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
Department of Nuclear Medicine and Radiology,
Erasmus MC, Rotterdam, the Netherlands

Avhandlingen baseras på följande delarbeten


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 177Lu-octreotate in nude mice bearing human small intestine neuroendocrine tumor GOT1. EJNMMI Research, 2016, in press.


Lutetium-177-octreotate treatment of small intestine neuroendocrine tumors

Radiation biology as basis for optimization

Johan Spetz

Department of Radiation Physics, Institute of Clinical Sciences, Sahlgrenska Cancer Center, Sahlgrenska Academy at University of Gothenburg, Sweden, 2016

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., ¹⁷⁷Lu-octreotate). Despite being highly effective in animal models (e.g., the human small intestine NET GOT1 transplanted to nude mice), ¹⁷⁷Lu-octreotate-based therapies have shown low cure rates in clinical studies. The cellular processes that underlie positive treatment response to ¹⁷⁷Lu-octreotate are largely unknown.

The aim of this work was to study the possibilities to optimize the therapeutic effects of ¹⁷⁷Lu-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 ¹⁷⁷Lu-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.

¹⁷⁷Lu-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 ¹⁷⁷Lu-octreotate resulted in prolonged time to progression. The global transcriptional and proteomic analyses of ¹⁷⁷Lu-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 ¹⁷⁷Lu-octreotate therapy and combination therapy using sonidegib and ¹⁷⁷Lu-octreotate could be beneficial to patients with NE-tumors.

Keywords: Peptide receptor radionuclide therapy, PRRT, somatostatin receptors, SSTR, midgut carcinoid, radiogenomics