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Mechanistic modelling of Radium-223 treatment of bone metastases

Despite the effectiveness of 223RaCl2 for treating castration resistant prostate patients with symptomatic bone metastatic disease, its mechanisms of action are still unclear. Even established dosimetric approaches differ considerably in their conclusions. With the rapid growth in the interest of alpha-targeted radionuclide approaches, in silico tumour models bring a new perspective to this as they can quantitatively simulate the interaction of α-particles with the predicted target(s). Here, we investigated three different mathematical models of tumour growth that take into account the radiation effect of Radium-223 treatments and compare the results to existing clinical data from the ALSYMPCA trial [1].

The well-established Gompertz growth model was applied to simulate metastatic tumour burden. Based on published measurements of Radium-223 uptake, we have incorporated the radiation effect of α-particles into the model and investigated three radium distribution scenarios - uniform exposure, exposure of only an outer layer, and exposure of a constant volume of the tumour. For each scenario, the times for various tumour stages to progress to the first symptomatic skeletal event were calculated.

Uniform and outer-layer exposure scenarios showed very poor agreement with the Kaplan-Meier patient curves from clinical data. However, the constant volume effect predicted very similar outcomes to the observed clinical results, suggesting that only relatively small fractions of the cell population see damage from Radium-223.

The commonly-used assumption of uniform Radium-223 distribution does not accurately reflect clinical responses. The suggestion that only a sub-population of the tumour might be affected by Radium-223 shows that there is a pressing need to further study the tumour and drug kinetics in order to schedule more effective treatments in the future. Given the clinical efficacy, even under these conditions additional preclinical studies are also required to test different radium distributions and their biological efficacy. This will ultimately aid in the design and implementation of future alpha-radionuclide targeted therapies.

[1] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-223.

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