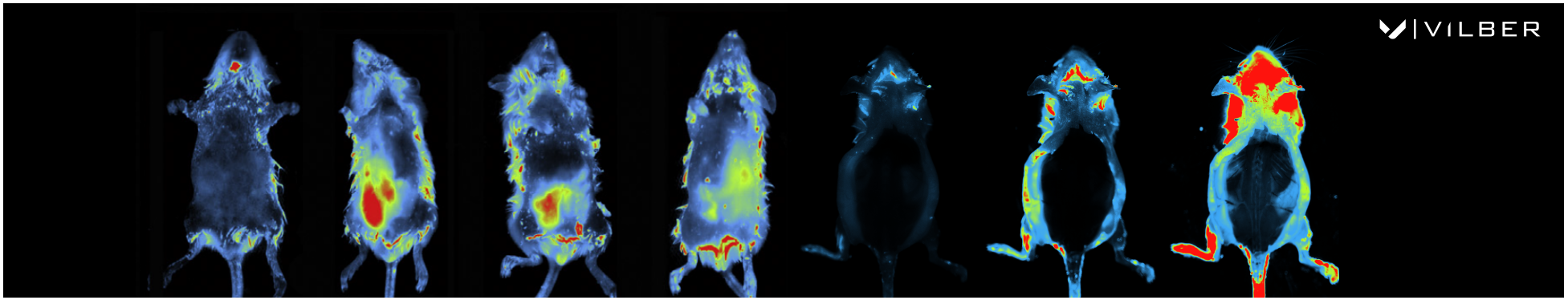

IN VIVO ANTITUMOR ACTIVITY OF LOCOREGIONAL ^{211}AT-TRASTUZUMAB IN THE TREATMENT OF PERITONEAL METASTASIS OF GASTRIC CANCER IN MICE

AUTHORS

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INTRODUCTION

Gastric cancer (GC) is one of the leading causes of cancer-related death worldwide. Recent advances identified reliable predictive biomarkers such as human epidermal growth factor receptor (HER2), thus introducing molecular targeted drug therapy. GC's HER2-positive, when amplified or over expressed, play an important role in the development and progression of certain aggressive types of breast cancer. Trastuzumab, an anti-HER2 mAb (monoclonal antibody), has been used previously as a targeted therapy for HER2-positive GC. It induces an immune-mediated response that causes internalization and downregulation of HER2 and yields excellent treatment outcomes. Radioimmunotherapy (RIT) is a targeted radioisotope treatment method that uses an antibody as a carrier of therapeutic radioisotopes. The selective targeting of radioisotopes to the tumor using a radiolabeled cancer-specific antibody enables the delivery of a high dose of radiation directly to cancer cells while minimizing the exposure of normal cells. ^{211}At is of particular interest because it emits highly cytotoxic α -particles that can kill a target cell, making it one of the most potent cell-killing agents available. Astatine-211 is therefore particularly suited to the targeted killing of disseminated or micrometastatic solid tumors that are usually resistant.

OBJECTIVE

Astatine-211-labeled trastuzumab (211At-trastuzumab or 211At-tras) emitting highly cytotoxic α -particles could be a potent agent for the targeted ablation of HER2-positive PMGC. This study thus investigated the therapeutic efficacy of a-RIT using 211At-tras in preclinical mouse models of HER2-positive peritoneal metastasis of gastric cancer.

MATERIAL & METHODS

Radioimmunotherapy in PMGC mice. The PMGC mouse models were established by i.p. injecting luciferase-transfected N87/Luc cells ($3x10^5$) into 5-week-old B17/Icr-scid/scidJcl (homo) female mice 1 week before the experiment. These PMGC model mice then underwent RIT at 1 week after cell inoculation. Mice received a single i.p. injection of PBS, trastuzumab, non-carrier ^{211}At (1 MBq), or ^{211}At-trastuzumab (0.1 or 1 MBq). Tumor growth in the PMGC mice was monitored every week using an *in vivo* bioluminescence imaging Fusion system (Vilber Lourmat, France). Bioluminescence from PMGC was captured for 10 s at 10 min after the injection of luciferin (10 mg/mL in PBS, 300 µL/mouse). The total bioluminescence intensity in the abdominal region was quantified using Bio-1D software (Vilber Lourmat).

RESULTS

Figure 1. Locoregional therapy with astatine-211 labeled trastuzumab (^{211}At-tras) in a mouse model of peritoneal metastasis of gastric cancer (PMGC) and tumor monitoring.

Representative bioluminescence images of tumor growth in the mouse model treated with PBS (control), unlabeled Tras, ^{211}At (1 MBq), or ^{211}At-tras (0.1 or 1 MBq) 8 days after N87/Luc implantation Images were captured on the day before treatment at Day 0 then at 3, 5 and 7 weeks after treatment. The color scale indicates the luminescence intensity per pixel. The tumor growth was monitored longitudinally in each group by the *in vivo* bioluminescence imaging Fusion system (Vilber Lourmat, France). Tumor growth was obvious in the PMGC mice injected with PBS, unlabeled Tras, free ^{211}At 1mBq, and 0.1 MBq ^{211}At-tras. In contrast, a single injection of 1 MBq ^{211}At-trastuzumab reduced the tumor burden at 3 weeks after injection, with the tumors becoming undetectable at 5–7 weeks after treatment. Tras and PBS injections had little to no effect on tumor growth in the PMGC model.

CONCLUSION

In the current study, it has been demonstrated that ^{211}At-trastuzumab specifically targets HER2-positive GC cells *in vivo* and thus successfully inhibits tumor growth and improves survival in PMGC model mice with time. These results demonstrate the abilities of the Fusion FX7 (Vilber Lourmat, France) in imaging targeted therapy and its biodistribution pattern in the treatment of peritoneal metastasis of gastric cancer in mice.

Figure 1.