Contribution ID: **59** Type: **not specified**

Sensitivity to a poly(ADP-ribose) polymerase 1 (PARP-1) targeting alpha particle therapeutic in neuroblastoma is characterized by increased relative biological effectiveness (RBE) compared to gamma irradiation

Introduction:
Neuroblastoma is the most common extracranial solid malignancy in childhood, with only up to 50% 5-year survival in high-risk cases. Neuroblastoma overexpresses the nuclear enzyme PARP-1, which can be targeted for specific delivery of alpha particles to DNA using an astatine-211 radiolabeled small molecule PARP-1 inhibitor called [211At]MM4.

Methods:
Using a panel of twenty human neuroblastoma cell lines previously screened *in vitro* for sensitivity to [211At]MM4, IMR5 and NLF were chosen as examples of a sensitive and a resistant cell line to assess RBE.
Next, radiopharmacologic properties of the two cell lines were characterized by performing radioligand saturation binding assays to measure the maximum number of binding sites for [211At]MM4 and to directly measure bound [211At]MM4.
For self-dose calculation, the geometric dimensions of the cells were measured by immunofluorescence microscopy. For cross-dose calculation, the cellular arrangements in the sensitivity screening condition was modeled with hexagonal circle packing.
Then, Monte Carlo simulation was performed with MIRDcell v2.0 to calculate the total radiation dose to the cell nucleus from astatine-211 and its daughters at 50% cell kill (D50). RBE against gamma rays was calculated using D50 for gamma irradiation with a cesium-137 source.
Finally, mouse tumor xenograft models were imaged with 18F-fluorthanatrace (FTT), a [211At]MM4 analog for positron emission tomography (PET), for correlative *in vivo* dosimetry.

Results:
In IMR5 cells, [211At]MM4 demonstrated 3 and 9 orders of magnitude greater cytotoxic potency compared to free 211At and its non-radioactive analog respectively, whereas the differences were 2 and 8 orders of magnitude in NLF.
IMR5 had more PARP-1 binding sites compared to NLF (Bmax= 2.3 vs 1.4 million sites/cell), but similar binding affinity of [211At]MM4 was seen (IMR5: Kd=2.7 nM, NLF: Kd=2.4 nM).
The nuclear and cell radii were measured at 6 μm and 8 μm respectively in IMR5, and 9 μm and 12 μm in NLF. The mean distance between adjacent cells was determined to be 86 μm.
The D50 in IMR5 was 0.076 Gy for [211At]MM4, 0.34 Gy for free 211At, and 0.7 Gy for gamma irradiation, yielding RBE of 9.2 for [211At]MM4. The D50 in NLF was 3.8 Gy for [211At]MM4, 4.6 Gy for 211At, and 3.6 Gy for gamma irradiation, yielding RBE of 1.0.
Using 18F-FTT mouse PET images, the tumor radiation dose from [211At]MM4 based on tumor size and amount of [211At]MM4 administered were modelled.

Conclusion:
Delivery of an alpha emitter directly to the neuroblastoma nuclear DNA by the astatinated PARP-1 inhibitor [211At]MM4 results in variable levels of enhanced cytotoxicity. Sensitivity to [211At]MM4 is characterized by increased RBE against gamma irradiation, warranting investigation of the underlying biological factors. Tumor dosimetry results from mouse models can be applied to future *in vivo* therapy experiments with [211At]MM4 for correlation between tumor dose and therapeutic efficacy.

Funding Agency

National Institutes of Health

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Presentation Type

Contributed Oral

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