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Case Report

Dendritic Cell Immunotherapy for De Novo HER2+ Metastatic Breast Cancer

Eliana Burgos[1], Paige Aiello[2], Amy Aldrich[2], Robert Weinfurtner[2], Brian J Czerniecki[2], Aixa E Soyano[2*]

[1]University of South Florida, Tampa, FL, USA

[2]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

***Corresponding Author:** Aixa Soyano, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

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Abstract

Introduction: Intratumoral delivery of conventional dendritic cells (cDC1) offers a promising new immunotherapy strategy for HER2-positive breast cancer by activating $CD4^+$ Th1 cells and other innate immune components. **Case presentation:** We present a case series of two young women presenting with de novo metastatic HER2-positive breast cancer treated with cDC1 therapy alongside HER2-targeted and endocrine therapies. The patients tolerated the treatment well and showed encouraging outcomes, including tumor reduction, healing of metastatic sites and early immune responses before starting chemotherapy. Imaging revealed significant partial responses or no active disease, and blood analyses confirmed immune activation. **Conclusion:** These findings demonstrate the feasibility and safety of cDC1 intratumoral therapy as an early intervention and suggest its potential role in improving clinical outcomes. Further research is warranted to refine patient selection and treatment regimens for optimal integration into standard care for metastatic HER2-positive breast cancer.

Keywords: Breast Cancer; Metastatic Breast Cancer; Dendritic Cells; Immunotherapy; Intratumoral Therapy.

Introduction

Breast cancer (BC) is the leading cause of cancer and the second cause of cancer-related death in women worldwide [1]. While targeted therapy has shown promise in HER2 positive BC, recurrence and mortality remain significant challenges. We have shown in preclinical models that intratumoral delivery of conventional dendritic cells (cDC1) pulsed with MHC class II derived HER2 peptides combined with anti-HER2 antibodies results in dramatic regressions of injected tumors as well as distant regression of non-injected tumors [2]. This represents a potential novel approach to enhancing anti-HER2 immune responses using the primary tumor to drive systemic immune responses in patients with de novo metastatic HER2 positive BC. This therapy promotes robust lymphocyte infiltration into tumors while diminishing inhibitory myeloid suppressor populations, potentially enhancing the effectiveness of chemotherapy. Additionally, intratumoral cDC1 immunotherapy demonstrates favorable safety profiles and manageable side effects [3]. We have further demonstrated in preclinical models that the addition of α-Galactosylceramide (α-GalCer) elevates the recruitment of non-conventional T cells such as natural kill T cells (NKT) and gamma-delta (γδ) T cells into the tumor microenvironment, further enhancing the activity of this immunotherapy [4]. Since these patients are extremely high risk for recurrence and have increased mortality, it was justified to attempt to improve their mortality using cDC1 immunotherapy.

We present three illustrative cases of patients with de novo metastatic HER2 positive BC who responded positively to cDC1 immunotherapy, with decreased tumor burden and indications of durable response. These early findings suggest that cDC1 immunotherapy could play a critical role in reducing recurrence and improving long-term outcomes. Ongoing research is essential to refine treatment protocols and identify biomarkers that can guide patient selection for this promising therapeutic strategy.

Case Presentation

Patient 1

- A 26-year-old female presented with a palpable mass in her left breast in February 2023. She had an unremarkable medical and family history. A breast ultrasound was performed but was unrevealing. By May 2023, she began experiencing low back pain extending into the posterior aspect of her bilateral lower extremities, more pronounced on the left side. The pain progressed, leading her to visit the local emergency room at the end of July 2023. She was prescribed a steroid dose pack and pain medications.

- On August 23, 2023, an MRI of the lumbar spine revealed diffuse metastatic disease throughout the visualized osseous structures with severe compression deformity involving the L2 vertebral body and retropulsion of fracture fragments resulting in moderate to severe spinal canal stenosis. A CT chest performed on September 8, 2023, showed a suspicious left breast mass, diffuse osteolytic metastases, and multiple pathologic rib fractures. The abdomen and pelvis CT scan did not reveal any primary neoplasm but confirmed diffuse osteolytic metastases and the severe pathologic fracture at L2.

- Subsequently, On September 13, 2023, bilateral diagnostic breast imaging depicted a left breast irregular mass with amorphous calcifications and nipple retraction.

- Due to ongoing lower extremity pain and weakness, a repeat MRI of the spine was performed which showed extensive metastases throughout the entire spine, with severe pathologic fracture at L2 compressing the cauda equina. A brain MRI showed widespread calvaria metastases and disease in the skull base and clivus but no intracranial disease. The patient was admitted and underwent a lumbar corpectomy and tumor resection with reconstruction and internal fixation. Biopsy of the L2 confirmed metastatic adenocarcinoma compatible with a breast primary, ER+ 100%, PR+ 30%, HER2 3+ positive. A left breast incisional biopsy revealed an invasive ductal carcinoma, grade 3, ER+ 100%, PR+ 40-50%, HER2 3+ positive. Her post-operative course of the lumbar corpectomy was complicated with wound dehiscence requiring wound debridement with cultures growing MRSA. She was started on a six-week course of Vancomycin.

- Due to post-op complications prohibiting the start of systemic chemotherapy she began anti-HER2 blockade with trastuzumab and pertuzumab subcutaneously (Phesgo®) and Tamoxifen. Starting December 12, 2023, the patient underwent apheresis and began an expanded access use of cDC1 immunotherapy pulsed with HER2+ peptides with weekly intratumoral cDC1 injections in the breast at 100 million cells using ultrasound guidance for 6 weeks with concurrent subcutaneous trastuzumab, pertuzumab and oral tamoxifen. She declined genetic testing.

