

PEP02 (liposome irinotecan) effectively inhibits human lung squamous cell carcinoma and small cell lung cancers in subcutaneous and orthotopic xenograft tumor models

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Background:

PEP02 is a nanoparticle liposome formulation of irinotecan (CPT-11), a topoisomerase I inhibitor, used for the treatment of various tumor types including lung cancers. In preclinical and clinical studies, PEP02 has been shown to greatly modify the pharmacokinetics and biodistribution of CPT-11 and its active metabolite, SN-38, thereby improving its therapeutic efficacy. In this report, we evaluated the in vivo efficacy of PEP02 in three xenograft models of human lung tumors.

Methods:

Xenograft models of subcutaneous H157 squamous cell carcinoma (SCC), known to be resistant to various EGFR inhibitors, and H841 small cell lung cancer (SCLC), known to be resistant to several conventional therapeutic agents, were established in mice and rats. Animals (10-12 per group) were treated by weekly iv injections after the tumor reached 200 cubic mm in size with placebo liposome, CPT-11 at 50 (mouse) or 25 (rat) mg/kg/wk, docetaxel at 8 (mouse) or 12 (rat) mg/kg/wk, or PEP02 at 15, 30 and 50 mg/kg/wk for three or four weeks. Tumor volumes were measured with digital calipers. For the orthotopic model, Kaplan-Meier survival curves were generated.

Results:

(1) PEP02 effectively suppressed H157 subcutaneous SCC tumor growth in a dose dependent manner, much more efficient than CPT-11 or docetaxel. PEP02 at 15, 30 and 50 mg/kg/wk inhibited tumor growth by 86.7%, 92.9% and 97.6%, respectively when compared with that of placebo liposome, and the suppressions persisted for 12 to 15 days after the last treatment. In contrast, CPT-11 and docetaxel only inhibited tumor growth by 29.8% and 71.4%, respectively. Retreatment of the regrowth was achieved with PEP02 at 50 mg/kg/wk which extended the tumor suppression until 130 days. (2) For the SCLC H841 xenograft, PEP02 at 15, 30 and 50 mg/kg/wk also impressively inhibited tumor growth by 81.7%, 96.3% and 98.3% respectively, much better than CPT-11 by 51.6%, when compared with that of placebo liposome. Inhibition of tumor growth persisted more than 20 days after the last treatment with PEP02 at 15 and 30 mg/kg/wk before tumor grew again. In contrast, complete tumor regression was achieved at 50 mg/kg/wk. (3) When implanted orthotopically in the left lung of athymic nude rats, H157 SCC tumor grew aggressively and metastasized contra-laterally to right lungs, and eventually rats died from tumor burden with a median survival of 24 days in the placebo liposome group. At

the maximum tolerated dose, CPT-11 at 25 mg/kg/wk or docetaxel at 12 mg/kg/wk did not extend rat survival at all. However, PEP02 at 15, 30 and 50 mg/kg/wk prolonged median survivals by 4, 12 and 26 days, respectively. In all three models, no obvious side effects or weight loss were noted in the PEP02 treated groups.

Conclusion:

PEP02 effectively inhibited tumor growth, regrowth, and prolonged survival in subcutaneous and orthotopic lung tumor xenograft models. PEP02 has great clinical potential for the treatment of human lung SCC and SCLC in which there are high unmet medical needs.