

Case Report



OPEN ACCESS

Received: Oct 12, 2021

Revised: Nov 23, 2021

Accepted: Dec 26, 2021

Published online: Jan 21, 2022

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The Prediction of HER2-Targeted Treatment Response Using ⁶⁴Cu-Tetra-Azacyclododecanetetra-Acetic Acid (DOTA)-Trastuzumab PET/CT in Metastatic Breast Cancer: A Case Report

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ABSTRACT

A 45-year-old woman diagnosed with breast cancer reported disease progression in the form of metastatic lung and recurrent breast lesions following chemotherapy and human epidermal growth factor receptor 2 (HER2)-targeted therapy. The patient underwent ⁶⁴Cu-tetra-azacyclododecanetetra-acetic acid (DOTA)-trastuzumab positron emission tomography/computed tomography (PET/CT) to evaluate the HER2 expression status. ⁶⁴Cu-DOTA-trastuzumab accumulated in the left breast and lymph nodes but not in the lung lesions. Following trastuzumab emtansine treatment, there was a significant improvement in the lesions with ⁶⁴Cu-DOTA-trastuzumab accumulation. However, the lesions that did not accumulate ⁶⁴Cu-DOTA-trastuzumab aggravated. Therefore, it was concluded that ⁶⁴Cu-DOTA-trastuzumab PET/CT can be used to predict the outcome of HER2-targeted treatment by evaluating HER2 expression in breast cancer patients.

Keywords: Breast Neoplasms; ⁶⁴Cu-DOTA-Trastuzumab; ERBB2 Protein, Human; Positron-Emission Tomography

INTRODUCTION

Numerous receptors expressed on the cancer cells have been studied as drug targets for cancer treatment. The human epidermal growth factor receptor (HER) has been identified as a potential target for representative molecular therapeutic agents [1]. Overexpression of HER

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Funding

This project was funded in part by a grant from the Korea Institute of Radiological and Medical Sciences (KIRAMS), funded by the Ministry of Science, ICT (MSIT), Republic of Korea (No. 50547-2021), and in part by grants from the National Research Foundation of Korea (NRF), funded by the Ministry of Science, ICT (MSIT), Republic of Korea (No. 2020R1A2C2102492).

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

Conceptualization: Lee I, Lim I, Choi CW, Seong MK, Kim HA, Lim SM; Data curation: Seong MK, Kim HA, Noh WC; Formal analysis: Lee I; Funding acquisition: Lim I; Investigation: Byun BH; Methodology: Lim I, Kim BI, Lee KC, Kang CM, Kim HA, Noh WC, Lim SM; Project administration: Lee I; Resources: Byun BH, Lee KC, Seong MK, Noh WC; Supervision: Lim I, Kim HA; Validation: Lee I, Byun BH, Kim BI; Visualization: Lee I, Byun BH; Writing - original draft: Lee I; Writing - review & editing: Lee I, Lim I, Choi CW, Lee KC, Kang CM, Seong MK, Kim HA, Lim SM.

is strongly correlated with rapid tumor progression [1]. Among the members of the HER family, HER2/neu (HER2) is overexpressed in breast cancer [2]. Numerous drugs targeting HER2 have been developed and have demonstrated significant therapeutic efficacy in breast cancer treatment, including trastuzumab, pertuzumab, and lapatinib [3].

To increase the efficiency of HER2-targeted therapy, treatment must be performed in accordance with the exact status of HER2 expression in the tumor. However, HER2 expression has been reported to vary at the time of the initial diagnosis and in cases of recurrent or metastatic lesions. Moreover, HER2 expression in lesions may change over time [4]. Therefore, routine evaluation of HER2 expression is crucial during treatment. HER2 expression in tumors is usually evaluated using an invasive biopsy method. However, a repeat biopsy may be inconvenient for patients. To overcome this limitation, non-invasive HER2 expression evaluation methods using radioisotopes have been developed [5].

A clinical trial was conducted to evaluate HER2 expression using trastuzumab labeled with radioisotopes such as ^{124}I and ^{89}Zr , and the degree of HER2 expression in tumors was presented [5,6]. Additionally, HER2-targeted positron emission tomography (PET) using ^{64}Cu -tetra-azacyclododecanetetracetic acid (DOTA)-trastuzumab was attempted to effectively display the expression of HER2 in breast cancer patients [6-8]. Moreover, our group has previously reported the evaluation of HER2 expression using non-invasive PET images with ^{64}Cu -1,4,7-triazacyclononane-1,4,7-triacetic acid-trastuzumab [5].

In this case report, the level of HER2 expression was identified in multiple lesions of a breast cancer patient using ^{64}Cu -DOTA-trastuzumab PET/computed tomography (CT) images. It was confirmed that the level of HER2 expression in each lesion may be different.

