

Eradication of Extensive Lymph-Node, Bone and Pleural Metastases of a Breast-Cancer Patient Treated With Radiation, Immunotherapy and Oral Recombinant Methioninase

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Abstract

Background/Aim: Metastatic breast cancer is a recalcitrant disease with a poor prognosis. Novel targets and therapies are necessary to improve the survival rate of patients with metastatic breast cancer. Previous pre-clinical and clinical studies, have demonstrated the effectiveness of oral recombinant methioninase (o-rMETase) against breast cancer. The present case report shows that combination treatment with radiation, immunotherapy, a low-methionine diet, and o-rMETase led to rapid eradication of extensive bone and other metastases in a patient with breast cancer.

Case Report: A patient with breast cancer with extensive metastases to the liver, lymph nodes, pleura and bones was diagnosed using [¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET). The patient was immediately started on systemic drug therapy with tamoxifen and leuporelin, but it failed to suppress the tumor. Then, combination treatment with radiation, immunotherapy with biological response modifier (BRM)-activated killer (BAK), a low-methionine diet, and o-rMETase was started as second-line treatment. Five months after beginning of the combination treatment, the patient had a subsequent FDG-PET scan and extensive eradication of almost all metastases was observed, with only a metastasis remaining in the liver.

Conclusion: o-rMETase in combination with immunotherapy and irradiation eradicated extensive metastases in a patient with breast cancer. Further investigation of this combination treatment for breast cancer is necessary including clinical trials.

Keywords: Breast cancer, metastasis, eradication, FDG-PET, radiation, immunotherapy, BAK, oral recombinant methioninase, methionine addiction, Hoffman effect.



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Introduction

Metastatic breast cancer is a recalcitrant disease with a 5-year survival rate of 11-33%, and its rate varies by subtype, with metastatic triple-negative breast cancer having the poorest prognosis (1). Novel targets and therapies are necessary to improve the survival rate of patients with metastatic breast cancer.

Methionine addiction is a fundamental and general hallmark of cancer and promising target for cancer therapy (2-4). A patient with invasive lobular carcinoma (ILC) of the breast with extensive axillary-lymph-nodes metastases was previously treated with neo-adjuvant first-line chemotherapy, a hormone blocker, a low-methionine diet and oral recombinant methioninase (o-rMETase) with complete eradication of the axillary-lymph-node metastasis (5). Another patient with bone-metastatic ductal breast cancer was treated with chemotherapy, a low-methionine diet, and o-rMETase and experienced remission (6). These reports suggest that the combination of chemotherapy and methionine restriction may be an effective treatment strategy for metastatic breast cancer with improved outcomes.

The present case report describes a breast-cancer patient with extensive lymph-node, bone and a pleural metastases, which occurred after first-line therapy. The patient was then treated with radiation, immunotherapy, a low-methionine diet, and o-rMETase. Based on the present case report, we discuss the possibility of improving metastatic breast-cancer outcomes by combining conventional therapy with methionine-restriction therapy.

Case Report

A patient presented in June 2023 with cancer of the left breast and metastases in the liver, lungs and bones. The patient was immediately started on systemic drug therapy with tamoxifen and leuporelin. One month later, the primary tumor in the left breast was treated with radiation therapy, and tamoxifen and leuporelin were discontinued due to side effects of severe joint pain. In November 2024,

the patient underwent an [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) scan to evaluate treatment efficacy, which showed extensive metastatic growth in lymph nodes, bone, and pleura (Figure 1A). Due to severe pain in the sternum, the patient received radiotherapy (8Gy/1fr). Since the first-line drug therapy failed to suppress the cancer, biological response modifier (BRM)-activated killer (BAK) therapy was initiated as a second-line treatment. Additionally, the patient went on a low-methionine diet and o-rMETase (twice daily, 250 units 30 min after the two major meals of the day) from December 2024. A subsequent FDG-PET scan performed in April 2025 showed almost total eradication of metastases with the exception of a metastasis in the liver (Figure 1B). The patient continues to receive BAK therapy in combination with methionine restriction, and her disease remains under control. She continues to live a normal daily life.

Discussion

The present report shows that widespread metastases including the lymph nodes, pleura and bone in a patient with breast cancer, that persisted five months after systemic drug therapy with tamoxifen and leuporelin and were eradicated following administration of radiation immunotherapy with BAK, a low-methionine diet and o-rMETase. The present results are consistent with previous studies showing extensive metastasis eradication in two breast-cancer patients taking chemotherapy, a low methionine diet and o-rMETase (5, 6).

