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Neutron Capture Enhanced Particle Therapy (NCEPT): In vitro proof of concept

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Introduction

Neutron Capture Enhanced Particle Therapy (NCEPT) is a novel adjunct to proton and heavy ion therapy, which enhances the radiation dose delivered to a tumour relative to surrounding healthy tissue by capturing thermal neutrons produced during ion irradiation. NCEPT utilises ^{10}B and ^{157}Gd-enriched tumour-specific neutron capture agents presently approved or in development for neutron capture therapy. NCEPT improves tumour control by increasing the dose to the target volume, while reducing the normal tissue complication probability by reducing the primary radiation dose, hence reducing the radiation dose to normal tissue. Additionally, NCEPT can target nearby satellite lesions outside of the primary treatment volumes with a therapeutic dose. In this work, we report the outcome of three successful rounds of in vitro experiments, conducted at the National Institutes for Quantum and Radiological Science and Technology (NIRS, QST) Heavy Ion Beam research facility, which have provided the first experimental proof of concept for NCEPT.

Methodology

Experiments were conducted at the Heavy Ion Medical Accelerator in Chiba (HIMAC), Japan in July 2018, February 2019 and February 2020. T98G (human glioblastoma) cells were cultured in T25 flasks and inserted into a 300 mm cube of PMMA, such that the cell layer was positioned at the middle of the depth range of the spread-out Bragg peak and normal to the the beam. Two flasks were located within the planned target volume, with a further two flasks laterally offset such that they were just outside of the target volume (one on the left and one on the right). The cells were then irradiated with polyenergetic beams of either ^{4}He or ^{12}C (100 mm $\times$ 100 mm $\times$ 60 mm SOBPs).

Flasks placed in the two middle positions received a heavy ion dose of 0 to 10 Gy, with or without pre-irradiation treatment with the neutron capture agents (NCAs) ^{10}B-BPA and ^{157}Gd-TPP-DOTA. The two flasks outside of the primary target volume were used evaluate the effect of NCEPT on satellite lesions (since the neutron field extends well beyond the target volume). The effects of irradiation on cell proliferation and survival with and without the NCAs, both inside and outside the target volume, were quantified using the Resazurin Cell Viability Assay and clonogenic assay.

Additionally, the effect of NCA concentration on the efficacy of NCEPT in-beam (in the middle of the SOBP), both for ^{10}B-BPA and ^{157}Gd-TPP-DOTA was assessed for ^{4}He or ^{12}C ion beams, with a fixed radiation dose of 3 Gy.

Results

Dose responses obtained via clonogenic assay for both NCAs and ion species are shown in Figure 1(a). A progressive reduction of cell viability in response to dose escalation (0 to 10 Gy) can be observed. A dramatic reduction in cell viability is observed at doses exceeding 2 Gy. The dose at which 50\% reduction in cell mass is achieved (IC50) was also estimated for carbon and helium ion therapy, with and without the presence of NCAs. To achieve a 50\% reduction in the mass of viable cells treated with carbon and helium ions alone, 3.1$\pm$0.1˜Gy and 3.54$\pm$0.4 Gy are required, respectively. The addition of ^{10}B-BPA and ^{157}Gd-TPP-DOTA reduces the IC50 dose by 42\% and 68\%, respectively.

Concentration response results are shown in Figure 1(b). At a primary carbon and helium ion dose of 3 Gy, 100-250 uM concentrations of both NCAs are sufficient to obtain a reduction in viable cell mass comparable to 8 Gy of carbon and 10 Gy of helium ion irradiation in the absence of the NCA. Concentrations in excess of approximately 10 uM are sufficient to obtain a measurable decrease in viable cell mass.

Out-of-field dose responses are shown in Figure 1(c). A very strong (and approximately linear) response to escalating primary ion dose is observed out-of-field with both ion species and NCAs. Without the presence of the NCA, the impact on cell viability outside of the primary treatment volume is minimal (less than 20% reduction in viable cell mass at 10 Gy primary dose, compared to more than than 95% reduction in the presence of NCAs.

Conclusion

The effectiveness of NCEPT on cell cultures inside and adjacent to the target volume has been evaluated. NCEPT achieves substantial reductions in T98g cell viability with both boron and gadolinium-based neutron capture agents in the target volume compared to untreated control cell cultures subjected to an equivalent primary radiation dose. Although cells outside of the primary target volume receive little dose from the heavy ion beam, the addition of neutron capture agents to these cells also results in a substantial reduction in cancer cell viability. This is due to the extension of the thermal neutron field beyond the target volume. The next steps for NCEPT include (1) evaluating NCEPT in vitro with proton therapy and (2) in vivo evaluation of NCEPT for heavy ions and protons using both neutron capture agents.

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