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ORIGINAL ARTICLE

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Preclinical application of ^{188}Re-Tin colloid for treatment of mouse tumor model with peritoneal effusion

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ABSTRACT

Re-188 is an excellent and practical radioisotope produced by W-188/Re-188-generator for therapy. We prepared Re-188-tin colloid for therapy of various diseases and tried to treat peritoneal effusion in animal model. Sarcoma-180 cells were injected into ICR mice to induce peritoneal effusion and the mice were grown for 3 d. Re-188-tin colloids (0.25, 0.5, and 1 mCi/mL per 30 g body weight) were injected into the mice and the mice were grown for 90 d. Planar gamma scintigraphy showed even distribution of Re-188-tin colloid radioactivity. Bax expression was found to be dose dependent to Re-188-tin colloid. Normal saline treated group showed the shortest survival time. Among the treated groups, 0.5 mCi dose group showed the longest survival time. In conclusion, Re-188-tin colloid was prepared successfully and showed the feasibility to use as a peritoneal effusion treatment in mice.

Key Word: Re-188-tin colloid, peritoneal effusion, radionuclide therapy

Introduction

Malignant ascites are usually caused by intraabdominal tumors. For example, the ovarian, pancreas, stomach, and uterus malignancies generally disseminate in the abdominal cavity (1). Treatment of this advanced malignant disease is difficult and shows poor prognosis (2).

Intraperitoneal administration of radiolabeled colloidal particles is one of the treatment modalities that has been used widely in an attempt to control ascites of malignant origin. Previously ^{198}Au and ^{32}P labeled colloids have been used for treatment of ascites (3-7). However, ^{198}Au colloid has gamma emission of 412 keV which causes an unnecessary radiation hazard, and particle size of the colloid was not large enough to be retained in the peritoneal space (3, 4). The high price also somewhat restricted availability of the ^{198}Au colloid. The ^{32}P colloid has a possibility of bone marrow toxicity because the released ^{32}P can be taken up by bone and bone marrow.

Recently, ^{188}Re was reported to be an attractive radionuclide for radiolabeling various kind of radiopharmaceuticals for therapeutic use (8-12). ^{188}Re with a 17 h half-life and a high energy beta-emission (E_{max} = 2.12 MeV) which has an average tissue penetration of 3.8 mm is an excellent radionuclide for therapy. With emission of a gamma photon (155 keV, 15%), it permits the imaging of radiopharmaceutical biodistribution by routinely available gamma camera systems. Carrier-free ^{188}Re can be obtained from a ^{188}W/^{188}Re-generator which makes it suitable for clinical use (13). It has been

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applied clinically for rheumatoid arthritis treatment (14), pain palliation of bone metastasis patients (15, 16) and liver cancer therapy (17-19). Therefore, ^{188}Re deserves consideration as a potential candidate in the treatment of ascitic tumors.

^{188}Re-sulfur colloid was developed for treatment of rheumatoid arthritis (20). However, its practical problem was the residual radioactivity in syringe after use, which makes the prediction of injection dose difficult and leads to the waste of radioactivity. Another agent ^{188}Re-tin colloid showed excellent particle size distribution and no adsorption to syringe (21).

This experiment was designed to validate the feasibility of ^{188}Re-tin colloid for treatment of malignant peritoneal effusion in animal model.

Materials and Methods

1. Preparation of ^{188}Re-tin colloid

To prepare ^{188}Re-tin colloid, 0.2 mL of 0.1 M HCl and 0.8 mL aliquot of ^{188}Re-perrehenate (~40 MBq) freshly eluted with saline from an alumina-based ^{188}W/^{188}Re-generator (Oak Ridge national Laboratory, Oak Ridge, U.S.A.) were injected into tin colloid kits (Department of nuclear medicine, Seoul National University Hospital, Seoul, Korea). Each vial was incubated at 100oC for 10 min. Labeling efficiency was checked by chromatography (ITLC-SG/normal saline) and radioactivity was monitored by TLC scanner (Imaging Scanner system 2000, Bioscan, U.S.A.). The radiolabeled 188Re-tin colloid was neutralized by adding adequate amount of 0.2 M sodium phosphate buffer (pH=8) solution. Particle size of colloids and stability test were reported in the experiment previously. (7)

2. Animal experiments

To obtain peritoneal effusion models, 5 10^6 /0.3 mL Sarcoma-180 cells were injected intraperitoneally into each ICR mouse and mice were grown for 3 d. ^{188}Re-tin colloid was intraperitoneally injected into each tumor-bearing mouse. The doses were 0.25, 0.5, and 1 mCi/mL per 30 g body weight. One group included 12 mice (Group 1, 2, 3). Control group (24 mice) was divided into two groups. One group was peritoneal effusion models injected with normal saline (Group 4) and the other group was normal mice injected with 1 mCi/mL ^{188}Re-tin colloid (Group 5)