CASE REPORT

A 45-year-old woman was diagnosed with left-sided breast cancer with lung metastasis. At the initial diagnosis, the HER2 status of the left breast tumor was identified with an immunohistochemistry (IHC) score of 3+. Following chemotherapy comprising six cycles of docetaxel, eight cycles of trastuzumab, and five cycles of pertuzumab, disease progression was observed in the form of pulmonary metastatic lesions and breast lesions. ^{64}Cu -DOTA-trastuzumab PET/CT (HER2 PET/CT) was performed to evaluate the HER2 expression in recurrent lesions, and ^{18}F -fluorodeoxyglucose (FDG) PET/CT was performed to evaluate the overall metastatic lesions.

The ^{64}Cu -DOTA-trastuzumab PET images were acquired using a GE Discovery 710 PET/CT (GE Healthcare, Milwaukee, USA). Following the administration of an intravenous trastuzumab (45 mg) injection, the participant was intravenously injected with ^{64}Cu -DOTA-trastuzumab (370 MBq) with an interval of at least 15 minutes. PET images were acquired 48 hours after the ^{64}Cu -DOTA-trastuzumab injection. The ^{18}F -FDG PET/CT was performed one day before the administration of ^{64}Cu -DOTA-trastuzumab injection. After 6 hours of fasting, 370 MBq of ^{18}F -FDG was intravenously injected. The blood glucose level before injecting ^{18}F -FDG did not exceed 7.2 mmol/L. PET images were acquired using a GE Discovery 710 PET/CT (GE Healthcare).

The ^{18}F -FDG PET/CT depicted the presence of multiple lesions in the left breast, lymph nodes, and both lungs (**Figures 1A and 2A**), while HER2 PET/CT showed accumulation of ^{64}Cu -DOTA-trastuzumab in the left breast and lymph nodes, but not in the lung lesions (**Figures 1B and 2B**). The response after three cycles of trastuzumab emtansine treatment evaluated using ^{18}F -FDG

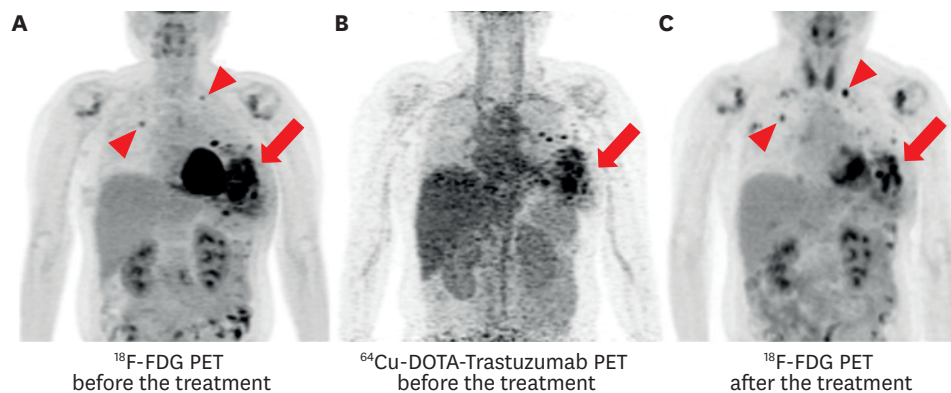


Figure 1. Maximum intensity projection images before and after the treatment. Recurrent lesions in the left breast (arrow) and a few pulmonary metastases (arrowheads) were observed on the ^{18}F -FDG PET images. (A) ^{64}Cu -DOTA-trastuzumab PET images showed recurrent lesions in the left breast (arrow). (B) After the treatment, the ^{18}F -FDG PET images show that while the extent and metabolic activity of the recurrent lesions in the left breast decreased (arrows), the size and metabolic activity of the metastatic lung lesions increased (arrowheads). (C) ^{64}Cu -DOTA-trastuzumab PET image was obtained 48 hours after the ^{64}Cu -DOTA-trastuzumab injection. FDG = fluorodeoxyglucose; PET = positron emission tomography; DOTA = tetra-azacyclododecanetetracetic acid.

