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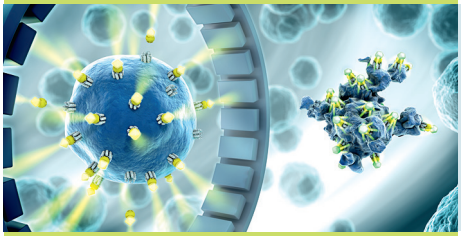
Abstract of Oral presentation



Higher Tumour Uptake and Residence Time Enhance the Therapeutic Index of the Radiolabeled Somatostatin Antagonists over the Agonists: The Influence of the Peptide Mass

Presenter

Dr. med. Guillaume Nicolas

Time

Wednesday, October 22, 2014
8:00 – 8:11 a.m.

Location

EANM Congress 2014
Gothenburg, Sweden
Room: G1/G2

ISTARD Session

Radionuclide Therapy & Dosimetry: ^{68}Ga and ^{64}Cu Labelled Peptides & Cell Dosimetry

Presentation number

OP605

Aim

Radiolabeled somatostatin (sst)-antagonists have shown higher uptake in sst receptor-expressing tumours than sst-agonists, possibly due to the higher number of available receptor binding sites. We aimed at evaluating the tumour residence time and therapeutic index of the sst2-antagonist OPS201, compared to the sst2-agonist DOTA-TATE in a theranostic approach.

Materials and Methods

OPS201 (DOTA-[Cpa-c(DCys-Aph(Hor)-DAph(Cbm)-Lys-Thr-Cys)-DTyr-NH2]) was radiolabeled with ^{68}Ga for PET imaging and with ^{177}Lu for therapy. ^{68}Ga-OPS201 and ^{177}Lu-OPS201 were compared head-to-head with ^{68}Ga-DOTA-TATE and ^{177}Lu-DOTA-TATE in terms of receptor affinity, tumour uptake, image contrast and pharmacokinetics. Pharmacokinetics, mass-dependence as well as PET and SPECT/CT imaging studies were performed with HEK-hsst2 xenografts in nude mice.

Results

^{68}Ga-OPS201 showed 1.3-fold higher tumour uptake compared to ^{68}Ga-DOTA-TATE, at 1h p.i. and higher tumour-to-liver and tumour-to-pancreas ratios (50.7 vs 41.3 and 50.7 vs 1.65, respectively). The maximal tumour uptake of ^{177}Lu-OPS201 and ^{177}Lu-DOTA-TATE was reached at 4h with the antagonist showing ~35% higher uptake. However, the kidney uptake was 1.8-fold higher with ^{177}Lu-OPS201 than with ^{177}Lu-DOTA-TATE. Both tracers accumulated in the sst-positive organs, such as pituitary, adrenals, stomach and pancreas.

The mean tumour residence time was 19.1h for ^{177}Lu-OPS201 and 7.5h for ^{177}Lu-DOTA-TATE, resulting in a 2.5 times higher tumour dose for the antagonist than for the agonist. The therapeutic index defined as tumour-to-kidney dose ratio was increased by 34% in favour of ^{177}Lu-OPS201. Importantly, injection of 10, 200 and 2000 pmol of ^{177}Lu-OPS201 caused no relevant saturation effect in the tumour (23.9, 24.9 and 18.8 %IA/g, respectively, at 4 h p.i., $p>0.05$) while the background significantly decreased. Consequently, the tumour-to-background ratios increased, (i.e. tumour-to-liver from 16 to 52 and 84 and tumour-to-bone marrow from 25 to 97 and 159, respectively, at 4 h p.i.). Nevertheless there was no significant change of the tumour-to-kidney ratio (3.9, 3.3 and 3.3, respectively). The tumour uptake of ^{177}Lu-DOTA-TATE, on the other hand, significantly decreased by 30% and 45%, when 200 or 2000 pmol were injected, respectively ($p<0.05$). Small-animal PET and SPECT/CT images reflected the biodistribution results.

Conclusion

The increased tumour uptake and prolonged residence time of ^{177}Lu-OPS201 as well as the favourable differential washout compared to ^{177}Lu-DOTA-TATE improve the therapeutic index. The mass-dependent study confirms the higher number of binding sites for the antagonists in vivo, compared to the agonist, providing important information that an optimized antagonist-mass will likely reduce liver and bone marrow toxicity.

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