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Pharmacokinetic variability of in vivo generated 213Bi and vector labeled 225Ac in murine cancer models

Since the approval of Xofigo® against metastatic castrated resistant prostate cancer there has been a growing interest in α-particle emitting radiopharmaceutical therapy. Actinium-225 (T1/2=10days) is one α-particle emitter of interest with a total emission of four α-particles in its decay chain (221Fr: T1/2=4.9min; 217At: T1/2=32.3ms; 213Bi: T1/2=45.6min; 213Po: T1/2=4.2μs). Using a chelator makes it possible to label 225Ac with different vectors, which can be used against different cancers. The bond between the chelator and the 225Ac atom is relatively weak (~10eV) and is broken when the α-particle is emitted from the 225Ac atom due to the high recoil energy (~100keV). Consequently the 225Ac decay daughters are not bound to the vector and are free to relocate. Depending on the vector's pharmacokinetics there will be different normal tissue uptake of vector labeled 225Ac. This suggests that depending on vector type the unbound decay daughters are present in different tissues at different concentrations, able to redistribute within the *in vivo* system.

In this study we investigated vector labeled 225Ac and unbound 213Bi, which has the longest half-life of the 225Ac decay daughters and is known to relocate and accumulate in the kidneys. We compared the pharmacokinetics of *in vivo* generated 213Bi and vector labeled 225Ac for three different vectors in murine cancer models (7.16.4 antibodies against breast cancer; anti-VLA-4 antibodies against melanoma; PSMA-targeted small molecule against castrate resistant prostate cancer). The mice were injected i.v. by the tail vein with the 225Ac labeled vectors and sacrificed at specific times after administration. The organs and tissues of interest were blood, liver, kidneys and spleen, which were harvested and directly measured in a gamma well counter in 1 minute intervals for up to 5 hours. The measured data was fitted with a bi-exponential function to determine the amount of unbound 213Bi and vector labeled 225Ac present in the different tissues.

All murine models showed accumulation of unbound 213Bi in the kidneys, accounting for ~60% of the mean absorbed dose to the kidneys. The main supplier of the unbound 213Bi to the kidneys for the small molecule and the anti-VLA-4 was the liver, and for the 7.16.4 the blood. In addition, vector labeled 225Ac has shown to be uniformly distributed for 7.16.4, and non-uniform for anti-VLA-4, PSMA-targeting small molecule and unbound 213Bi within the kidneys, suggesting the need for small scale dosimetry for an accurate absorbed dose calculation.

This study shows that the delivery of 225Ac using different vectors changes the pharmacokinetics and supply of unbound 213Bi to the kidneys. This is important for translation to clinical studies as in vivo imaging of 225Ac does not distinguish between the vector labeled 225Ac and unbound 213Bi, resulting in an possible overestimation of the absorbed dose to the kidneys and underestimation of the supplying tissues.

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