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Alpha-radioimmunotherapy against liver metastasis of HER2-positive gastric cancer in a mouse model

Gastric cancer (GC) is one of the leading causes of cancer-related death worldwide. Almost 1/3 of GC patients have distant metastasis at the time of diagnosis and 4-14% are liver metastasis (LM). The therapeutic efficacy of current standard treatments for LMGC is still limited and the five years survival is less than 10%. HER2 became a target for GC because 20% of GC is HER2-positive (HER2+) and trastuzumab, anti-HER2 antibody, is clinically used for the treatment of HER2-positive GC.

Alpha-emitter is getting higher attention, because of the high linear energy transfer and short range, and astatine-211 (211At) can be point out as one of the promising one. Adopting alpha emitter into radioimmunotherapy (RIT), ideal targeted radionuclide therapy can be provided with target specific antitumor effect and minimum toxicity to untargeted normal tissues.

The aim of this study is to evaluate the therapeutic efficacy of alpha-RIT against HER2+ LM of GC (LMGC) using 211At-labeled trastuzumab (211At-trastuzumab).

Luciferase-labeled NCl-N87, a HER2+ human GC cell line, was transplanted through the splenic vein to establish LMGC mouse model. 211At was labeled to trastuzumab by tin-halogen exchange. Biodistribution of 211At-trastuzumab in LMGC mice was evaluated up to 24h post intravenous (i.v.) injection. Tumor accumulation of 211At-trastuzumab were increased along with the time and reached about 12% at 24 h post injection and mainly excreted from urine. Experimental therapy was performed by injecting 211At-trastuzumab to LMGC mice from tail vein. Mice in three control groups received injection of PBS, intact trastuzumab or 211At labeled non-specific IgG (211At-HuIgG). Tumor was monitored by luminescence imaging to evaluate the antitumor effect. Monitoring body weight and the number of white blood cells and biochemistry examination of liver and kidney function were performed in order to check the toxicity. 211At-trastuzumab effectively eradicated the LMGC in our mouse model while the tumors in control groups were aggressively grown. No severer toxicity was observed.

This study provided the proof of concept that alpha-RIT using 211At-trastuzumab has high potential as a novel therapeutic option for HER2+ LMGC.

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