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In Vivo Antitumor Efficacy of Accelerator-Based Lithium Neutron Capture Therapy

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Background / Objective: Boron neutron capture therapy (BNCT) is a promising cancer treatment based on the $^{10}B(n,\alpha)^{7}Li$ reaction. However, clinical BNCT faces limitations including suboptimal boron selectivity and accumulation. Lithium-6 (^{6}Li) offers distinct physical advantages for neutron capture therapy: the capture reaction $^{6}Li(n,\alpha)^{3}H$ deposits 100% of its released energy within the cell (as opposed to 84% for boron), and the total energy yield is twice that of the boron reaction. This study represents the first preclinical evaluation of lithium neutron capture therapy (LiNCT) efficacy in vivo using an accelerator-based neutron source suitable for clinical translation.

Methods: Male C57BL/6 mice with subcutaneous B16 skin melanoma received 6Li-enriched lithium chloride (450 mg/kg) either perorally (n=28) or intraperitoneally (n=45). Lithium biodistribution in tumor, blood, skin, liver, kidney, and brain was measured at 1–4 hours post-administration using ICP-AES. Neutron irradiation was performed at the VITA accelerator-based neutron source ($^{7}Li(p,n)^{7}Be$, 2.1 MeV protons, 1.6 mA, ~1.5 hours, fluence 2.5 mA·h). Tumor growth dynamics and survival were assessed using generalized linear mixed model (GLMM) and Kaplan–Meier analysis with log-rank test.

Results: Intraperitoneal administration achieved significantly higher peak tumor lithium concentration (54.1 μg/g at 1 hour) compared to peroral administration (30.2 μg/g at 4 hours). Optimal tumor-to-skin and tumor-to-blood ratios were 4.7 and 1.4, respectively, at 1-hour post-intraperitoneal injection. LiNCT with intraperitoneal lithium significantly increased median survival (34 days vs. 15 days in controls, 127% increase in life span, $p<0.0001$) and significantly reduced tumor growth (2–4 fold) during the first three weeks compared to all control groups (Control, LiCl-only, Neutron-only). Peroral LiNCT showed only non-significant trends toward improved survival and tumor control ($p=0.086$).

Conclusion: This first in vivo demonstration of accelerator-based LiNCT using a murine melanoma model shows that intraperitoneal lithium delivery achieves sufficient tumor lithium concentrations for significant antitumor efficacy. These results provide new opportunities for developing neutron capture

therapy using lithium alone or in combination with boron, warranting further studies toward clinical applicability of LiNCT.

Keywords: Lithium neutron capture therapy (LiNCT); Lithium chloride; Skin melanoma; Accelerator-based neutron source