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Investigating the potential of 212Pb-rituximab as an alpha-radioimmunotherapy for the treatment of Non-Hodgkin's Lymphoma

Background: Non-Hodgkin's Lymphoma (NHL) is the 8th most commonly diagnosed cancer in men and 11th in women. Immunotherapy with anti-CD20 monoclonal antibody rituximab in combination with chemotherapy is used as a first line treatment and significantly improves response rate and survival. However, many relapses are observed. Radioimmunotherapy (RIT) is then an emerging second line option for NHL. RIT with beta-emitters (Bexxar®, Zevalin®) has been developed but hematological toxicity was observed (1). The development of RIT with alpha-emitters is attractive because of the high linear energy transfer (LET) and short path length of alpha-radiation in tissues, resulting in higher tumor cell killing and lower toxicity to surrounding tissues.

In this study, we investigated the potential of alpha-RIT with 212Pb-rituximab in both in vitro and in vivo models. 212Pb is used as an in vivo generator of the high-energy alpha-particle emitting radionuclide 212Bi (2).

Results: Inhibition of proliferation of the mouse lymphoma EL4-hCD20-Luc cell line was correlated with a dose-dependent increase in apoptosis after incubation with 212Pb-rituximab compared to 212Pb-irrelevant mAb or cold antibodies.

Dose range finding (DRF) and acute toxicity studies were performed in order to determine the safety profile and safe administration doses. To evaluate in vivo efficacy of 212Pb-rituximab, 8-week-old C57BL/6JRj mice were injected intravenously with 25 x 103 EL4-hCD20-Luc cells and treated either 11 days or 20 to 30 days post cell injection with 277.5 kBq 212Pb-rituximab or relevant controls (including 277.5 kBq 212Pb-irrelevant mAb, cold rituximab and saline). Therapeutic efficacy was monitored by bioluminescence imaging (BLI) and overall survival. Mice treated with 212Pb-rituximab 20 to 30 days post cell injection (BLI-detectable tumors) exhibited marked tumor growth inhibition compared to controls, with a median survival of 28 days for 212Pb-rituximab-treated group instead of 9 to 13 days for control groups.

Strongly improved median survival (above 105 days) was observed for mice treated with 212Pb-rituximab 11 days after cell injection, whereas median survival was reached 36.5 days post-treatment for 212Pb-irrelevant mAb, 64 days for cold rituximab and 27 days for saline control.

Conclusion: These results show 212Pb-rituximab efficacy on a murine syngeneic lymphoma model with significant tumoral regression and increased survival. This study highlights alpha-RIT potency in B-NHL treatment.

References:

(1) C. Bodet-Milin et al., Frontiers in Oncology, 2013

(2) K. Yong and M.W. Brechbiel, Dalton Trans. 2011

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