Comparative Study with Two Folic Acid Radioconjugates Showing Differences in Anti-Tumor Efficacy and Kidney Dose Burden

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Introduction: The folate receptor (FR) is overexpressed in various cancer types and shows a high affinity to the vitamin folic acid [1]. Therefore it is reasonable to target the FR with folic acid radio-conjugates for cancer diagnosis and therapy [2]. However, a drawback so far was the high kidney uptake due to renal FR expression. In view of a therapeutic application using particle-emitting radiation (e.g. ^{177}Lu) the risk of nephrotoxic side effects arises. To overcome this problem, we recently developed a folate conjugate containing an albumin-binder (cm09) which resulted in a prolonged circulation time and consequently increased tumor-to-kidney ratio [3].
Aims: The aim of this study was to compare the therapeutic efficacy and potential kidney toxicity of a conventional DOTA-folic acid conjugate (EC0800) and a novel DOTA-folate conjugate containing an albumin-binder (cm09) radiolabeled with the therapeutic isotope ^{177}Lu.
Methods: The biodistribution of ^{177}Lu-EC0800 and ^{177}Lu-cm09 was evaluated by SPECT/CT imaging of KB (FR+) tumor bearing mice. In a therapy study in KB xenografted mice the anti-tumor efficacy of ^{177}Lu-EC0800 (20 MBq) and ^{177}Lu-cm09 (20 MBq) was compared. Radionephrotoxicity after the administration of 20 MBq of ^{177}Lu-EC0800 or ^{177}Lu-cm09, resulting in estimated absorbed kidney doses of ~100 Gy and ~70 Gy, respectively, was investigated in a long-term study in nude mice over 8 months.
Results: The SPECT/CT images revealed a tumor-to-kidney ratio of ~0.1 for ^{177}Lu-EC0800 and ~1 for ^{177}Lu-cm09. The increased tumor uptake of ^{177}Lu-cm09 improved the therapeutic efficacy and resulted in complete tumor remission in 4 out of 5 mice which is superior to a treatment with ^{177}Lu-EC0800 where the tumor growth was not considerably reduced compared to control animals. The long-term study investigating the kidney toxicity revealed a 3-fold higher creatinine and a 1.3-fold higher blood urea nitrogen plasma value at terminal state for mice administered with ^{177}Lu-EC0800 compared to animals injected with ^{177}Lu-cm09. The average survival was reduced to 164 days in the group treated with ^{177}Lu-EC0800 whereas more than 50% of the animals were still alive at the end of the study (8 months) in the group injected with ^{177}Lu-cm09.
Conclusion: Our results demonstrate that the integration of an albumin-binding entity into the folate conjugate is a strategy to improve the anti-tumor efficacy and to prevent severe nephrotoxic side effects during FR-targeted radionuclide therapy. Therefore, ^{177}Lu-cm09 is the most favorable radiofolate ever tested for therapy of FR-positive tumors in mice. Therefore, this folic acid radioconjugate will be tested in more detail in future pre-clinical therapy studies.

Keywords: Folate receptor, folic acid radioconjugate, albumin-binder, radionuclide tumor therapy, nephrotoxicity.

References:
[1] Parker N, Turk MJ, Westrick E. Anal Biochem 2005, 338: 284-93.
[2] Müller C. Curr Pharm Des 2012, 18: 1058-83.
[3] Müller C, Struthers H, Winiger C. J Nucl Med 2013, 54: 124-31.