We have previously shown that o-rMETase is effective in patient derived orthotopic xenograft (PDOX) mouse models of triple-negative breast cancer (7-9). In a syngeneic mouse model of triple-negative breast cancer, we showed that o-rMETase prevented local recurrence and lung metastases after resection of the primary tumor (10). Orally-administered *E.coli*-expressing o-rMETase inhibited mouse triple-negative breast cancer in a nude-mouse model (11). In vitro studies have shown that rMETase synergistically inhibits human breast-cancer

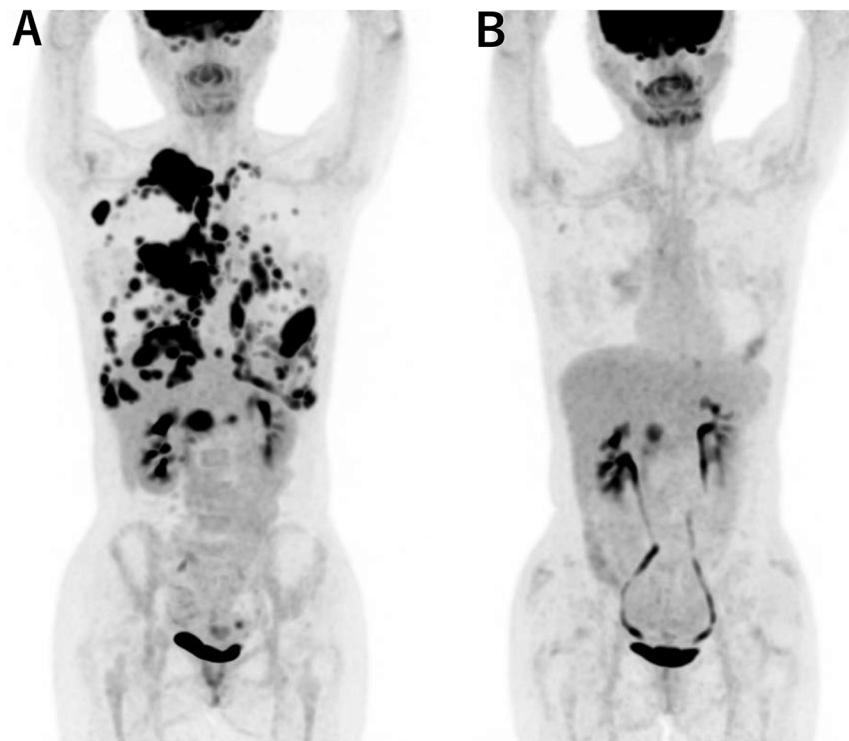


Figure 1. A female patient was diagnosed with left breast cancer with extensive metastases in her liver, lymph nodes, lungs, and bones using an [^{18}F]-fluorodeoxyglucose positron emission tomography (FDG-PET) (A). After five months of treatment with a combination of radiation, immunotherapy with biological response modifier (BRM)-active killer (BAK), a low-methionine diet, and oral recombinant methioninase (o-rMETase), the extensive metastases were almost eradicated as seen with FDG-PET (B).

cells in combination with either chloroquine, ivermectin, or olaparib (12-14).

BAK therapy is a type of adoptive immunotherapy that uses autologous peripheral blood lymphocytes activated with biological response modifiers, such as interleukin-2 and interferon-alpha. The activated CD56-positive killer cells, including natural killer (NK) and $\gamma\delta$ T cells, are reinfused to enhance antitumor immunity (15). BAK therapy has shown promising results in patients with advanced solid tumors, including breast cancer, that prolonged survival and improved quality of life (15).

Previously, there have been no reported cases in which systemic BAK therapy has led to near-complete eradication of extensive metastatic lesions in a patient with breast cancer. The present case report is the first to demonstrate that a combination of BAK therapy, radiotherapy, and methionine-restriction therapy may

offer a promising therapeutic strategy for patients with advanced breast cancer. Future studies could use such agents in combination with o-rMETase in the clinic. o-rMETase has also been used clinically in combination with chemotherapy for pancreatic cancer (16), rectal cancer (17, 18), and glioma (19) with promising results. o-rMETase has also shown clinical promise in prostate cancer (20). More extensive clinical studies, including controlled clinical trials are needed to be performed with o-rMETase. rMETase is effective because it targets methionine addiction, a fundamental hallmark of cancer (2-4, 21-47).

Conflicts of Interest

The Authors declare no competing interests regarding this work.

Authors' Contributions

YA was a major contributor to writing the manuscript and RMH revised the article. QH and SL produced recombinant methioninase. TS, CH, KM, BMK, JSK, YM, NY, KH, ShM, KI, TH, SeM, HT, QH, SL and SD critically read and approved the final paper.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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