First Experience of Lithium Neutron Capture Therapy in a Mouse Model of Cutaneous Melanoma

Iuliia Taskaeva[1,2], Anna Kasatova[1,2], Nataliya Bgatova[2], Timophey Bykov[1], Evgeniia Sokolova[1], Vladimir Richter[1,3], Sergey Taskaev[1]

[1] *Budker Institute of Nuclear Physics, Novosibirsk, Russia*

[2] *Research Institute of Clinical and Experimental Lymphology – Branch of the Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences, Novosibirsk, Russia*

[3] *Institute of Chemical Biology and Fundamental Medicine, Novosibirsk, Russia*

E-mail: taskaeva.iuliia@gmail.com

Currently, although novel boron-delivery agents are under investigation, clinical protocols for boron neutron capture therapy (BNCT) rely primarily on second-generation compounds, such as boronophenylalanine and sodium borocaptate. The use of lithium instead of boron in NCT represents a promising therapeutic approach due to the physical properties of lithium. The well-established pharmacological protocols may facilitate the introduction of lithium to NCT by providing precise control of tissue lithium concentrations. In this study, we aimed to assess the anticancer efficacy of LiNCT using a mouse melanoma model. To the best of our knowledge, this is the first report assessing LiNCT efficacy in an *in vivo* melanoma model.

The series of experiments was divided into four stages and was carried out using a total of 115 mice (C57BL/6) with implanted B16 skin melanoma and a lithium compound (lithium chloride enriched with ^{6}Li, 450 mg/kg): analysis of lithium accumulation in the organs of mice (study 1) and subsequent LiNCT (study 2) after peroral administration of the lithium compound; analysis of lithium accumulation in the organs of mice (study 3) and subsequent LiNCT (study 4) after intraperitoneal administration of the lithium compound. After tumor growth induction, mice were randomly divided into groups for each experiment: to assess lithium biodistribution—1, 2, 3, and 4 hours; to assess the efficacy of LiNCT – into "Control" (intact tumor), "Li" (control group receiving lithium compound only), "Neu" (neutron irradiation control group), and "LiNCT" (neutron irradiation after lithium compound administration) groups. Animals were irradiated in specially designed restrictors at the VITA accelerator at the Budker Institute of Nuclear Physics in Novosibirsk, Russia. Neutron irradiation was performed for 1.5 hours at 2.5 mAh and 2.1 MeV.

The maximum lithium concentrations in the tumor were 28 ppm (1 hour) and 30 ppm (4 hours) after peroral administration, and 54 ppm (1 hour) after intraperitoneal administration. Although a trend towards improved survival and tumor growth dynamics in the Neu and LiNCT groups was observed, no significant differences were found compared to the control groups after peroral lithium administration. With intraperitoneal lithium administration, the log-rank test showed a significant increase in survival in the LiNCT group compared to the other three control groups. Moreover, the LiNCT group exhibited statistically significantly slower tumor growth (2–4 times) compared to the control groups during the first three weeks of the experiment. Thus, LiNCT demonstrated a pronounced cytotoxic effect on tumor cells at the initial stages after irradiation.

Our study demonstrates, for the first time, the dynamics of lithium accumulation in tumors using the B16 skin melanoma model. Lithium is effectively accumulated by tumor cells at doses required for a successful lithium neutron capture reaction, especially with intraperitoneal administration. Moreover, our results clearly demonstrate the importance of lithium concentration in the tumor for successful neutron capture by tumor cells, as well as the effectiveness of LiNCT after intraperitoneal lithium administration.

The study was supported by the grant from the Russian Science Foundation (project No. 19-72-30005).