

KONDO-1: Radiation Biology on BNCT - what we have known and don't know –

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Boron Neutron Capture therapy (BNCT) is a form of tumor-selective particle radiation therapy consisting of two components. First, a boron-10 (^{10}B)-containing compound is administered to the patient to obtain a sufficient and high tumor ^{10}B concentration relative to surrounding normal tissue. Second, the tumor is irradiated with epithermal neutrons which become thermalized at depth in tissues. The resulting short range (5-9 μm) of the α and ^7Li particles, released from the $^{10}\text{B}(\text{n},\alpha)^7\text{Li}$ neutron capture reaction are high linear energy transfer (LET) radiation with 1.47 MeV and 0.84 MeV respectively and play the most critical role in the biological effects in BNCT. Clinically, two boron compounds, L-p-boronophenylalanine (BPA), an analog of an essential amino acid, phenylalanine, and sodium borocaptate (BSH) have been used. Their mechanisms of accumulation in tumor are different. BSH accumulate passive and diffuse way in disrupted blood brain barrier in the tumor, while BPA accumulate in tumor by active uptake of amino acid.

High LET radiation is known to produce complex DNA double strand breaks (DSBs) which remain unrepaired relative to low LET radiation. We indicated DSBs produced by α and ^7Li particles, released from the $^{10}\text{B}(\text{n},\alpha)^7\text{Li}$ neutron capture reaction also remain unrepaired in brain tumor with orthotopic model, while gamma-ray induced DSBs disappeared in 24 hrs. Therefore, the remaining DSBs would devote to the biological effects of BNCT. In terms of DNA repair pathway, DSBs induced by BNCT are partially repaired by DNA ligase IV, a key player of non-homologous end joining DSB repair pathway.

Even after tumor-selective BNCT, recurrence was inevitable not only in glioblastoma, the most miserable tumor but also head and neck cancers. Reasons for recurrence after BNCT have not been fully elucidated, but they may reflect tumor characteristics. In fact, we've found cerebrospinal fluid dissemination, frequent cause of death with better local control after BNCT occurs more frequently in the small cell subtype of IDH1R132H mutation-negative glioblastoma. Another conceivable reason may be the heterogeneous distribution of BPA in the tumor. In our preliminary study, BPA accumulates in 2-4 times larger proportion of glioma stem like cells which are resistant to usual chemo-radiation therapy than differentiated glioma cells in vitro and in vivo. Glioma stem cells may be targeted by BPA-BNCT. Therefore, the resistant mechanism should be unique and be elucidated to overcome.