Distributions of 188Re radioactivities in the mice bodies were checked using gamma camera at 3, 24, and 48 h post-injection. The expression of BAX proteins in tumor cells was checked by western blotting with antibodies against human BAX. Peritoneal viscera histopathology was observed in each group at 24 and 48 h after injection of ^{188}Re-tin colloid. The effects of ^{188}Re-tin colloid to survival time and body weight were monitored. Statistical analysis was performed using SPSS version 10.7.

Results

Labeling efficiency of the ^{188}Re-tin colloid was higher than 99%. To test the stability of ^{188}Re-tin colloid, it was stored for 24 h at room temperature and did not show any decrease of radiochemical purity. ^{188}Re-tin colloids were also stable in serum at 37˚C for 72 h.

Homogeneous distribution of radioactivity in the abdomen was found at 24 and 48 h images of treated mice (Figure 1). Dose dependent expression of Bax protein was confirmed at 48 h (Figure 2). In histopathology, we found that mice treated with ^{188}Re-tin colloid showed the degeneration in the liver, the white pulp atrophy, attached cell cluster and neutrophil infiltration in the spleen, the cell cluster attached in the intestine, glandular degeneration in the stomach. Significant decrease of body weight due to radiation toxicity was observed in 1 mCi group 8~10 days after

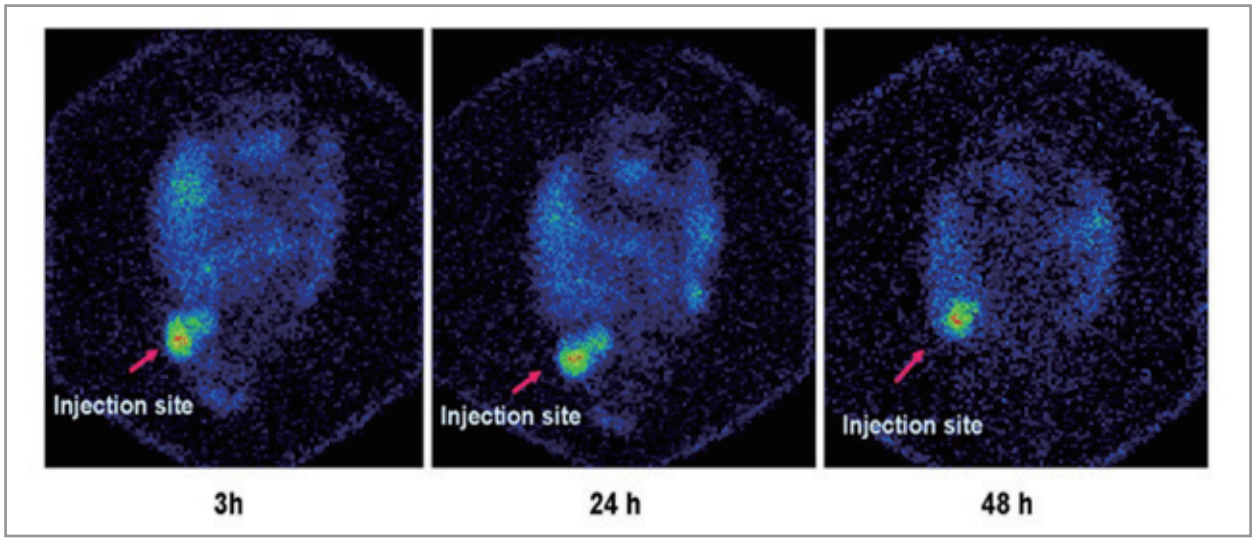

Figure 1. Imaging of mice after intraperitoneal injection of ^{188}Re-tin colloid (0.5 mCi).

treatment (Figure 3). Survival times of 1, 0.5, 0.25 mCi treated groups were 59.0±8.5, 63.6±7.1, and 54.8±7.0 d, respectively, that were significantly increased compared to saline treated Group 4 (20.0±1.9 days) ($p<0.001$) (Figure 4). Mean survival time of treated groups was 80 d when analyzed by Kaplan-Meier test.

Discussion

Intraperitoneal administration of radioactive labelled colloidal particles is widely used in an attempt to control such malignant ascites and micrometastasis (1-8).

