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Reduction of Tumor Biomarkers from very High to Normal and Extensive Metastatic Lesions to Undetectability in a Patient With Stage IV HER2-positive Breast Cancer Treated With Low-dose Trastuzumab Deruxtecan in Combination With Oral Recombinant Methioninase and a Low-methionine Diet

MOTOKAZU SATO[1,2,3,4], QINGHONG HAN[1], RYOSUKE MORI[1], KOHEI MIZUTA[1,2], BYUNG MO KANG[1,2], SEI MORINAGA[1,2], NORITOSHI KOBAYASHI[3], YASUSHI ICHIKAWA[3], ATSUSHI NAKAJIMA[4] and ROBERT M. HOFFMAN[1,2]

[1]*AntiCancer Inc., San Diego, CA, U.S.A.;*
[2]*Department of Surgery, University of California, San Diego, CA, U.S.A.;*
[3]*Department of Oncology, Yokohama City University School of Medicine, Yokohama, Japan;*
[4]*Department of Gastroenterology and Hepatology, Yokohama City University School of Medicine, Yokohama, Japan*

Abstract. *Background/Aim: Breast cancer is the most common and the deadliest cancer among women in the world. Treatment options for HER2-positive metastatic breast cancer patients are limited. Trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate (ADC), has recently been introduced as second-line chemotherapy for HER2-positive metastatic breast cancer. The aim of the present study was to evaluate the efficacy of methionine restriction with oral recombinant methioninase (o-rMETase) and a low-methionine diet combined with T-DXd, on a patient with HER2-positive recurrent stage IV breast cancer. Case Report: A 66-year-old female was diagnosed with HER2-positive metastatic breast cancer. Computed tomography (CT) indicated peritoneal dissemination, thickening of the sigmoid colon and splenic flexure and widespread bone metastases. The patient was previously treated with fulvestrant, trastuzumab, pertuzumab, paclitaxel and capecitabine which were ineffective. T-DXd was administered as a second-line chemotherapy. Since the patient experienced strong side effects, the dose of T-Dxd was decreased. The patient began methionine restriction using o-rMETase and a low-methionine diet along with T-DXd. After the start of the combined treatment, CA15-3 and CA27.29, tumor markers for breast cancer, decreased rapidly from a very high level. The levels of both tumor markers are currently normal. Additionally, peritoneal-dissemination nodules, ascites and the thickness of the sigmoid colon and splenic flexure are no longer detected on CT. The patient maintains a high performance status, without severe side effects of the combination treatment. Conclusion: Methionine restriction consisting of o-rMETase and a low-methionine diet, in combination with T-DXd as second-line chemotherapy, was highly effective in a patient with HER2-positive stage IV breast cancer.*

Correspondence to: Robert M. Hoffman, Ph.D., AntiCancer Inc., 7917 Ostrow St, Suite B, San Diego, CA 92111, U.S.A. Tel: +1 6198852284, e-mail: all@anticancer.com

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Breast cancer is the most prevalent and the most fatal cancer among women in the world (1). It has been reported that approximately 14-22% of female breast cancer patients overexpress human epidermal growth factor 2 (HER2) (2). HER2 positivity is associated with an increased risk for the development of systemic metastasis (3). The survival rate of stage IV breast cancer is much lower than those of the other stages; the 5-year survival rate is 20-35% (2). While HER2-targeted drugs have improved the prognosis for breast cancer, with a median survival time from 14 months to 29 months (4), they have not effected complete responses (CR) for metastatic breast cancer (5).

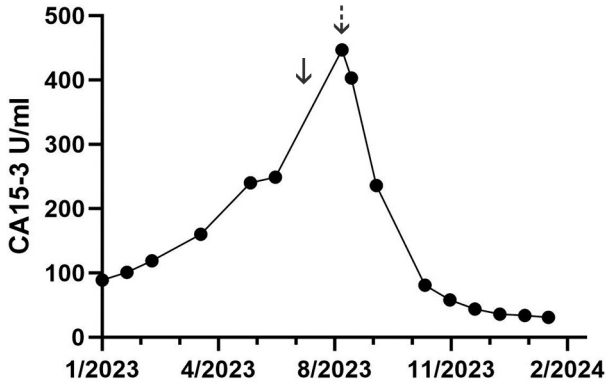

Figure 1. *Time course of changes in CA15-3 levels (U/ml) in a patient with HER2-positive metastatic breast cancer treated with trastuzumab deruxtecan (T-Dxd), oral methioninase (o-rMETase), and a low-methionine diet. Dashed arrow indicates the start of T-Dxd. Solid arrow indicates the start of rMETase.*

