Treatment for peritoneal dissemination of gastric cancer using ^{211}At

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Peritoneal dissemination is one of the miserable patterns of recurrence of cancer. This recurrence pattern is the most common in gastric cancer. There is no way to cure it and there are only treatment methods to decelerate the cancer growing by chemotherapy or immunotherapy. External irradiation is also difficult for avoiding intestinal irradiation. We developed murine gastric cancer cell lines, YTN that can be transplanted into C57BL/6, immunocompetent mouse.[1] YTN16 can develop peritoneal dissemination in C57BL/6 mice with 100% rate, when 1×10^7 cells are injected into the peritoneal cavity. We also have less aggressive subline YTN2. Comparing mRNA expression between YTN16 and YTN2, using microarray, Fibroblast Growth Factor Receptor 4 (FGFR4) was highly expressed in YTN16. Since α-emitting ^{211}At is reported to be an effective therapy for peritoneal dissemination,[2] we sought to develop the treatment for YTN16 peritoneal dissemination using ^{211}At-FGFR4 Ab.

YTN16 peritoneal dissemination mouse model was made as we reported and 3 weeks later, ^{211}At was administered and the accumulation of ^{211}At into peritoneum was measured using a gamma-counter after 4.5 hours, 16 hours, and 23 hours after administration. The 1 MBq of free ^{211}At was administered through intra venous (0.2 mL), intra peritoneum (1.0 mL), and intra gastric (0.5 mL). The ^{211}At-FGFR4 Ab (1 MBq-16.4 μg Ab) was administered through intra venous (0.2 mL) and intra peritoneum (1.0 mL). As shown in Fig. 1, ^{211}At conjugated with Ab accumulated in peritoneum 16 hours and 23 hours after administration.

Next, to confirm the treatment effect of ^{211}At, we sacrificed the mice 5 weeks after transplantation of YTN16, through ^{211}At treatment 10 days before sacrifying. The severity of peritoneal dissemination could be diagnosed macroscopically. As shown in Fig. 2, intraperitoneal

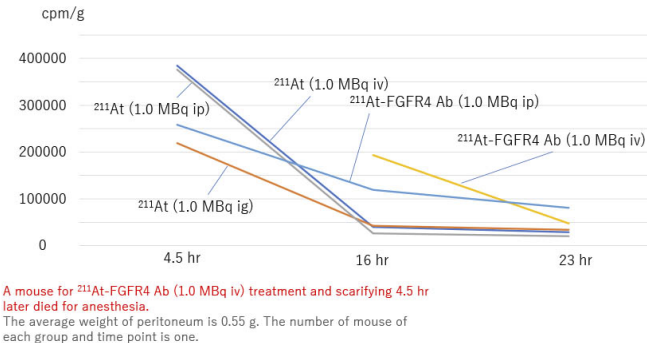

Fig. 1. ^{211}At accumulation in peritoneum.

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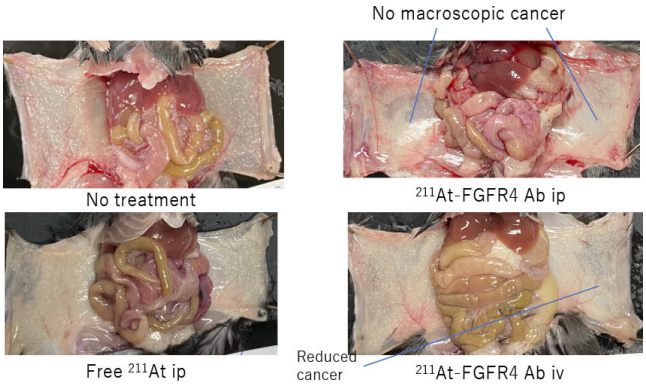

Fig. 2. Treatment effect of ^{211}At for peritoneal dissemination.

administration of ^{211}At-FGFR4 Ab was most effective followed by intravenous administration of ^{211}At-FGFR4 Ab, and intraperitoneal administration of free ^{211}At.

Finally, the effect for overall survival of mice was analyzed by Kaplan-Mayer curves. As shown in Fig. 3, ^{211}At-FGFR4 Ab significantly prolonged the overall survival of mice with gastric cancer peritoneal dissemination.

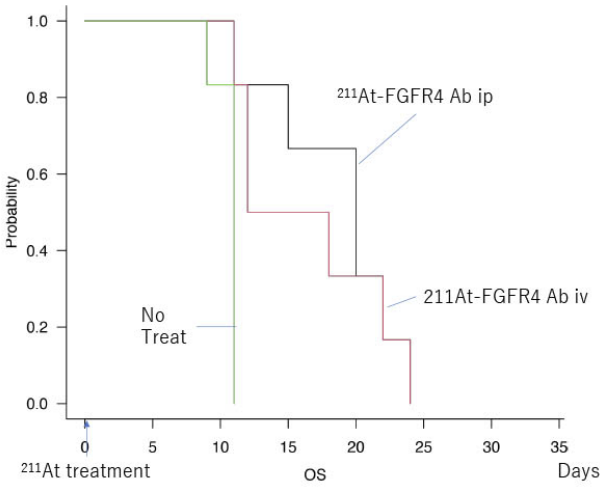

Fig. 3. Kaplan-Mayer analysis for treated mice.

The ^{211}At-Ab treatment for peritoneal dissemination was effective for reducing the cancer and elongating overall survival. More improvement is needed for prolonging the survival. Especially effective methods for gathering ^{211}At to cancer faster are needed.

References

1) M. Yamamoto *et al.*, Cancer Sci. **109**, 1480 (2018).
2) H. K. Li *et al.*, Cancer Sci. **108**, 1648 (2017).