^{89}Zr-Labeled trastuzumab, a humanized monoclonal antibody against epidermal growth factor receptor 2

^{89}Zr-Trastuzumab

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Chemical name:	^{89}Zr-Labeled trastuzumab, a humanized monoclonal antibody against epidermal growth factor receptor 2	
Abbreviated name:	^{89}Zr-Trastuzumab	
Synonym:		
Agent Category:	Antibody	
Target:	Epidermal growth factor receptor 2 (EGFR2)	
Target Category:	Receptor	
Method of detection:	Positron emission tomography (PET)	
Source of signal / contrast:	^{89}Zr	
Activation:	No	
Studies:	• *In vitro* • Rodents	Structural information is not available in PubChem.

Background

[PubMed]

Trastuzumab, a humanized monoclonal antibody (mAb) that targets epidermal growth factor receptor 2 (HER2), is commercially available in the United States (US) and is approved by the US Food and Drug Administration for the treatment of HER2-overexpressing breast cancer (BC). This immunopharmaceutical is also being evaluated in

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combination with other anti-cancer drugs in clinical trials for the treatment of metastatic BC. In the clinical setting, the overexpression or amplification of HER2 is determined in tumor biopsies and indicates a poor prognostic outcome for the BC patient (1). Usually, the HER2 status of a tumor is established in the primary tumor after a biopsy, but the HER2 levels may not be the same at all locations in the tumor, and the receptor levels can change after the initiation of BC therapy (2). Although repeated determination of HER2 levels in tumor biopsies during the course of therapy could be a good indicator of treatment effectiveness, taking biopsies is an invasive process, and clinicians and patients are averse to using this technique. In addition, it is difficult to biopsy small and inaccessible tumors of the patient (1).

Recently, as an alternative to biopsies, whole-body HER2 immunoscintigraphy with ^{111}In-labeled trastuzumab using single-photon emission computed tomography (SPECT) was shown to be a suitable non-invasive technique for the detection of HER2-positive xenograft tumors in mice (3). Using SPECT, tumors could also be detected in patients with BC (4). In an effort to develop a HER2 imaging agent with superior spatial resolution and signal/noise ratio compared to ^{111}In-trastuzumab, Dijkers et al. (1) developed ^{89}Zr-labeled trastuzumab (^{89}Zr-trastuzumab; ^{89}Zr has a half-life of 78.41 hr)) for use with positron emission tomography (PET). The ^{89}Zr-labeled mAb was then evaluated for the detection of HER2-positive xenograft tumors in mice, and results obtained with this labeled mAb were compared with those obtained with ^{111}In-trastuzumab using SPECT (1).

Other sources of information regarding EGFR

Other EGFR imaging agents in MICAD.

Human EGFR ligands in PubMed.

Human EGFR on OMIM (Online Mendelian Inheritance in Man).

Human EGFR gene.

Protein and nucleotide information regarding EGFR.

Synthesis

[PubMed]

The synthesis of ^{89}Zr-trastuzumab has been described by Dijkers et al. (1). The radiolabeling efficiency for ^{89}Zr-trastuzumab was reported to be 77.6 ± 3.9% (n = 3), and the radiochemical purity of the final product was 98.1 ± 1.1% (n = 3) with a specific activity of 67.2 ± 2.4 MBq/mg (1.814 ± 0.064 mCi/mg) (1). For the procedures used to store ^{89}Zr-trastuzumab, see Dijkers et al. (1). The labeled mAb was reported to be stable at 4°C with <0.1% degradation/day for up to 7 days. Similarly, the degradation of ^{89}Zr-trastuzumab in human serum was <0.5%/day at 37°C for up to 7 days.

For comparative studies, ^{111}In-trastuzumab was also produced as described by Dijkers et al. (1). The radiolabeling efficiency and radiochemical purity of this labeled mAb were 89.3 ± 2.1% and 97.0 ± 1.0%, respectively. The specific activity of ^{111}In-trastuzumab was 78.2 ± 3.1 MBq/mg (2.11 ± 0.083 mCi/mg) (1), and the stability of ^{111}In-labeled trastuzumab was reported to be similar to ^{89}Zr-trastuzumab (as given above) at 4°C and 37°C.