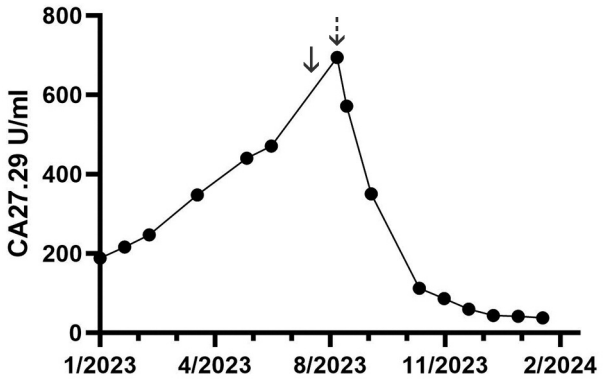

Figure 2. *Time course of changes in CA27.29 levels (U/ml) in a patient with HER2-positive metastatic breast cancer treated with trastuzumab deruxtecan (T-Dxd), oral methioninase (o-rMETase), and a low-methionine diet. Dashed arrow indicates the start of T-Dxd. Solid arrow indicates the start of rMETase.*

Methionine addiction is a fundamental and general hallmark of cancer known as the Hoffman effect (6-9). Methionine addiction of cancer cells is at least partly caused by excess transmethylation, resulting in a significantly greater need for exogenous methionine compared to normal cells, despite normal or greater than normal endogenous synthesis of methionine from homocysteine by the cancer cells (6, 10-14). Consequently, cancer cells are unable to survive without external methionine, even though cancer cells produce methionine at a high rate (6, 12-14).

Our laboratory has developed recombinant methioninase (rMETase) to target methionine addiction (15). When introduced orally, this enzyme breaks down methionine in the gut, leading to a reduction in methionine levels in the circulation and in tumors (16). Oral administration of rMETase (o-rMETase) has demonstrated efficacy to inhibit breast cancer in patient-derived orthotopic xenograft (PDOX) models (17-20).

Methionine restriction including o-rMETase selectively arrests cancer cells in the late-S/G_2 phase of the cell cycle (21, 22). Since S-phase is the main target of cytotoxic chemotherapy, methionine restriction is synergistic with cytotoxic chemotherapy. There have been many reports that o-rMETase has synergistic efficacy with many chemotherapy drugs without side effects (23).

Previously, rMETase combined with first-line chemotherapy eliminated axillary metastases in a patient with invasive lobular breast cancer (24). Since trastuzumab deruxtecan (T-DXd) includes irinotecan, a topoisomerase I inhibitor, we hypothesized that treatment with T-DXd along with methionine restriction, using o-rMETase and a low-methionine diet, would have synergistic efficacy for HER2-positive breast cancer. We have recently shown high synergy of irinotecan and rMETase on colon cancer cells *in vitro* (25).

In the present case report, a 66-year-old female with HER2-positive recurrent stage IV metastatic breast cancer, treated with a low-dose T-DXd, combined with oral rMETase and a low-methionine diet, demonstrated a rapid decrease from very high levels of breast-cancer biomarkers to normal levels, and regression of metastatic lesions.

Materials and Methods

Production and formulation of rMETase. rMETase was produced by fermenting recombinant *Escherichia coli* transformed with the *methioninase* gene from *Pseudomonas putida*. The purification of *methioninase* involved a high-yield method that had a heat step at 60˚C, polyethylene glycol precipitation, and ion exchange column chromatography using diethylaminoethyl (DEAE)-Sepharose FF (26).

Methionine restriction and rMETase administration. The patient went on a methionine-restricted diet, following the Nutritional Oncology Research Institute (NORI) protocol (27). This procedure recommends less than 2 mg/kg body weight methionine intake per day. rMETase was administered orally twice a day approximately 30 min after each meal at a dose of 250 units as a supplement.

