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225Ac-NM600 targeted alpha therapy extends survival in a model of triple negative breast cancer.

Triple negative breast cancer (TNBC) remains the most lethal breast cancer histology. Currently, approved targeted therapies for TNBC do not exist, and novel tumor-targeted interventions to complement/supplant the current standard of care using chemotherapy are urgently needed [1]. Our research group has developed a series of tumor-avid alkyphosphocholine analogs (APC) that can carry a radiolabel for both imaging and targeted radionuclide therapy of breast cancer. In this study we investigated the potential of NM600, our lead APC analog, radiolabeled with the alpha emitter ²²⁵Ac, for targeted alpha therapy (TAT) in a mouse model of TNBC. Radiolabeling yields were nearly quantitative (>95%) with a specific activity of 3.4 GBq/μmol. Excipient and serum stability of ²²⁵Ac-NM600 at 8 days was 90% and 95%, respectively. Longitudinal ex vivo biodistribution studies were performed in Balb/C mice bearing mammary adenocarcinoma 4T1 tumor grafts injected with 20 kBq ²²⁵Ac-NM600 at 4, 24, 48, 96, and 216 h post injection (p.i.). Elevated radioactivity was observed in the blood (15.2 ± 1.2 %ID/g) at 4 h p.i. and gradually declined overtime with a 23.1 ± 1.9 h biological half live (n = 3). Due to the hepatobiliary excretion of ²²⁵Ac-NM600, distribution in normal tissue was most prominent in the liver, peaking at 28.1 ± 3.6 %ID/g at 96 h p.i. ²²⁵Ac-NM600 uptake in 4T1 tumors progressively increased from 6.7 ± 3.0 %ID/g at 4 h to 26.1 ±15.6 %ID/g (n = 3) at the final timepoint, 216 h p.i.. Biodistribution did not change when ²²⁵Ac-NM600 was administered with a 50-fold lower specific activity. In therapy studies, three groups of mice bearing 4T1 tumors (~150 mm3, n = 5) were administered either excipient (control), 20 kBq, or 40 kBq ²²⁵Ac-NM600, and tumor progression and animal survival were monitored for 60 days. Significant tumor regression (P < 0.001) was observed in both treatment arms compared to control within a week following treatment; however, a survival benefit was only achieved in the 20 kBq group, in which all mice showed controlled disease and no signs of acute toxicity. The administration of 40 kBq was acutely radiotoxic. These preliminary results demonstrate the potential of TAT using NM600 for the treatment of TNBC and warrant further treatment optimization and the exploration of potential long-term toxicities.

1. Bianchini, G., et al., Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol, 2016. 13(11): p. 674-690.

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