Göteborg, 2016

Lutetium-177-octreotate treatment of small intestine neuroendocrine tumors

Radiation biology as basis for optimization

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin, Göteborgs Universitet, kommer att offentligen försvaras i Hörsal Arvid Carlsson, Academicum, Medicinaregatan 3, Göteborg, fredagen den 27 januari, klockan 9:00

av: **Johan Spetz**

Fakultetsopponent: **Professor Marion Hendriks-de Jong**

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Avhandlingen baseras på följande delarbeten

I. Eva Forssell-Aronsson, Johan Spetz, Håkan Ahlman: **Radionuclide therapy via SSTR: Future aspects from experimental animal studies**. *Neuroendocrinology*, **2013**; 97(1):86-98.

II. Johan Spetz, Nils Rudqvist, Britta Langen, Toshima Z Parris, Johanna Dalmo, Emil Schüler, Bo Wängberg, Ola Nilsson, Khalil Helou, Eva Forssell-Aronsson: **Time-dependent transcriptional response of GOT1 human small intestine neuroendocrine tumor after ^{177}Lu-octreotate therapy**. *In revision.*

III. Johan Spetz, Mikael Montelius, Evelin Berger, Carina Sihlbom, Maria Ljungberg, Khalil Helou, Ola Nilsson, Eva Forssell-Aronsson: **Profiling proteomic responses in small intestinal neuroendocrine tumor GOT1 after ^{177}Lu-octreotate therapy.** *Submitted*.

IV. Johanna Dalmo, Johan Spetz, Mikael Montelius, Britta Langen, Yvonne Arvidsson, Henrik Johansson, Toshima Z Parris, Khalil Helou, Bo Wängberg, Ola Nilsson, Maria Ljungberg, Eva Forssell-Aronsson: **Priming increases the anti-tumor effect and therapeutic window of ^{177}Lu-octreotate in nude mice bearing human small intestine neuroendocrine tumor GOT1**. *EJNMMI Research*, **2016**, in press.

V. Johan Spetz, Britta Langen, Nils Rudqvist, Toshima Z Parris, Johanna Dalmo, Bo Wängberg, Ola Nilsson, Khalil Helou, Eva Forssell-Aronsson: **Transcriptional effects of ^{177}Lu-octreotate therapy using a priming treatment schedule on GOT1 tumor in nude mice**. *Manuscript*.

VI. Johan Spetz, Britta Langen, Nils Rudqvist, Toshima Z Parris, Khalil Helou, Ola Nilsson, Eva Forssell-Aronsson: **Hedgehog inhibitor sonidegib potentiates ^{177}Lu-octreotate therapy of GOT1 human small intestine neuroendocrine tumors in nude mice**. *Submitted.*

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

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Lutetium-177-octreotate treatment of small intestine neuroendocrine tumors

Radiation biology as basis for optimization

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Abstract

Patients with neuroendocrine tumors (NETs) often have metastatic spread at the time of diagnosis. NETs frequently express somatostatin receptors (SSTR) that can be targeted by radiolabeled somatostatin analogs (*e.g.* ^{177}Lu-octreotate). Despite being highly effective in animal models (*e.g.* the human small intestine NET GOT1 transplanted to nude mice), ^{177}Lu-octreotate-based therapies have shown low cure rates in clinical studies. The cellular processes that underlie positive treatment response to ^{177}Lu-octreotate are largely unknown.

The aim of this work was to study the possibilities to optimize the therapeutic effects of ^{177}Lu-octreotate in the GOT1 model in nude mice.

A literature study of available data on radiolabeled somatostatin analogs on NETs in animal models was performed, to identify strategies for treatment optimization. To test these strategies, GOT1-bearing BALB/c nude mice were treated with non-curative amounts of ^{177}Lu-octreotate in different treatment schedules including single administrations, priming (fractionated) administrations and combination treatment with hedgehog inhibitor sonidegib. Biodistribution and dosimetry studies were performed and anti-tumor effects were monitored by measuring tumor volume. Global transcriptional and proteomic responses in tumor samples were evaluated using RNA microarray and liquid chromatography mass spectrometry, respectively.

^{177}Lu-octreotate therapy of GOT1 tumors xenotransplanted in nude mice resulted in tumor volume reduction. Priming administration resulted in increased anti-tumor effects and increased therapeutic window. Combination therapy using sonidegib and ^{177}Lu-octreotate resulted in prolonged time to progression. The global transcriptional and proteomic analyses of ^{177}Lu-octreotate treated tumor samples revealed time-specific responses in terms of affected biological functions.

In conclusion, time-dependent changes in p53-related cell cycle regulation and apoptosis, angiogenesis, endoplasmic reticulum stress, and oxidative stress-related processes suggest possible niches for combination therapy at different time points after radionuclide therapy. Priming ^{177}Lu-octreotate therapy and combination therapy using sonidegib and ^{177}Lu-octreotate could be beneficial to patients with NE-tumors.

Keywords: Peptide receptor radionuclide therapy, PRRT, **s**omatostatin receptors, SSTR, midgut carcinoid, radiogenomics

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