Case Report

A 66-year-old female was diagnosed with HER2-positive, stage IV metastatic breast cancer. Computed tomography (CT) revealed peritoneal dissemination, thickening of the sigmoid colon and splenic flexure and widespread osseous sclerotic metastases. The patient was initially treated with fulvestrant, trastuzumab, pertuzumab, paclitaxel and capecitabine, which were ineffective. As second-line chemotherapy, T-DXd (5.4 mg/kg) was introduced in August

Table I. *Time course of changes in CA15-3 and CA27.29 levels (U/ml) in a patient with HER2-positive stage IV breast cancer treated with trastuzumab deruxtecan (T-Dxd), oral methioninase (rMETase) and a low-methionine diet. rMETase was started in June 2023 and T-Dxd was started in August 2023.*

Date (Month/Year)	1/2023	2/2023	4/2023	6/2023	8/2023	9/2023	10/2023	11/2023	1/2024
CA15-3 (U/ml)	89	119	160	249	447	236	81	44	31
CA27.29 (U/ml)	188.5	246.9	347.4	471.1	694.4	350.1	112.2	59.7	37.8

2023 along with methionine restriction consisting of o-rMETase and a low-methionine diet which were started in June 2023.

After the start of T-DXd, the patient felt extreme fatigue. Since the patient experienced adverse effects, the dose of T-DXd was decreased from 5.4 mg/kg to 4.4 mg/kg in September 2023. Cancer marker CA15-3, which previously reached a peak of over 400 U/ml in August 2023, rapidly decreased and is currently normal at 31 U/ml (Figure 1, Table I). Similarly, cancer marker CA27.29, above 600 U/ml in August 2023, rapidly declined to 37.8 U/ml and is within normal range (Figure 2, Table I).

Furthermore, the CT scan conducted in October 2023 revealed the disappearance of peritoneal dissemination nodules and ascites. Additionally, there was improvement in the thickness of the sigmoid colon and splenic flexure. The bone metastases were stable.

The patient maintains a high performance status without severe adverse effects on the combination of a low-dose T-DXd and o-rMETase.

Discussion

This is the first report of combining T-DXd and methionine restriction, comprising o-rMETase and a low-methionine diet. First-line chemotherapy for HER2-positive metastatic breast cancer comprises pertuzumab and trastuzumab (anti-HER2 antibodies), combined with a taxane (28-30). Based on the results of recent clinical trials (31-33), T-DXd is used as second-line chemotherapy for HER2-expressing metastatic breast cancer (34). However, since it has only been introduced into clinical practice for a short period of time, its clinical efficacy has not yet been optimized.

In the present case, a combination of low-dose T-DXd and methionine restriction with a low-methionine diet and o-rMETase resulted in a rapid decrease in tumor markers and regression of distant metastases.

We first found that methionine restriction is synergistic with chemotherapy almost 40 years ago (35). Subsequently, a large amount of research has shown that there is synergy between methionine restriction, specifically with rMETase and/or a low-methionine diet, and all types of chemotherapy (23). Cancer cells selectively arrest in the late-S/G_2 phase of the cell cycle in response to methionine depletion (21, 22). Hence, chemotherapy drugs targeting S-phase exhibit enhanced efficacy when combined with methionine restriction. In the present case, as irinotecan's action is in S-phase, our hypothesis is that the combination treatment was synergistic. The procedure of combining methionine restriction with chemotherapy is termed the Hoffman protocol (23, 35).

Our previous study showed a complete response of a breast-cancer patient with axillary lymph-node metastases treated with first-line chemotherapy along with o-rMETase and a low-methionine diet (24).

The present study suggests that methionine restriction is promising in combination with second-line chemotherapy for metastatic breast cancer and further clinical studies are needed. o-rMETase is effective as it targets the fundamental basis of cancer, methionine addiction (6-14, 36-53).

Conflicts of Interest

The Authors declare no competing interests regarding this work.

Authors' Contributions

MS and RMH wrote the article. QH provided methioninase. MS, QH, RM, KM, SM, BMK, NK, YI, AN, and RMH critically reviewed the article.

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