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Preclinical Evaluation of Radionuclide Therapy Targeting CXCR4 and Thioredoxin Reductase in Atypical Carcinoid and Neuroendocrine Carcinoma

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BACKGROUND: Atypical carcinoid (AC) and small cell lung cancer (SCLC) are currentlyincurable. There is thus a critical need for new diagnostic and therapeutic strategies. Chemokine receptor 4 (CXCR4), a G protein coupled receptor, is known to drive proliferation and metastases in breast cancer and multiple myeloma. Additionally, thioredoxin reductase (TR) upregulation in tumor cells is associated with resistance to ionizing radiation and platinum-based therapy. Previous data have demonstrated CXCR4 expression in AC and SCLC cell lines and patient specimens, as well as specific PET imaging of xenografts in mice with 68 Ga-Pentixafor, a CXCR4 antagonist. We hypothesize that targeting both CXCR4 and TR in AC and SCLC will provide a paradigm shift in the therapy of lung NET and NEC. We evaluated the efficacy and toxicity of 177 Lu-Pentixather (CXCR4 antagonist) and auranofin (TR inhibitor) in an animal model.

METHODS: In vitro cytotoxicity of 177 Lu-pentixather +/- auranofin was evaluated by cell survival and clonogenic assay. Maximum tolerated dose, efficacy and toxicity of 177 Lu-pentixather +/- auranofin was determined in tumor-bearing NSG mice. TR reduction was assessed by different regimen of auranofin administration in mice.

RESULTS: ^{177} Lu-pentixather demonstrated dose- and time-dependent cytotoxicity and combination with auranofin enhanced the cell death significantly (P<0.05). 177 Lu -pentixather (0.7 mCi/mouse +/- auranofin) inhibited tumor progression and was well tolerated. A dose of 1.4 mCi/mouse induced better tumor control, but resulted in dose-limiting weight loss as well as hematologic and liver toxicities with and without auranofin. Auranofin dose was optimized at 4 mg/kg/day for 3 days to achieve 50% reduction in TR without causing hematological, hepatic nor renal toxicity.

CONCLUSION: CXCR4 targeted radionuclide therapy in combination with TR inhibition is a potential new strategy for AC and SCLC, this therapy regimen may require hematopoietic stem cell rescue.

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