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Optimization of dosimetry in alphatherapy: microlocalisation of 223Ra in mouse models of metastasis from prostate cancer and renal cell carcinoma.

Background: In nuclear medicine, beyond providing a starting administered activity for clinical studies, dosimetry has an important role in determining optimal treatment regimens and to identify patients in whom treatment is likely to have little benefit. For alpha-emitter radiopharmaceuticals, a personalized dosimetry is challenging because of the short range of alpha-particles. So, in order to better assess the relationship between dose and biological effects, it is crucial to characterize the distribution of alpha-emitter radiopharmaceuticals at the microscopic level, as recommended by the MIRD pamphlet 22. This is then the aim of this work which focused on 223Ra, the first alpha-emitter to be use in clinical routine.
Methods: Three animal models were developed: a control model with healthy mice, a diseased model with osteoblastic/osteolytic metastasis and a diseased model with osteolytic metastasis. The metastasis cells were selected to modelize the osteoblastic lesions generated by the prostate cancer which are treated in clinical routine and the osteolytic lesions generated by the renal cell carcinoma which are the subject of a new clinical trial.
Mice were dosed with 223Ra (30 kBq, n=5-6 per experimentation group) and killed at 15 min, 4, 24, 48 and 96 hours for prompt dissection. Tissue activity was assayed by gamma counting for several organs in order to determine the macroscopic biodistribution of 223Ra.
Both tibias of diseased mice were then used to achieve fresh frozen, undecalcified tissue sections. Microdistribution analysis was performed using a digital autoradiographic system. Autoradiographies of both tibias for each euthanasia time were acquired.
Results: Differences of uptake between both types of metastases were studied. Results showed a rapid renal clearance and an important uptake in the bones from 15 min for each model. No significant difference was observed at a macroscopic scale between the healthy tibia and the diseased tibia in each mouse of the metastasis models.
The autoradiographies showed differences of localizations of 223Ra uptakes between the healthy tibia and the diseased one. In both tibias, 223Ra is homogeneously distributed in the cortical and trabecular bone. Moreover, there is an important uptake of 223Ra in the growth plate, in both tibias. This uptake is higher in the healthy tibias than in the diseased ones. 223Ra does not localize directly to the tumor, regardless of type. Instead, activity accumulates at the apposite bone surface surrounding the lesion.
The differences of 223Ra repartition between the healthy tibia and the diseased tibia and between metastasis due to prostate cancer and metastasis due to renal cell carcinoma have been quantified. Finally, a biokinetic model was deduced for each metastasis model thanks to the images at different times.
Conclusion: These data will have important implications for the design and interpretation of clinical studies evaluating treatment with 223Ra, to guide clinical application with adapted dosing, and ultimately for more effective application in human. This work conducted prior to clinical trial is crucial and will allow us to develop a methodology for clinical routine and for other alpha-emitter radiopharmaceuticals.

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