Preclinical Evaluation of a Novel Alpha-Particle Emitting Therapeutic Agent for Intraperitoneal Therapy of Peritoneal Metastases

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Objectives

We have developed a composition of microparticles and an α-emitting radionuclide, specifically designed for local treatment of peritoneal carcinomatosis. The inorganic microparticles act as carriers for the α-emitter radium-224 (^{224}Ra). This novel α-radiation therapy has a range in tissue of less than 100 µm and is designed to confine the radiation exposure to the intraperitoneal (IP) cavity, including peritoneal surfaces and liquid volumes. The therapeutic efficacy and safety of the ^{224}Ra-microparticles in mice with human IP xenografts are presented.

Methods

$CaCO_3$ microparticles with median diameters of 17-21 µm were radiolabeled by precipitation of ^{224}Ra on the particle surface[1]. The ^{224}Ra-microparticles were evaluated in immunodeficient athymic nude mice inoculated IP with human ovarian cancer cells SKOV-3luc or ES-2[2]. Both cell lines represent epithelial adenocarcinoma. SKOV-3luc has a solid tumor growth pattern, whereas inoculation with the ES-2 cell line leads to aggressive development of ascites and at later stages invasive tumor growth. Different activity levels of ^{224}Ra-microparticles were administered IP as a suspension, with a volume between 250-400 µl per mice. Tumor growth, survival, and blood parameters were assessed. A maximum of 100 µl blood was collected from the vena saphena lateralis in EDTA tubes at 3 time points during the ES-2 study for hematology analyses of platelets, white and red blood cells. Blood was collected from heart puncture in sedated animals prior to euthanasia for hematology analyses in the SKOV-3luc study and for clinical chemistry in the ES-2 study (urea, aspartate and alanine aminotransferases and alkaline phosphatase).

Results

Intraperitoneal treatment with ^{224}Ra-microparticles resulted in inhibition of tumor growth in mice inoculated with SKOV-3luc (Fig. 1). A significant reduction in IP tumor weight was obtained in all treatment groups. Further, treatment with ^{224}Ra-microparticles in the ES-2 xenograft model with aggressive development of ascites gave a survival benefit (Fig. 2). A wide dose range of ^{224}Ra-microparticles was assessed, and the results showed that all doses tested resulted in at least a doubling of median survival compared to the control group. Analyses of blood samples of mice treated with ^{224}Ra-microparticles showed no radiation related effects on neither hematology nor clinical chemistry parameters. Selected hematology data from mice treated with up to 1000 kBq/kg of activity are shown in Fig. 3. An increased white blood cell count in control animals during disease progression was observed in the ES-2 (day 13 Fig. 3) and SKOV-3luc model (not-shown), and in the group given the lowest dose in the ES-2 study (day 26 Fig. 3). No changes related to treatment were observed.

^{224}Ra-microparticles inhibit solid tumor growth

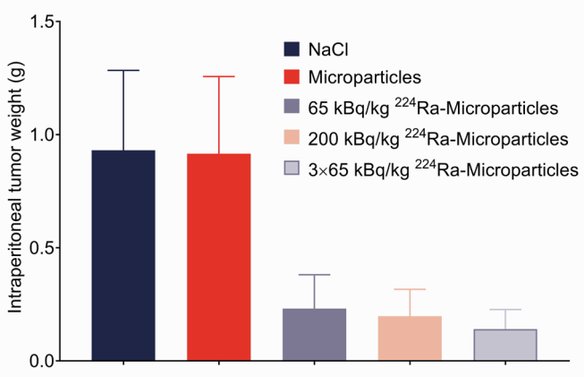
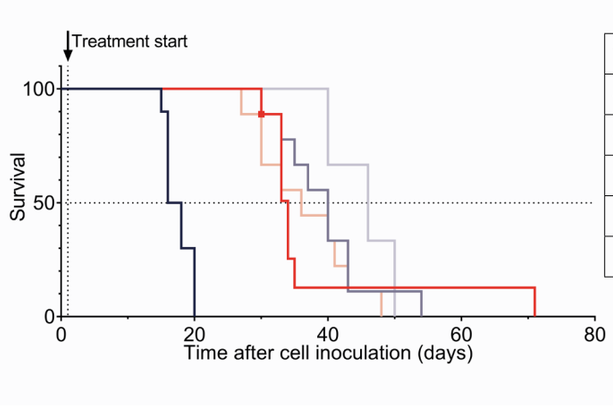


Figure 1. All mice were euthanized on day 44 or 45 after treatment and all visible tumors harvested and weighed. The mice were treated 3 days after IP inoculation of 5 million SKOV-3luc cells. The mice received either a single injection of saline, non-labeled $CaCO_3$ microparticles or a low or high dose of ^{224}Ra microparticles. One group received 3 injections of the low dose separated by 48 hours. Each treatment group was comprised of 8 animals.

^{224}Ra-microparticles increase survival in an ascites model



Treatment group	Median Survival
NaCl	17
150 kBq/kg ^{224}Ra-Microparticles	34
300 kBq/kg ^{224}Ra-Microparticles	40
2x150 kBq/kg ^{224}Ra-Microparticles	36
1000 kBq/kg ^{224}Ra-Microparticles	46

Figure 2. End-points for euthanization of mice were abdominal distention impairing mobility, rapid weight loss and a decreased body condition score. The mice were treated 1 day after IP inoculation of 1 million ES-2 cells. The mice received either a single injection of saline or different doses of ^{224}Ra microparticles. One group received two injections separated by 7 days. Each treatment group comprised of 3 to 10 animals.

Hematology of mice treated with ^{224}Ra-labeled microparticles

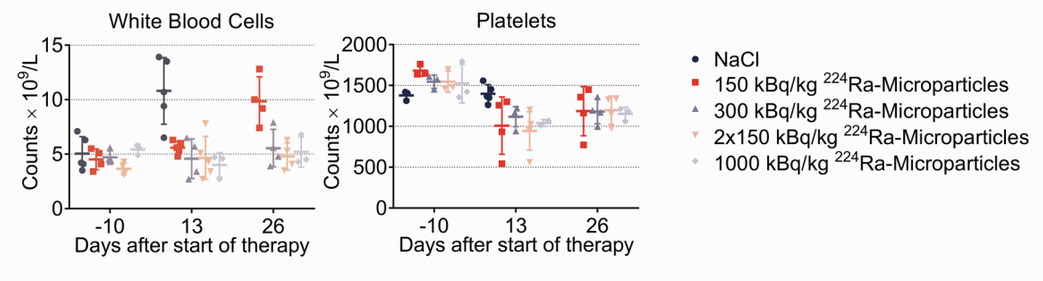


Figure 3. Levels of white blood cells and platelets from mice in the ES-2 survival study shown in Fig. 2. Blood was collected 10 days prior to start of study, and 13 and 26 days after treatment start.

Conclusions

The presented preclinical data show that only a few kilobecquerels per mouse of ^{224}Ra-microparticles were needed to yield therapeutic effects. The treatment was well-tolerated up to doses of 1000 kBq/kg. Intraperitoneal α-therapy with ^{224}Ra-microparticles demonstrates a significant potential for treatment of residual microscopic IP disease.

References
1. Westrøm et al., submitted (Nucl Med Biol.): Ra-224 labeling of Calcium Carbonate Microparticles for Internal α-Therapy: Preparation, Stability and Biodistribution in Mice.
2. Westrøm et al., in prep: Therapeutic Effect of α-Emitting ^{224}Ra-labeled Calcium Carbonate Microparticles in Mice with Intraperitoneal Ovarian Cancer.

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