Therapy with ^{177}Lu-octreotate – pharmacokinetics, dosimetry and kidney toxicity

AKADEMISK AVHANDLING

som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Waldemar Sjölander, Medicinaregatan 7, Göteborg onsdagen den 28 maj 2014 kl. 13.00

Av
Maria Larsson

Fakultetsopponent
Cecilia Hindorf
Strålningsfysik, Skånes universitetssjukhus, Lund

Avhandlingen är baserad på följande delarbeten:

I. Larsson M, Bernhardt P, Svensson J, Wängberg B, Ahlman H, Forssell-Aronsson E. Estimation of absorbed dose to the kidneys in patients after treatment with ^{177}Lu-octreotate: comparison between methods based on planar scintigraphy. EJNMMI Research, 2(1): 49, 2012.

II. Larsson M, Bernhardt P, Svensson J, Wängberg B, Forssell-Aronsson E. Mean absorbed dose to liver, spleen, bone marrow and metastases in patients with neuroendocrine tumours after treatment with ^{177}Lu-octreotate.

III. Schüler E, Larsson M, Parris T, Johansson M, Helou K, Forssell-Aronsson E. Biomarkers for radiation-induced renal toxicity following ^{177}Lu-octreotate administration in mice.

IV. Larsson M, Österlund A, Schüler E, Forssell-Aronsson E. Evaluation of DMSA and lysine as kidney protecting agents in normal mice injected with ^{111}In-octreotide.

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Maria Larsson
Department of Radiation Physics, Institute of Clinical Sciences at Sahlgrenska Academy, University of Gothenburg, SE−413 45 Gothenburg, Sweden

Abstract

^{177}Lu-octreotate is used for treatment of patients with somatostatin receptor expressing neuroendocrine tumors in some clinics using a standard schedule. Renal and bone marrow toxicity are the main limiting factors. Results are in general positive, but no optimization of treatment schedule has been performed and animal studies suggest that higher cure rate might be possible. To optimize the treatment and minimize toxicity, individual biodistribution and dosimetric data are needed. The biological effects on kidney tissue of ^{177}Lu must be studied, together with better ways to block the radionuclide retention in kidneys.

The aims of the project were to determine the pharmacokinetics in patients and to perform dosimetric estimations for kidneys, bone marrow, liver, spleen and tumors after ^{177}Lu-octreotate administration, to examine the radiobiological effects of ^{177}Lu in the kidneys in an animal model, and to study how kidney blocking agents lysine and dimercaptosuccinic acid (DMSA) affect the uptake of ^{111}In-octreotide in the kidneys.

The pharmacokinetics in patients who received 3.5-8 GBq ^{177}Lu-octreotate up to six times combined with amino acids for kidney blocking, were determined using planar scintigraphy and conjugate view method. Large individual variations were observed in absorbed dose per administered activity to all tissues, e.g. 0.33-2.4 Gy/GBq to kidneys, 0.047-0.54 Gy/GBq to liver, 0.28-4.4 Gy/GBq to spleen, and 0.010-0.093 Gy/GBq to bone marrow. Tumors received up to 20 Gy/GBq.

Long-term effects on the kidneys after injection of 0-150 MBq ^{177}Lu–octreotate were evaluated in normal mice. Effects on renal functions, e.g. glomerular filtration, reabsorption, and excretion were observed after high administered activity using ^{99m}Tc-DTPA–scintigraphy and urea level in blood. Results may be important for defining potential biomarkers for early prediction of late renal toxicity and impairment.

Blocking of the uptake of ^{111}In-octreotide in the kidneys was studied in normal mice using lysine and DMSA. The results indicated that the uptake of ^{111}In depends on the amount of lysine and DMSA administered, and the time for injection of respective agent. Lysine combined with DMSA did not give better blocking, probably due to less optimal time schedule.

In conclusion, this work demonstrates the importance and some possibilities to optimize treatment of patients with neuroendocrine tumors using ^{177}Lu-octreotate.

Keywords: PRRT, ^{177}Lu-octreotate, ^{111}In-octreotide, dosimetry, biokinetics, scintigraphy, conjugate view method, renal function, renal toxicity, lysine, DMSA, ^{99m}Tc-DTPA, ^{99m}Tc-DMSA

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