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Chemotherapy-mediated upregulation of SSTR2 in NET tumors in mice and in tumor biopsies from lung- and gastroenteropancreatic-NET patients

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BACKGROUND

The peptide receptor radionuclide therapy (PRRT) is recommended for somatostatin receptors (SSTR) positive neuroendocrine tumors (NET). However, complete remissions with PRRT remain anecdotal and NET patients with low SSTR-positivity are excluded from this treatment. Hence, any approach to increase SSTR2 expression can improve therapeutic efficacy of PRRT. Based on previous *in vitro* studies with NET cell lines, we **hypothesize** that a brief treatment with chemotherapeutic agents, such as temozolomide (TMZ) will upregulate SSTR2 expression in NET leading to a combination strategy to improve the efficacy of subsequent PRRT.

METHODS

For ***in vivo*** study, we used BON-1 NET cell line-derived subcutaneous tumors in immunodeficient mice (n=4-5), treated them five days with 25 mg/kg TMZ or mock, and examined the biodistribution by ɣ-counter of ^{68}Ga-DOTA-octreotate at day 7, as well as SSTR expression in harvested tumors by RT-PCR. To validate this concept from clinical perspective, we treated ***ex vivo*** fresh tumor biopsies from above mouse model (n=6, 3 mice) and from lung- (n=6, 4 patients) and gastroenteropancreatic-NET (n=4, 3 patients) patients, with 100 µM TMZ for 5 days, followed by analyses of SSTR expression by immunoblotting and RT-PCR.

RESULTS

In mouse model of BON-1-derived NET tumor, the biodistribution study of ^{68}Ga-DOTA-octreotate revealed a significantly higher uptake of radioactivity at day-7 in BON-1 tumors, but not in healthy tissues, which was confirmed by a 2-fold and 1.7-fold upregulation of mRNA for SSTR2 and 5 respectively. The fresh tumors from mice treated ex vivo with TMZ for five days resulted in a specific and significant upregulation of SSTR2 mRNA (and not other SSTR) from 5-11 days ($p<0.01$-0.001). Having confirmed the validity of *ex vivo* approach, we began screening lung- and gastroenteropancreatic-NET patients' biopsies for their SSTR-expression response to the *ex vivo* TMZ treatment. Our initial results reveal a trend for the upregulation of SSTR2 mRNA between 7 to 9 days after start of chemotherapy treatment for lung- and GEP-NET.

CONCLUSIONS

Our preliminary observations suggest that a short course of chemotherapy to upregulate SSTR2 is a promising approach to increase the efficacy of subsequent PRRT. Our results could lead to clinical trials to examine which NET patients could selectively benefit from this approach during their PRRT treatment, and could also allow NET patients with low SSTR positivity to become eligible to receive PRRT.

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