In Vitro Studies: Testing in Cells and Tissues

[PubMed]

The *in vitro* binding characteristics of ^{89}Zr-trastuzumab and ^{111}In-trastuzumab were determined using SKVO3 cells (human ovarian cancer cell line, overexpressing HER2) and GLC4 cells (human small cell cancer cell line, HER2 negative) by a flow cytometric method (1). Little change in the immunoreactive fraction of ^{89}Zr-trastuzumab was noted during 7 days of storage either at 4°C (from 0.87 to 0.85 ± 0.06) or at 37°C in human serum (from 0.87 to 0.78 ± 0.01). A similar trend in the immunoreactivity of ^{111}In-trastuzumab was reported at the two storage temperatures.

Animal Studies

Rodents

[PubMed]

Dijkers et al. investigated the biodistribution of ^{89}Zr-trastuzumab in athymic mice bearing SKOV3 cell xenograft tumors (n = 5 animals/group) (1). The animals were injected with escalating doses of the radiolabeled mAb (5 MBq ^{89}Zr-trastuzumab corresponding to 100, 250, and 500 μg trastuzumab per mouse) through the penile vein, and microPET imaging was performed on the mice on days 1, 3, and 6 after the injection. Although tumor uptake of the label was apparent at 6 h after injection of the radiochemical, the radioactivity was present primarily in the blood at this time point. Subsequently, a decrease in radioactivity in the blood was noted from day 1 to day 6, with a corresponding increase in label in the tumor. *Ex vivo* analysis of the tissue showed that tumor uptake of the label was similar (30–33% of injected dose/gram tissue (% ID/g); P = 0.75) at the three doses. However, the tumor/blood ratios decreased with increasing doses (7.3, 5.3, and 4.7 at 100, 250, and 500 μg trastuzumab, respectively) and did not differ significantly ($P \geq 0.47$) at each dose. Among the various organs examined, maximum uptake of radioactivity was observed in the liver and spleen (9.0% ID/g; both organs have a significant blood supply), and little accumulation of the label was observed in the muscle and brain tissue (<1.0% ID/g). The tumor/liver ratios (3.3, 4.6, and 4.0 at 100, 250, and 500 μg trastuzumab, respectively) did not differ significantly ($P \geq 0.18$) at the three injected doses.

Dijkers et al. compared the biodistribution of ^{89}Zr-trastuzumab and ^{111}In-trastuzumab in athymic mice bearing either SKOV3 or GLC4 xenograft tumors (n = 5 animals/group) (1).

The animals were injected with the same respective radiolabeled mAb as before, and accumulation of radioactivity in the various organs was determined at day 1 and day 6 after the injection. Both labeled mAbs had a similar pattern of uptake in the HER2-overexpressing tumors (19.3 ± 2.0% ID/g and 33.4 ± 7.6% ID/g at 1 d and 6 d, respectively, for ^{89}Zr-trastuzumab and 17.7 ± 1.9% ID/g and 39.3 ± 9.5% ID/g at 1 d and 6 d, respectively, for ^{111}In-trastuzumab; $P = 0.47$). The HER2-negative tumors had a lower accumulation of radioactivity with both labeled mAbs, with 7.1 ± 0.7% ID/g and 6.8 ± 0.8% ID/g for ^{89}Zr-trastuzumab and ^{111}In-trastuzumab ($P = 0.56$), respectively, at day 6 after injection. The amount of label in the blood of mice bearing HER2-positive tumors decreased from 20.4 and 18.6% ID/g for ^{89}Zr-trastuzumab and ^{111}In-trastuzumab, respectively, at day 1 to 4.3 and 5.3% ID/g, respectively at day 6. The tumor/liver ratios were 5.2 and 7.3 for ^{89}Zr-trastuzumab and ^{111}In-trastuzumab, respectively, at day 6.

The investigators observed a good correlation ($R^2 = 0.972$) in the tumor uptake of both radiobiopharmaceuticals and concluded that, because of its high spatial resolution, ^{89}Zr-trastuzumab could be used in the clinical setting after further evaluation.

Other Non-Primate Mammals

[PubMed]

No references are currently available.

Non-Human Primates

[PubMed]

No references are currently available.

Human Studies

[PubMed]

No references are currently available.

Supplemental Information

[Disclaimers]

No information is currently available.

References

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