Estimating the impact of ^{212}Bi demetallation from administration of ^{212}Pb-rhPSMA-10.1 and the risk of significant Kidney Absorbed Radiation Doses

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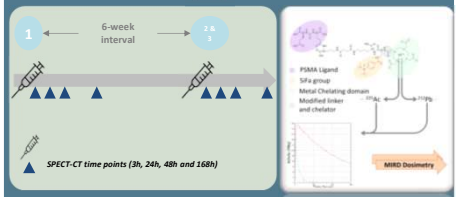
Background & Objectives

- First long-term safety data with a ^{212}Pb-labelled radiopharmaceutical reported significant renal adverse events at two years of follow-up, with 17.1% ≥G3 renal AEs.
- Demetallation and redistribution of ^{212}Bi from parent ^{212}Pb RLT may offer a potential explanation.
- A simulated novel PSMA-targeted RLT (^{212}Pb-rhPSMA-10.1) was modelled to investigate the potential impact of this demetallation phenomenon.

This modelling uses dosimetry data from the Phase 1 portion of an ongoing Phase 1/2 study of ^{177}Lu-rhPSMA-10.1 in men with mCRPC[1], adjusted to account for the physical half-life of ^{212}Pb and using organ amplification factors from a pre-clinical experiment on daughter redistribution from Ziltsmann-Kolbe *et al*.

Methods

N= 13 N= 34



- Dosimetry data acquired using 4 SPECT/CT timepoints was used to generate simulated time-activity curves for organs-at-risk including the kidney for a simulated ^{212}Pb-rhPSMA-10.1 and ^{225}Ac-rhPSMA-10.1 RLT substituting the physical half-life and decay properties of ^{177}Lu with ^{212}Pb. Absorbed doses were calculated using MIRD methodology.
- The impact of daughter radionuclide translocation was modeled using various rates of demetallation based on published non-clinical data for ^{225}Ac[2], using the implication that daughter redistribution from RLT in plasma circulation is the dominant factor.
- A clinical dosing regimen of 6 x 200MBq of ^{212}Pb-rhPSMA-10.1 was simulated, consistent with ongoing ^{212}Pb clinical trials.

Results

- Dosimetry data from the phase 1 study was used in conjunction with organ amplification factors from non-clinical experiments to generate estimates for kidney doses resulting from daughter redistribution.
- **Figure 1** shows the estimated number of free bismuth atoms generated into plasma during circulation over time for various demetallation rates of 200MBq of ^{212}Pb and compared to 8MBq of ^{225}Ac, assuming equivalent biological plasma half-life measured from ^{177}Lu-rhPSMA-10.1.

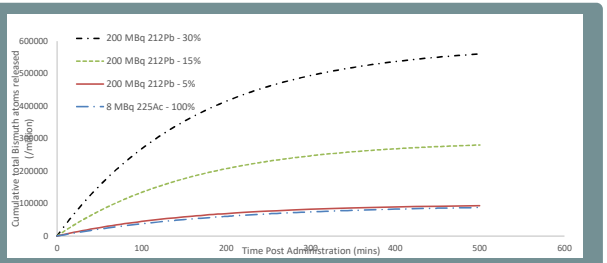


Figure 1 Number of free bismuth atoms generated into plasma circulation – approx. 2hr biological plasma half-life.

Determining the Impact of plasma half-life, physical half-life and demetallation rate

Figure 2 shows estimates for total kidney dose across 6 cycles of 200MBq of ^{212}Pb-rhPSMA-10.1.

Normal Organs

Due to the preferential accumulation of free ^{212}Bi in kidneys, as is suggested by ICRP report 137[3], this generation of free bismuth has the potential to lead to very high renal absorbed doses. The accumulation in other normal organs including salivary glands is unknown, but non-clinical results indicate similar preferential uptake.

Demetallation

Rates of demetallation are hard to ascertain with high degrees of certainty. Depending on the source, rates have been reported from as low as 5% from in-vitro experiments in certain lead-specific chelates to as high as 36%.[4,5,6,7,8]

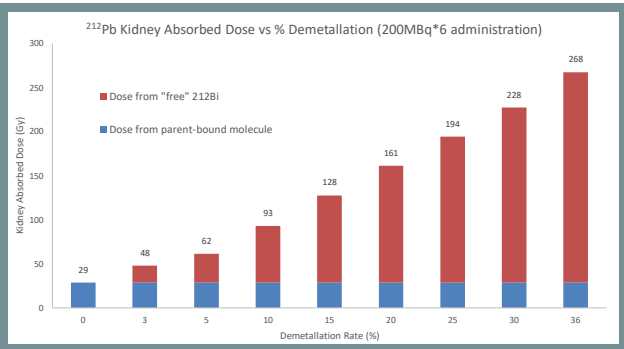


Figure 2 ^{212}Pb-rhPSMA-10.1 Kidney absorbed doses vs % demetallation (200MBq x 6 administrations).

Conclusions & Discussion

- Due to the high injected radioactivity per cycle necessitated by a short physical half-life, ^{212}Pb-rhPSMA-10.1 would undergo a significant proportion of total decays in the first few hours after injection when plasma radioactivity is highest thus releasing pronounced levels of free ^{212}Bi into circulation.
- The presence of free ^{212}Bi has been confirmed in Phase 0 studies involving ^{212}Pb-labelled RLT[9].
- The total amount of free ^{212}Bi released is highly dependent on the "demetallation rate" of the parent radioligand.
- Due to preferential uptake of free ^{212}Bi into normal organs such as the kidneys, this may represent a significant risk of inducing renal toxicity as has been detected in recent long-term safety data with ^{212}Pb-labelled RLT. This toxicity may not present for months or even years after dosing.
- Given the risk, methods should be developed to estimate the rate of demetallation in humans and patient life expectancy in clinical trials should be considered.
- It is noted that although daughter recoil for ^{225}Ac can be assumed to be 100% the impact on generation of ^{213}Bi and kidney accumulation is reduced by the lower starting injected activity, rapid systemic clearance and much slower physical half-life. Multiple daughter decays then from parent compound trapped in tumor have an overall positive benefit to the therapeutic ratio and do not contribute to redistribution according to pre-clinical experimentation.

Representative Time Activity Curve Adjustments

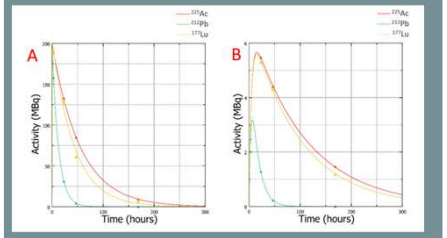


Figure 3 Example tumor and kidney time–activity curves with best-fits from a single patient simulating different radionuclides based on different physical half-lives but otherwise identical pharmacokinetics.

Panel A shows kidney TACs, Panel B shows tumor TACs

References

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