Title

More Bang For Your Becquerel: A Novel Approach to "Dosing" in ^{177}Lu-PSMA Radioligand Therapy

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Keywords / Topics

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Aim

The currently licenced ^{177}Lu-PSMA Radioligand Therapy (RLT) follows a 6-cycle dosing regimen with fixed injected radioactivity at fixed intervals. ^{177}Lu-rhPSMA-10.1, a novel PSMA RLT, is under investigation in a Phase 1/2 trial, of which the Phase 1 component is now complete. In the Phase 1 component, PSMA-positive mCRPC patients experiencing disease progression following standard-of-care treatment were enrolled and underwent up to 3 cycles of 5.55 or 7.40 GBq ^{177}Lu-rhPSMA-10.1 at 6-week intervals. Multi-bed SPECT/CT was conducted at 3-, 24-, 48-, and 168-hours post-administration to calculate tumour and organ absorbed doses.

Dosimetry results from the Phase 1 component of this study showed favourable normal organ doses that were broadly consistent across cycles as depicted in Figure 1. However, tumour absorbed dose coefficients (Gy/GBq) peaked at cycle 1 and declined thereafter (Figure 2). This suggests that administering a higher proportion of radioactivity in early cycles (i.e. "front-loading") has the potential to increase cumulative tumour absorbed dose, without increasing normal organ doses.

The aim of this work was to model the impact of front-loading administered radioactivity on absorbed tumour dose, with a view to informing Phase 2 dosing strategies.

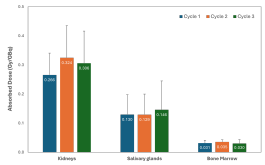

Fig. 1: Mean absorbed doses of 177Lu-rhPSMA-10.1 in Kidneys, Salivary Glands and Bone Marrow for each cycle of treatment. Organ absorbed dose appears to be independent of cycle number

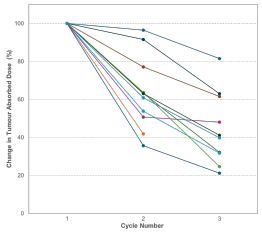

Fig. 2: Mean percentage change in tumour absorbed dose relative to Cycle 1 for each patient who received at least two cycles of treatment.

Materials and Methods

Using Phase 1 dosimetry data as a baseline, cumulative tumour absorbed doses were modelled for two dosing regimens that incorporated various degrees of "front-loading" of radioactivity. For this exercise, cumulative administered radioactivity was selected based on a 23 Gy absorbed dose limit to the kidneys and the kidney absorbed dose values from Phase 1. Dosing regimen 1 considered the scenario of administering 10 GBq in cycles 1 and 2, followed by five cycles of 7.4 GBq (cumulative administered activity of 57 GBq). Dosing Regimen 2 considered administering 14.8 GBq in cycles 1 and 2, followed by four cycles of 7.4 GBq with all cycles at 6 weekly intervals (cumulative administered activity of 59.2 GBq). These regimens were compared against a flat dosing regimen fractionating 59.2 GBq evenly across eight cycles. A visual depiction of these dosing regimens is shown in Figure 3.

To accurately model the expected cumulative absorbed tumour dose for each of these dosing regimens, the reduction in tumour dose with cycle, observed in phase 1, was extrapolated out to 8 cycles. For simplicity, it was assumed that the tumour dose continued to reduce with cycle number and that the level of reduction was independent of the initial administered radioactivity.

Cumulative tumour doses were calculated for each of these 3 dosing regimens based on a common starting absorbed dose coefficient of 4 Gy/GBq. When quantitatively comparing the cumulative tumour doses, adjustments were made accounting for the minor differences in total administered radioactivity in each dosing regimen.

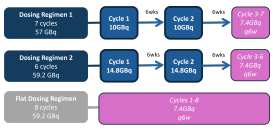

Fig. 3: A visual depiction of the selected dosing regimens for which cumulative

absorbed doses were modelled. The total number of cycles, cumulative radioactivity and the "front-loading" aspect of each dosing regimen is shown.