Radiocolloid is an inert material which is stabilized either in vitro or in vivo. After intracavitary administration, the colloid either evenly attaches on the mesothelial membranes and the tumor tissue surface, subsequently physiological degradation, probably by microphages in the peritoneum or in lymph nodes. Free-floating malignant cells receive therapeutic radiation from the beta particles emitted during radionuclide decay (4, 10). Due to these potential complications, proper management of malignant effusion and prevention of recurrence are important in prolonging survival and sustaining the quality of the patient's life.

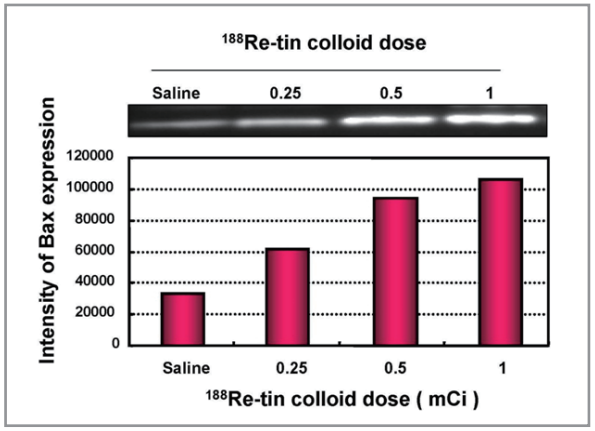

Figure 2. Expression of Bax protein in ^{188}Re- tin colloid treated Sarcoma180 tumor model mice for 48 h.

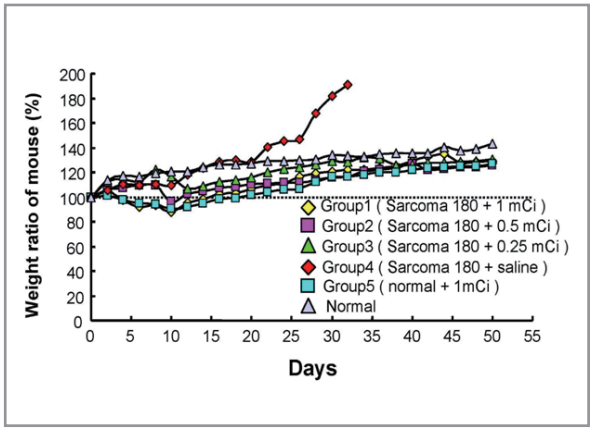

Figure 3. Change of body weights after ^{188}Re-tin colloid treated Sarcoma180 tumor model mice.

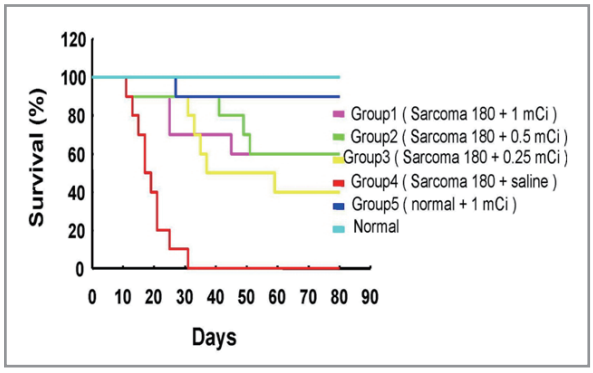

Figure 4. Survival curves of ^{188}Re-tin colloid treated Sarcoma180 tumor model mice.

In this research, the^{188}Re- tin colloid, which we used, emits high energy β-particles and the colloid size (>1 μm, 94.8%) is suitable for the therapy of peritoneal effusion. Particle size and physical properties are important, because they determine the uptake and retention by particular organs and therapeutic effect. After injection into the abdominal cavity, the latter 48 h image showed the more even distribution of 188Re-tin colloid in the cavity. Compareed to the untreated Group 4, therapeutic effect by 188Re-tin colloid treatment was clearly demonstrated by increased survival time of treated groups obviously, especially in the Group 2. Such radioactive biological effect also observed in dose dependent expression with cell apoptosis correlation with Bax protein.

In the Group 5, after intraperitoneal injection of ^{188}Re-tin colloid into normal mice, body weights were reduced and one mouse died. It may be considered to be connected with the toxicity of radiation biological effect. In the Group 1, 2 and 3, body weights of mice were reduced according to the dose dependent manner. These results were considered with the biological toxic effect and therapeutic effect of radioactivity. Such result also was observed in the histopathology detection.

Conclusion

^{188}Re-tin colloid showed homogeneous distribution in the abdomen of peritoneal effusion mouse model and excellent life-extending effects were found. The optimum dose for 30 g mouse was found to be 0.5 mCi in this experiment.

Acknowledgments

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