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Evaluation of novel antibodies to Centrin-1 for radioimmunotherapy of pancreatic cancer

Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer death in the US with a very low survival rate. Unlike other solid malignancies, a biopsy of the pancreas is very invasive and recommend only with a mass suspected to be PDAC. Centrin1 (CETN1), a cancer/testis antigens (CATs), has been showed a 25-fold upregulation in 50% of the tumors from pancreatic cancer patients. Since testes are an immunoprivileged site, CETN1 could be a perfect target of radioimmunotherapy as the side effects of the treatment would be minimal. In this study, we developed novel antibodies (69-11 and 76-6) that are highly specific to CETN1, compared to its compensatory protein CENT2, which is widely expressed in all eukaryotic cells. 69-11 and 76-6 are either labeled with 213Bi, an alpha emitter, or with 177Lu, a beta emitter, for the treatment study. The radiolabeled antibodies were administered to PDAC xenografts-bearing nude mice. The localization of the radiolabeled antibodies in the tumors and normal organs was determined with microSPECT/CT imaging. The tumors were monitored for 50 days. The toxicity assessment included weekly blood chemistry and kidney and liver functions assessment when PDAC-bearing mice were sacrificed at the end of the study. Labeling with 213Bi converted CETN1-specific antibodies into a very effective radioimmunotherapy reagent with tumor growth significantly (P=0.01) slowed down by either 100 or 200 μCi single injection. Importantly, the effect of the antibodies on the tumors was CETN1-specific, as 200 μCi control IgG had no effect on the tumor growth. In spite of impressive localization in the tumor demonstrated during the imaging experiments, 177Lu-labeled antibody was not very effective in slowing down tumor growth with no difference from 177Lu-IgG control (P=0.06) and was several folds less effective than 213Bi-labeled antibody. Both 213Bi and 177Lu groups showed only transient hematologic toxicity and absence of liver and kidney toxicity attesting to the very high safety margin of targeting CETN1 with radioimmunotherapy. In conclusion, the novel antibodies have the ability to detect CETN1 in vivo and in vitro, are highly efficacious and safe for treatment of PDAC, and warrant further work on developing them into clinical agents for diagnosis and therapy of PDAC.

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