Improved radionuclide therapy of neuroblastoma

Preclinical evaluation of ^{177}Lu-labeled somatostatin analogs

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet kommer att offentligen försvaras i Arvid Carlsson, Academicum, Göteborg, onsdagen den 17 maj, kl 13:00.

av **Arman Romiani**

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This thesis is based on the following studies, referred to in the text by their Roman numerals:

I. Saadati S., Spetz J., Sandblom V., Schüler E., Romiani A., Shubbar E., Lind D.E., Palmer R.H., Hallberg B., Parris T.Z., Helou K., Forssell-Aronsson E. **Binding and internalization of ^{177}Lu-octreotate in cell lines of neuroblastoma, breast cancer, and non-small cell lung cancer.** *Submitted.*

II. Romiani A., Spetz J., Shubbar E., Lind D.E., Hallberg B., Palmer R.P., Forssell-Aronsson E. **Neuroblastoma xenograft models demonstrate the therapeutic potential of ^{177}Lu-octreotate.** *BMC Cancer, 21(1):950, 2021.*

III. Romiani A., Simonsson K., Pettersson D., Al-Awar A., Rassol N., Bakr H., Lind D.E., Umapathy G., Helou K., Palmer R.H., Hallberg B., Forssell-Aronsson E. **Comparison between ^{177}Lu-octreotate and ^{177}Lu-octreotide in neuroblastoma-bearing mice: biodistribution, therapeutic effects and influence on apoptosis-related genes.** *Manuscript.*

IV. Romiani A., Pettersson D., Simonsson K., Bakr H., Lind D.E., Palmer R.H., Hallberg B., Helou K.,Forssell-Aronsson E. **Synergistic antitumor effects of ^{177}Lu-octreotide combined with an ALK inhibitor in a high-risk neuroblastoma xenograft model.** *Manuscript.*

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Preclinical evaluation of ^{177}Lu-labeled somatostatin analogs

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Avdelningen för Medicinsk strålningsvetenskap, Institutionen för kliniska vetenskaper, Sahlgrenska akademin, Göteborgs universitet, Sverige, 2023

Abstract

Today, about half of the children diagnosed with high-risk neuroblastoma (HR-NB) survive due to considerable treatment improvements during the last decades. However, there is still much to be done for the other half who are not cured with current treatments. In addition, children with HR-NB often have metastatic spread at diagnosis, requiring systemic treatment. HR-NBs have some specific biological characteristics that can be targeted for treatment systemically. For example, *ALK* encodes for the anaplastic lymphoma kinase receptor found mutated in about 15% of HR-NBs. Another example is somatostatin receptors (SSTRs), expressed between 60-90% in all NBs. These SSTRs can be targeted with ^{177}Lu-labeled somatostatin analogs (e.g., ^{177}Lu-octreotate and ^{177}Lu-octreotide). However, the usefulness of ^{177}Lu-labeled somatostatin analogs in HR-NB patients has yet to be thoroughly investigated. The aim of this work was to evaluate the therapeutic usefulness of ^{177}Lu-labeled somatostatin analogs from studies on HR-NB cell lines and HR-NB xenograft mouse models.

Experiments performed on two different HR-NB cell lines demonstrated high specific binding and internalization of ^{177}Lu-octreotate compared to other cell lines of various tumor types. This led to further studies in mouse models. Despite high uptake and absorbed dose to tumor, treatment with single injections of ^{177}Lu-octreotate or ^{177}Lu-octreotide led to modest therapeutic effects, where ^{177}Lu-octreotide caused a more substantial anti-tumor effect. In addition, fractionation with ^{177}Lu-octreotate resulted in prolonged survival. However, a synergistic effect was observed when combining lorlatinib and ^{177}Lu-octreotide for the tumor with ALK-mutation. The combination treatment also led to an elevated apoptotic transcriptional response.

In summary, this thesis demonstrates that ^{177}Lu-labeled somatostatin analogs can be beneficial in the treatment of patients with disseminated HR-NBs overexpressing SSTRs. However, since many HR-NBs may have specific mutations or amplifications, a combination with other drugs (e.g., lorlatinib) might be needed to overcome potential radioresistance and to enhance the anti-tumor effects.

Keywords: Peptide receptor radionuclide therapy, somatostatin receptors, neuroblastoma, internalization, biodistribution, dosimetry, apoptosis, gene expression, lorlatinib

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