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Application of a trabecular and cellular model of bone marrow dosimetry for targeted 223Ra therapy

Objectives: There is growing awareness in the radiopharmaceutical therapy community that dosimetry-based treatment planning is a highly desirable objective, potentially leading to greater efficacy and safety for patients. Ra-223, a bone-seeking radionuclide, has been used extensively as a therapeutic for bone metastases of prostate cancer. However, dosage follows a strict regimen based on mass and attempts to understand the dosimetry of Ra-223 have had limited success, in part due to the low count rate of emissions, the disseminated and dynamic natures of the disease and organ at risk, the multiplicity of radioactive daughters as well as the short range and high LET of the alpha-particles, making it the most difficult dosimetry of any radiopharmaceutical to date. We propose to take the next step in Ra-223 bone marrow dosimetry by combining (a) small scale geometrical trabecular and cellular model, (b) detailed alpha-particle absorbed fractions from human cadaver studies, (c) high resolution autoradiography of resected mouse femurs and (d) clinical pharmacokinetics.

Methods: Human pharmacokinetics, time-integrated activity (TIA) and whole organ absorbed dose values, including blood and bone were taken from the literature for patients treated with 100 kBq/kg. The time integrated activity (number of decays) in the bone was apportioned to the bone matrix, endosteal layer and marrows cavities based on murine imaging data obtained using high resolution storage phosphor autoradiography as well as alpha-Camera images of resected mouse femurs sectioned on a cryostat. These TIAs were converted to absorbed dose to the endosteal layer, the bone matrix and the marrow as a function of marrow distance from bone surface different depths using absorbed fractions obtained from human cadaver data from a previous publication. The trabecular and cellular model was used to obtain cell dose histograms.

Results: The activity and therefore TIA was primarily concentrated in the endosteal layer. Consequently, due to the short range of the emitters, the absorbed dose was predominantly deposited near the bone surface, either in the endosteal layer or the shallow marrow. The dose cell histograms results were used to plot the percentage of marrow cells that received less than a potentially toxic dose (2 or 4 Gy) as a function of the average absorbed dose. The results show a heterogeneous distribution of cellular absorbed dose, strongly dependent on the position of the cell within the marrow cavity, such that increasing the average marrow cavity absorbed dose, or equivalently, increasing the administered activity results in only a small increase in number of marrow cell with cytotoxic dose.

Conclusion: Small scale modeling has been successful at interpreting localized dose in other organs, such as the kidneys and salivary glands. The dynamic and systemic nature of the bone marrow make it a more complex organ at risk, yet the use of small scale modeling offers insight into the lack of expected bone marrow toxicity as calculated from average absorbed dose and is a significant step towards reconciling dosimetry and toxicity.

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