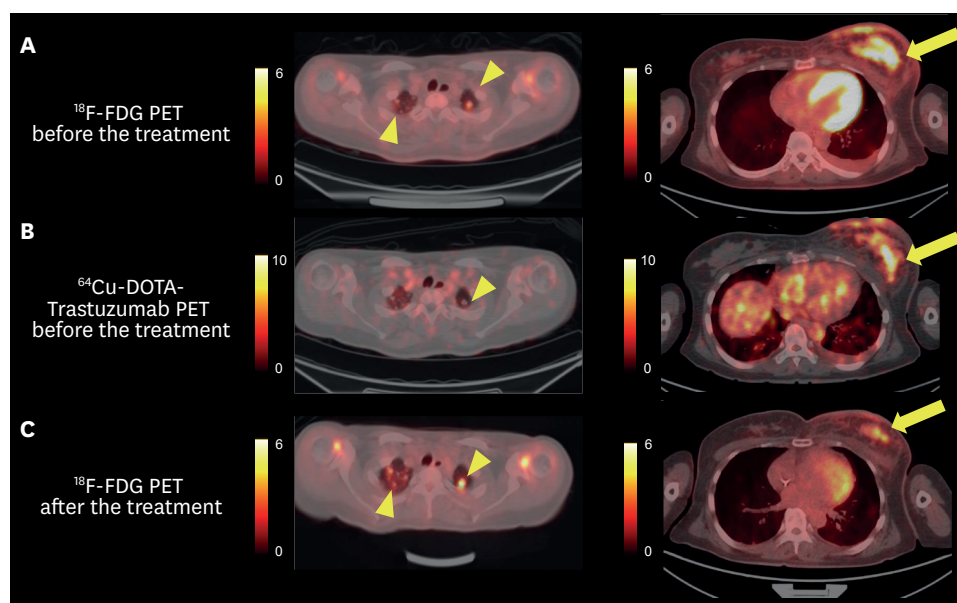


Figure 2. ^{18}F -FDG PET/CT and ^{64}Cu -DOTA-trastuzumab PET/CT images before and after the treatment. Before the treatment, the uptake of ^{18}F -FDG was definitely observed at the lesions of lung metastases (arrowheads, left side of panel A), whereas the uptake of ^{64}Cu -DOTA-trastuzumab at the same lung lesions was not clear (arrowheads, left side of panel B). The uptake of both ^{18}F -FDG (right side of panel A) and ^{64}Cu -DOTA-trastuzumab (right side of panel A) were definitely observed at the recurrent lesions of the left breast (arrows). After the treatment, the size and metabolic activity of a few metastatic lung lesions increased (arrowheads, left side of panel C). The SUV_{max} of the left upper lung lesions increased from 3.2 (left side of panel A) to 5.6 (left side of panel C). However, the extent and metabolic activity of the recurrent lesions in the left breast decreased (arrows, right side of panels A and C). The SUV_{max} of the recurrent lesion in the left breast decreased from 12.0 (right side of A) to 6.4 (right side of panel C). ^{64}Cu -DOTA-trastuzumab PET image was obtained 48 hours after the ^{64}Cu -DOTA-trastuzumab injection. FDG = fluorodeoxyglucose; PET = positron emission tomography; CT = computed tomography; DOTA = tetra-azacyclododecanetetracetic acid; SUV_{max} = maximum standardized uptake value.

PET is shown in **Figures 1C** and **2C**. A follow-up ^{18}F -FDG PET/CT demonstrated a reduction in the size and metabolic activity in the left breast lesions, exhibiting ^{64}Cu -DOTA-trastuzumab accumulation (arrow, right side of **Figure 2C**). However, increased size and metabolic activity on the follow-up ^{18}F -FDG PET/CT were observed in the metastatic lung lesions without ^{64}Cu -DOTA-trastuzumab uptake (arrowheads, left side of **Figure 2C**).

This study was approved by the Korean Ministry of Food and Drug Safety and the Institutional Review Board (IRB) of KIRAMS (IRB No. KIRAMS 2017-09-005). All procedures were performed following the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

DISCUSSION

Owing to the heterogeneity of tumors, HER2 expression differs between primary and metastatic lesions in breast cancer. Moreover, the expression varies according to disease progression. Therefore, it is important to evaluate HER2 expression to improve the outcome of HER2-targeted treatments. Numerous studies have reported the use of HER2 PET to evaluate HER2 expression in tumors using a non-invasive method. HER2 PET employs whole-body imaging rather than the biopsy of a limited number of lesions [5-8]. Therefore, it is an effective method for evaluating HER2 expression in the body, which, in turn, can be used to optimize HER2-targeted treatments. Further, in a recent study, patient-specific response to neoadjuvant chemotherapy and HER2-targeted therapy was predicted by combining ^{64}Cu -DOTA-trastuzumab PET and magnetic resonance imaging data with a mathematical model [9].

In this case, when the patient showed disease progression post treatment, ^{64}Cu -DOTA-trastuzumab uptake was observed in the lesions in the left breast and left axillary lymph nodes using HER2 PET. However, metastatic lung lesions did not indicate a discernible uptake of ^{64}Cu -DOTA-trastuzumab. This implied that the lesions in the left breast and left axilla had tumors with higher HER2 expression, whereas the metastatic lung lesions were HER2-negative tumors. Following treatment with trastuzumab emtansine, the follow-up ^{18}F -FDG PET/CT demonstrated a mixed response. The lesions in the left breast and axilla improved; however, the metastatic lung lesions aggravated. This treatment response was consistent with the HER2 expression status observed in HER2 PET images. While lesions with positive HER2 expression responded well to the treatment, HER2-negative lesions did not respond to trastuzumab emtansine.

A limitation of this case report is that the correlation between the uptake of lung lesions on ^{64}Cu -DOTA-trastuzumab PET and IHC results was not confirmed due to the lack of direct biopsy of the lung lesions. However, a previous study reported that the uptake of ^{64}Cu -DOTA-trastuzumab in the lesions was strongly correlated with the IHC score [8]. Therefore, HER2 PET sufficiently predicts HER2 status, even without biopsy results.

The outcome of this case study suggests that ^{64}Cu -DOTA-trastuzumab, a HER2-targeted PET ligand, can be utilized to evaluate HER2 expression in multiple lesions of patients with breast cancer.

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