Radionuclide therapy with tissue factor targeting Lu-177-FVIIai inhibits growth in an experimental mouse model of human pancreatic cancer

Objectives: Tissue factor (TF) is related to aggressiveness and invasiveness of cancer and there is a correlation between tumor TF expression, metastatic potential, and patient outcome. The aim of the study was to test the therapeutic potential and toxicity of a novel compound for localized TF targeted radionuclide therapy. The radionuclide therapy was based on Factor VII (FVII), the natural ligand to TF. In the current study, we investigated the biodistribution, therapeutic potential and toxicity of 177Lu labeled site inhibited FVIIa (177Lu-FVIIai) in an experimental mouse model of pancreatic cancer.

Methods: p-SCN-Bn-CHX-A"-DTPA was conjugated to FVIIai followed by radiolabeling with 177Lu (177Lu-CHX-A"-DTPA-FVIIai). A pancreas xenograft mouse model (BxPC3) was used to test the therapeutic potential of 177Lu-FVIIai. NMRI nude mice with subcutaneous BxPC3 tumors were used. The mice were randomized into groups receiving 177Lu-FVIIai, FVIIai, or vehicle when the tumor volumes were about 50 mm3. 177Lu-FVIIai was administered in doses of 15 MBq, 7.5 MBq or 2 x 7.5 MBq (n=8 mice/group). Tumor growth was monitored three times weekly. Biodistribution of 177Lu-FVIIai was studied ex vivo in several organs at 1, 4, 24, 72 and 168 hours after injection. The in vivo biodistribution of 177Lu-FVIIai was evaluated by SPECT/CT imaging. Furthermore, competition and dose escalation experiments (1-30 MBq) were performed. In a parallel set of NMRI mice, toxic effects of 177Lu-FVIIai were evaluated by hematology, histology and 99mTc-DMSA scintigraphy. Results: FVIIai was successfully radiolabeled with 177Lu with a specific activity of 10-25 GBq/µmol after EDTA scavenging and PD-10 purification. Treatment with FVIIai did not change tumor growth compared to the vehicle groups. The mice that received 15 MBq 177Lu-FVIIai had a significantly reduced tumor growth from day 0 to day 19 compared with mice from the control groups (425.5±44.8% versus 614.2±49.1%; p=0.02). The groups receiving 7.5 MBq or 2 x 7.5 MBq 177Lu-FVIIai had no significant different tumor growth compared with controls on day 19. Tumor uptake of 177Lu-FVIIai measured ex vivo was 1.16±0.04, 1.97±0.18, 1.95±0.07, 1.01±0.06, 0.31±0.02 percent injected dose per gram (%ID/g) at 1, 4, 24, 72 and 168 hours post-injection, respectively. Injection with unlabeled FVIIai 10 minutes before 177Lu-FVIIai injection significantly reduced tumor uptake of 177Lu-FVIIai (from 2.5±0.16 %ID/g to 1.7±0.05 %ID/g; p<0.05). Escalating the dose of 177Lu-ASIS from 1-30 MBq did not change tumor uptake (%ID/g). A transient decrease in leucocyte counts was observed for the mice receiving 15 and 7.5 MBq 177Lu-FVIIai. Ten weeks after injection of 177Lu-FVIIai kidney uptake of 99mTc-DMSA was significantly decreased in all the treatment groups compared to the vehicle group when measured by SPECT imaging. Conclusion: FVIIai was successfully radiolabeled with 177Lu. 177Lu-FVIIai showed anti-tumor activity in a mouse model of human pancreatic cancer. Treatment with 177Lu-ASIS induced a transient decrease in leucocyte counts and a decreased kidney function ten weeks after injection.

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