Göteborg, 2022

Optimisation of radionuclide therapy by reduction of normal tissue damage
^{177}Lu-octreotate therapy combined with α_1-microglobulin

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin, Göteborgs universitet, kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, den 1 juni, 2022, klockan 09:00

av **Charlotte Andersson**

Fakultetsopponent: Docent Marika Nestor,
Uppsala Universitet, Institutionen för immunologi, genetik och patologi, Medicinsk strålningsvetenskap

Avhandlingen baseras på följande delarbeten

I. Andersson C., Shubbar E., Schüler E., Åkerström B., Gram M., and Forssell-Aronsson E. *Recombinant α_1-Microglobulin Is a Potential Kidney Protector in ^{177} Lu-Octreotate Treatment of Neuroendocrine Tumors.* Journal of Nuclear Medicine, 2019;60:1600-1604

II. Rassol N., Andersson C., Pettersson D., Al-awar A., Shubbar E., Åkerström B., Gram M., Helou K. and Forssell-Aronsson E. *Co-administration with A1M does not influence apoptotic response of ^{177}Lu-octreotate in GOT1 neuroendocrine tumors*. (Manuscript)

III. Andersson C., Shubbar E., Parris T., Langen B., Larsson M., Schüler E., Olsson BM., Strand SE., Åkerström B., Gram M., Helou K. and Forssell-Aronsson E. *Effects of recombinant α_1-microglobulin on the early proteomic response in risk organs after exposure to ^{177}Lu-octreotate.* (Manuscript)

IV. Andersson C., Simonsson K., Shubbar E., Gram M., Helou K. and Forssell-Aronsson E. *Early apoptotic response in kidney after ^{177}Lu-octreotate administration with or without potential radioprotector α_1-microglobulin*. (Manuscript)

V. Andersson C., Pettersson D., Shubbar E., Gram M., Helou K., Johansson M. and Forssell-Aronsson E. *Assessment of potential nephrotoxicity biomarkers after ^{177}Lu-octreotate administration and effects of antioxidant α_1-microglobulin.* (Manuscript)

SAHLGRENSKA AKADEMIN
INSTITUTIONEN FÖR KLINISKA VETENSKAPER

GÖTEBORGS UNIVERSITET

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Optimisation of radionuclide therapy by reduction of normal tissue damage
^{177}Lu-octreotate therapy combined with α_1-microglobulin

Charlotte Andersson

Ämnesområdet Medicinsk Strålningsvetenskap, Institutionen för kliniska vetenskaper, Sahlgrenska akademin, Göteborgs universitet, Sverige.

Background: ^{177}Lu-octreotate is used to treat patients with neuroendocrine tumours (NETs) often resulting in prolonged life and better quality of life, but is today seldom a cure for these patients. Optimisation of ^{177}Lu-octreotate therapy can be achieved by reducing the risk of side effects on the main dose limiting organs, kidneys and bone marrow, enabling higher administered activity. One proposed option is co-administration with the antioxidant α_1-microglobulin (A1M).

Aims: 1) to investigate if co-administration with A1M results in a negative (protective) effect on the tumour response to ^{177}Lu-octreotate 2) to study the normal tissue response in mice following ^{177}Lu-octreotate administration with or without A1M and A1M alone, 3) and to propose biomarkers for ^{177}Lu-octreotate induced kidney damage.

Methods: Biodistribution of ^{177}Lu was investigated in mice bearing human GOT2 NET after injection of ^{177}Lu-octreotate with or without A1M. Tumour volume and regulation of apoptosis related genes were studied on human GOT1 NET in mice after injection of ^{177}Lu-octreotate with or without A1M and A1M alone. Effects on normal tissues were studied in mice injected with ^{177}Lu-octreotate with or without A1M and A1M alone. Early proteomic responses were investigated in kidney tissues and bone marrow. Regulation of apoptosis related genes was investigated in kidney tissues. Late effects on kidneys were studied based on expression of proposed markers for kidney damage.

Results and conclusions: No negative impact of A1M were observed on the therapeutic effects of ^{177}Lu-octreotate in NET. A tissue-dependent early proteomic response was observed in kidney tissue, including regulation of previously observed radiation responsive proteins. No clear changes in regulation of these radiation-induced proteins was observed after co-administration of A1M. Regulation of pro- and anti-apoptotic genes was observed in kidney cortex and kidney medulla following ^{177}Lu-octreotate exposure. Indication of an A1M initiated pro-survival response was observed in kidney medulla when ^{177}Lu-octreotate was combined with A1M. Promising results were found for KIM-1, CDKN1A and S100A6 as biomarkers for ^{177}Lu-octreotate induced late kidney injury, and RBP4 as an early responding urinary biomarker. No clear protective effect of A1M on late radiation induced effects on kidneys were observed.

Keywords: Neuroendocrine tumours, kidney, bone marrow, proteomics, gene expression, apoptosis, biomarkers, radioprotector

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