[^{177}]Lu-pentixather: preclinical and first patient results with a highly promising CXCR4-directed endoradiotherapeutic agent

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Abstract

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Objectives Recent patient studies revealed superb CXCR4 targeting characteristics of [^{68}Ga]pentixafor for in vivo PET-quantification of CXCR4 expression. To exploit this innovative targeting concept for CXCR4-directed PRRT, [^{177}Lu]pentixather, a structural analog of [^{68}Ga]pentixafor, was developed and evaluated.

Methods CXCR4-affinities and receptor selectivities were determined using Jurkat and transiently transfected CHO-K1 cells. CXCR4-specific uptake of [^{177}Lu]pentixather was studied in various human cancer cell lines. Biodistribution was carried out in Daudi lymphoma bearing SCID mice. After pretherapeutic dosimetry (238 MBq), a first MM patient received 15.2 GBq [^{177}Lu]pentixather. Tracer kinetics 1-15d p.i. were assessed via SPECT/CT and planar scintigraphy. Therapy response was monitored via [^{18}F]FDG-PET/CT.

Results [^{177}Lu]pentixather binds to human CXCR4 with unchanged excellent affinity and selectivity. Its uptake in human cancer cells closely reflects the CXCR4 expression determined by FACS. In Daudi xenografts, [^{177}Lu]pentixather shows high CXCR4-specific accumulation and persistent retention (6.8±0.7, 3.3±0.4, 2.1±0.1 and 2.1±0.4 %iD/g at 6, 48 and 96h and 8d p.i.). In the MM patient, high uptake and long retention (>15d) of [^{177}Lu]pentixather in lesions lead to tumor doses of 10-58 Gy. Doses to kidney, liver and bone marrow were 8.5, 5.5 and 1.8 Gy. [^{18}F]FDG-PET/CT at 21d p.i. revealed partly complete, partly partial metabolic response.

Conclusions [^{177}Lu]pentixather shows outstanding CXCR4-targeting properties both in vitro and in vivo. Adequate clearance kinetics and tumor retention lead to the deposition of high therapeutic doses in tumors with low doses to non-target tissues. The promising therapy response achieved with [^{177}Lu]pentixather-PRRT warrants the further evaluation of pentixather labeled with therapeutic radioisotopes in a larger cohort of patients.