Results

Modelled cumulative organ absorbed doses remained below the external beam radiotherapy derived dose limits for all dosing regimens explored. Figure 4 shows the modelled relationship between cycle number and tumour absorbed dose extrapolated out to 8 cycles of treatment. This relationship was based upon the observed reduction in Phase 1 across 3 cycles of treatment. The reduction in tumour dose with cycle was shown to follow a power-law trend of the form $y=An^{-0.74}$, with y being tumour absorbed dose (Gy), A being the baseline tumour absorbed dose at cycle 1 (Gy) and n being the integer cycle number.

Figure 5 shows the temporal cumulative tumour absorbed dose for the three modelled dosing regimens and the visual impact of "front-loading". The rate at which absorbed dose is accumulated for each cycle is based on the observed kinetics of ^{177}Lu-rhPSMA-10.1 in tumour. With a starting absorbed dose coefficient of 4 Gy/GBq, the cumulative absorbed tumour doses for dosing regimens 1 and 2 were found to be 113 Gy and 137 Gy respectively. For a flat dosing regimen, the tumour absorbed dose was found to be 102 Gy. When adjusting for equivalent cumulative radioactivity, Regimen 1 increased tumour absorbed dose by 15%, while Regimen 2 achieved a 34% increase compared to a flat dosing regimen.

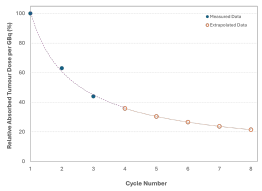

Fig. 4: The predicted relationship between cycle number and tumour absorbed dose for up to 8 cycles of treatment. The solid dots show the measured data from Phase 1 and the orange circles show the predicted values based on an extrapolated fit from the first 3 datapoints. The reduction in tumour dose with cycle follows a power-law trend of the form

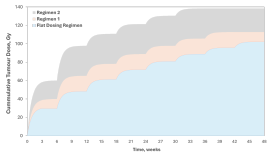

Fig. 5: Temporal cumulative tumour absorbed dose curves for the three modelled dosing regimens. All curves start from a fixed cycle 1 tumour absorbed dose coefficient of 4 Gy/GBq. The rate at which absorbed dose is accumulated for each cycle is based on the observed kinetics of 177Lu-rhPSMA-10.1 in tumour.

y=An^(-0.74), with y being tumour absorbed dose (Gy), A being the baseline tumour absorbed dose at cycle 1 (Gy) and n being the integer cycle number.

Conclusion

Front-loading administered radioactivity in PSMA targeted RLT appears to improve cumulative tumour absorbed dose compared to a flat dosing regimen, without any proportional increase in normal organ dose or administered radioactivity. This approach exploits the therapeutic index being at its peak during early cycles and the improvement correlates with the proportion of activity front-loaded. However, this approach must be carefully considered in the context of potential increased toxicity risks.

As a result of this work, the Phase 2 component of this study will compare the efficacy and safety of this "font-loading" dosing strategy with a fixed per-cycle activity approach, where the interval between the first 3 cycles is shortened to 3 weeks, to explore PSMA RLT dose optimisation with ^{177}Lu-rhPSMA-10.1.

References

None

Scott Nathaniel

Disclosure - 1 All clinical nuclear medicine image or data shown and used in the submitted abstract were obtained based on a successful EARL PET/CT | PET/MR accreditation:

Disclosure - 2 I or one of my co-authors hold a position as an employee, consultant, assessor or advisor for a pharmaceutical, device or biotechnology company. If yes, please specify name/position/company:

All authors are employees of, and hold stock grants/options in Blue Earth Therapeutics.

Disclosure - 3 I or one of my co-authors receive support from a pharmaceutical, device or biotechnology company. If yes, please specify name/position/company/which project and whether support is in kind or monetary:

Nothing to declare

Disclosure - 4 I or one of my co-authors hold property rights/patents for (radio)pharmaceuticals, medical devices or medical consulting firms. If yes, please specify name/position/company:

Daniel Stevens, Chief Medical Officer at Blue Earth Therapeutics

Disclosure - 5 I or one of my co-authors have written articles for (radio)pharmaceutical, medical device, biotechnology or consulting companies during the last 5 years. If yes, please specify name/position/company/article/ journal and co-authors:

Nothing to declare