Preclinical safety and activity of intraventricular Rhenium-186 Nanoliposome (186RNL) for leptomeningeal metastases

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BACKGROUND

Leptomeningeal disease (LMD) is a clinical complication that occurs when cancer cells invade the leptomeninges and cerebrospinal fluid of patients with malignant tumors. Survival is poor once diagnosed (~ 3 to 6 months) , and limited treatment options exist.

Rhenium-186 nanoliposome (RNL) therapy is a liposomal beta emitter with a short pathlength of 1.8mm, thereby allowing high specific activity radiotherapy with limited exposure to surrounding tissues. Recent studies of RNL on glioblastoma with animal models have shown that RNL increases survival and produces no overt symptoms [1]. Phase 1 and 2 clinical trials studying RNL in recurrent glioblastoma are currently being conducted [2] with no toxicity observed to date with absorbed doses of over 700Gy.

While external beam radiation (XRT) is used for the treatment of LMD, dose is limited due to potential CNS toxicity with craniospinal radiation falling out of favor due to poor tolerance. We hypothesized that given the short pathlength and favorable radiation properties of RNL, intraventricular treatment would be safe at markedly higher doses than conventional XRT leading to better survival.

This study investigates the maximum tolerable dose (MTD), safety, and efficacy in rat models of LMD.

METHODS

- A total of five different radioactivity dosages of RNL, including a control group, were tested (n=3) – 0.480, 0.800, 1.000, 1.150, and 1.340 mCi to determine the MTD and safety of 186RNL. These amounts were injected in 20 µL of water to achieve higher amounts of radioactivity. Radioactivity was measured before and after each injection using a dose calibrator machine to ensure that the correct radioactivity dose was being injected. Weight and food intake measurements were taken daily for each rat injected for a period of 38 days following surgery to determine the symptomatic effects of RNL. A gamma camera was used to image rats and determine RNL and radioactivity retention over time.
- Glioma C6-Luc and breast cancer MDA-MB-231-Luc cells were injected intra-ventricularly in rat brains, divided into control and treatment groups. Tumor size was monitored through bioluminescence using the IVIS instrument.

RESULTS

1. Maximum tolerable dose (MTD)

Five different RNL doses we tested in non-tumor bearing rats. Radiation was retained at the site if injection over a period of 48 hrs (Fig 1A and B). Weight (Fig 1C) and food intake(Fig 1D) measurements were taken, and symptoms assessed for each rat for 4 weeks. All animals lost weight in the 1st week; however, thereafter regained and maintained for 3 weeks. There was increased food consumption after the first week. No overt neurological symptoms were detected in all rats after 186RNL injection for the duration of the experiment (4 weeks).

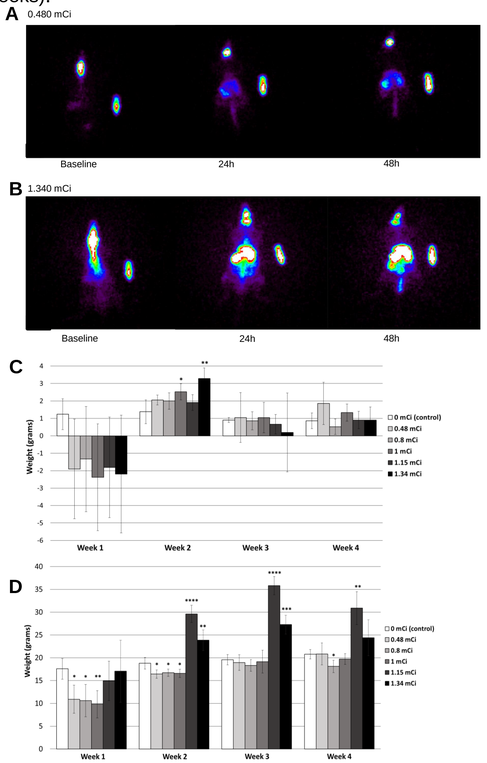

Figure 1. 186RNL is well tolerated at high doses. Gamma camera images for two rats that received minimum 0.480 mCi (**A**) and maximum 1.340 mCi (**B).** Weight (**C**) and food consumption (**D**) were measured.

2. 186RNL shows efficacy in glioma C6-Luc LMD rat model

Wistar rats were injected with 10^4 C6-Luc glioma cells, then injected with either empty liposomes or 0.689 mCi of 186RNL. The mean absorbed radioactivity for the 186RNL-treated cohort was 1,094 Gy (+/- 218.59) and was retained at 2 days after injection (Fig 2A). Bioluminescent imaging was used to track tumor growth. 186RNL-treated rats had significantly lower luciferase relative to controls (p=0.0286) (Fig 2B). Kaplan Meier plot showed a statistically significant difference in overall survival with the 186RNL-treated animals outliving the controls (p=0.0377) (Fig 2C).

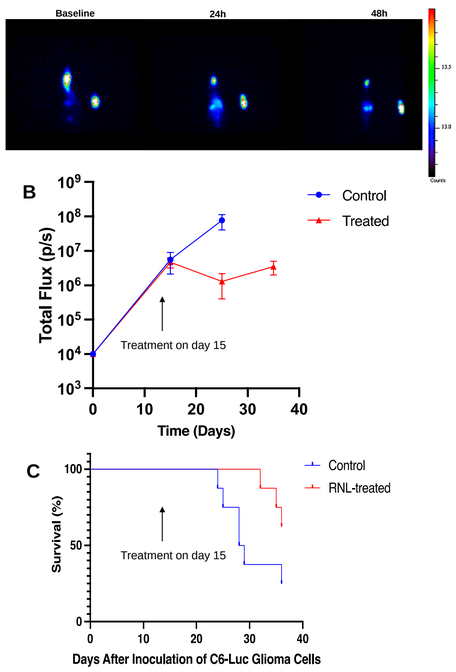

Figure 2. RNL treatment showed efficacy in the C6-Luc LMD model. A. Gamma images showing retention of radiation at 48 hours after RNL injection. **B.** Tumor volume measured by bioluminescence. P-value = 0.0286 **C.** Kaplan-Meier survival curve. P-value = 0.0377

3. 186RNL shows efficacy in breast cancer MDA-MB-231-Luc LMD rat model

Female RNU rats were inoculated with 200k MDA-MB-231-Luc cells, then injected with either empty liposomes or 0.516mCi of 186RNL on day 6 after inoculation. Bioluminescent imaging was used to track tumor growth. We observed a statistically significant difference in tumor burden beginning 6 days after treatment that reached 10-fold by 2 weeks post treatment when control animals began expiring.

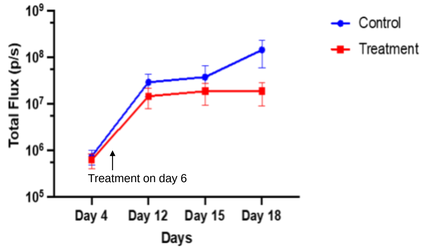

Figure 3. RNL reduced tumor growth in MDA-MB-231-Luc LMD model. Bioluminescence measurement showed that the control animals had larger tumor volume than the RNL treated animals.

CONCLUSION

- Rats administered with the highest doses, 1.340mCi (≈1340Gy) and 1.15mCi (≈1150Gy), presented minimal weight loss the first week after surgery, but gained it back in subsequent weeks. Additionally, the rats showed no overt neurological symptoms until the end. This suggests that the maximum tolerable dose was not reached.
- RNL shows encouraging efficacy in pre-clinical LMD models and has potential as a therapeutic for LMD due to its low toxicity at high doses.

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