the orthotopic COLO357 pancreatic xenograft model. This therapeutic approach offers potential advantages for pancreatic cancer treatment, and this type of model system may be useful in preclinical evaluation.

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