Therapy of neuroendocrine tumors with ^{177}Lu-octreotate

Human tumor cell types and models and optimization of treatment

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid
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Av
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Avhandlingen är baserad på följande delarbeten:

I. Dalmo J, Rudqvist N, Spetz J, Laverman P, Nilsson O, Ahlman H, Forssell-Aronsson E. *Biodistribution of ^{177}Lu-octreotate and ^{111}In-minigastrin in female nude mice transplanted with human medullary thyroid carcinoma GOT2*. Oncology reports 27: 174-181, 2012

II. Spetz J, Dalmo J, Nilsson O, Wängberg B, Ahlman H, Forssell-Aronsson E. *Specific binding and uptake of ^{131}I-MIBG and ^{111}In-octreotide in metastatic paraganglioma –tools for choice of radionuclide therap*y. Hormone and Metabolic Research, 44(5): 400-404, 2012

III. Arne, G., Nilsson B., Dalmo J, Kristiansson E, Arvidsson Y, Forssell-Aronsson E, Nilsson O and Ahlman H. *Gastrointestinal stromal tumors (GISTs) express somatostatin receptors and bind radiolabeled somatostatin analogs.* Acta Oncol 52(4): 783-792, 2013

IV. Dalmo J, Spetz J, Montelius M, Langen B, Arvidsson Y, Johansson H, Parris T, Helou K, Wängberg B, Nilsson O, Ljungberg M, Forssell-Aronsson E. *Increased therapeutic effect using priming administration before the main administration of ^{177}Lu-octreotate in nude mice bearing human carcinoid tumor GOT1*. Manuscript

V. Dalmo J, Westberg E, Barregård L, Svedbom L, Johansson M, Törnqvist M, Forssell-Aronsson E. *Evaluation of retinol binding protein 4 and carbamoylated haemoglobin as potential renal toxicity biomarkers in adult mice treated with ^{177}Lu-octreotate.* Manuscript

GÖTEBORGS UNIVERSITET

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Abstract

Neuroendocrine (NE) tumors (NET) have often metastasized at the time of diagnose, which makes it hard to cure patients with NET. Radiolabeled hormone analogues (especially somatostatin analogues, SS) can be used for diagnostics (e.g. ^{111}In-octreotide) and therapy (e.g. ^{177}Lu-octreotate). For development of the treatment methods, realistic tumor cell lines and models are valuable. Human NET cell lines and models are few, and there is a need to find suitable models for different types of NET, with e.g. relevant expression of hormone receptors, e.g. somatostatin receptors (SSTR), cholecystokinin-2/gastrin receptors, and catecholamine transporters.

In this work, several types of human NET models (paraganglioma, gastrointestinal stromal tumor (GIST), human medullary thyroid cancer (GOT2), and midgut carcinoid (GOT1)) were studied, with the aim to evaluate the binding and/or uptake of radiolabeled hormone analogues (^{177}Lu-octreotate, ^{111}In-octreotide, ^{111}In-MG0, and ^{131}I-MIBG). Activity concentration in tumor and non-tumor tissues was measured *in vitro* or *in vivo* in different NETs. The activity concentration after ^{111}In-octreotide injection indicated a large variation in somatostatin receptor expression in different NETs. A specific uptake and internalization of radiolabeled ^{111}In-octreotide or ^{177}Lu-octreotate was found *in vitro* in paraganglioma and in GIST, respectively, as well as a specific uptake of ^{131}I-MIBG in paraganglioma. The tumor uptake of ^{111}In-octreotide and ^{131}I-MIBG in the patient with paraganglioma, and of ^{111}In-octreotide in several individuals with GIST showed that some of these patients might benefit from radionuclide therapy. All studied human NETs in this work will serve as good models in the development of increased therapeutic effect of different NETs.

^{177}Lu-octreotate is today routinely used for treatment of carcinoids and endocrine pancreatic tumors, but needs to be optimized. A novel treatment schedule was tested, giving a priming administration of ^{177}Lu-octreotate before administering the therapeutic amount. This procedure resulted in higher mean absorbed dose to tumor tissue and increased therapeutic effect compared with those for a single administration.

To improve the individual following-up after fractionated treatment with ^{177}Lu-octreotate, the possibility to use urinary retinol binding protein (RBP) and valine hydantoin (VH) in blood as biomarkers for radiation induced nephrotoxicity was studied. RBP4 was shown to be a potential biomarker for nephrotoxicity, before kidney injury was demonstrated by morphology.

Keywords: somatostatin, radionuclide therapy, receptor up-regulation, RBP, nephrotoxicity
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