- Follow-up breast imaging indicated a response to treatment with a disappearance in the left breast mass. (Figure 1A, 1B). Follow up MRI brain demonstrated significantly improved dural extension of disease and reduced enhancement of the calvarium. (Figure 1C).

- A follow-up CT Thorax, Abdomen, Pelvis (TAP) on January 29, 2024, showed interval sclerosis of osseous metastasis. (Figure 1D). A bone scan confirmed healing metastasis.

- 4 cycles of docetaxel, trastuzumab and pertuzumab were added. She also received a booster of cDC1 every 3 months for 1 year.

- Her latest restaging CT TAP and bone scan from 4/9/25 continue to show partial response to treatment (including sclerosis of the bone lesions and disappearance of the breast mass biopsy proven).

- The patient continues to receive treatment with systemic trastuzumab, pertuzumab and Tamoxifen. Clinically, the patient is without back pain, shortness of breath or limitations in activities of daily living.

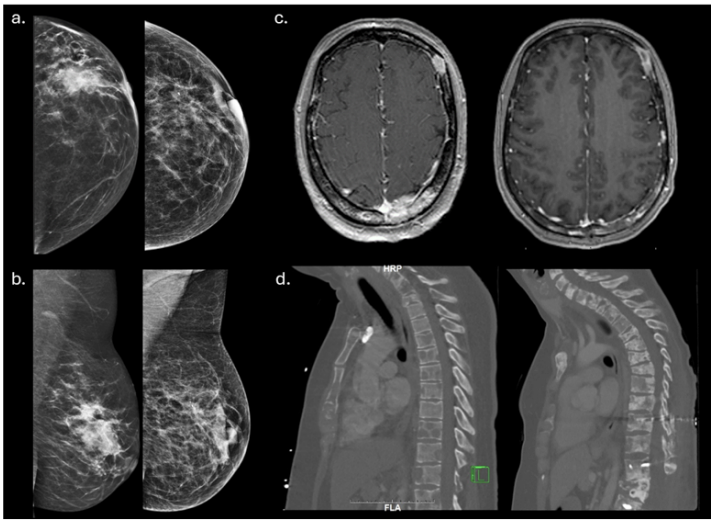

Figure 1: Patient 1: **(a)** Craniocaudal (CC) Mammogram pre-(left) and post-treatment (right) with cDC1 vaccine demonstrating interval decrease in mass density. **(b)** Mediolateral Oblique (MLO) Mammogram pre-(left) and post-treatment (right) with cDC1 vaccine demonstrating interval decrease in mass density. **(c)** Brain MRI pre-(left) and post-treatment (right) with cDC1 vaccine. Post-treatment MRI demonstrates significantly reduced enhancement in calvarium and improved dural extension. **(d)** CT Thorax, Abdomen, Pelvis pre-(left) and post-treatment (right) with cDC1 vaccine demonstrates diffuse pre-treatment lytic metastases converting to post-treatment sclerotic bone metastases.

Patient 2

- A 30-year-old female with history of anxiety/depression, Graves' disease and hypothyroidism noted a palpable left breast mass in April 2023 while pregnant, which was attributed to

hormonal changes. The mass continued to grow throughout her pregnancy, and she delivered on December 1, 2023.

- On December 7, 2023, a bilateral mammogram and left breast ultrasound demonstrated numerous fine pleomorphic calcifications and an irregular mass in the left breast. The left breast mass occupied all 4 quadrants. The left axilla showed multiple masses. A left breast core biopsy confirmed invasive ductal carcinoma, grade 3, ER+ 25%, PR+ 15%, HER2 3+ positive. Staging CT TAP showed suspected metastatic left axillary and subpectoral lymphadenopathy and multiple hepatic and osseous metastases. A bone scan was also suspicious for widespread osseous metastases. Genetic testing was negative for pathogenic mutations.

- The patient underwent a liver biopsy, confirming metastatic carcinoma consistent with breast primary, ER+ 1%, PR<1%, HER2 3+ positive.

- She began a single patient IND for cDC1 immunotherapy pulsed with HER2 peptides intratumorally at 200 million cells alongside with trastuzumab and pertuzumab subcutaneously. She experienced chills, headaches and epigastric pain after her injections which subsided with rescue medications.

- Follow up bone scan after initial 6-week immunotherapy series showed overall decrease in degree of pre-existing radiotracer avid foci suggesting treatment response and no new bone lesions. Similarly, a follow up breast MRI showed significant interval decrease in overall enhancement with masses centered in the left upper outer quadrant and decrease in level 1 and 2 adenopathy on the left (Figure 2A). CT TAP showed decrease in liver metastasis (Figure 2B).

- She proceeded to receive chemotherapy with docetaxel every 3 weeks in combination with continued trastuzumab and pertuzumab for 6 cycles with completion on 10/11/24.

- Restaging scans on 10/15/2024 and 1/24/25 showed partial response to treatment with resolution of liver metastasis, stable posttreatment changes of the left breast, stable osseous lesions (with decrease in uptake on bone scan) and no new suspicious mass, nodule or adenopathy.

- Given residual left breast mass (decreased from baseline) patient was interested in further cDC1 immunotherapy, for which protocol was addended to include 6 more weeks of cDC1 pulsed with HER2 and α-GalCer. She underwent apheresis on 1/27/25. She continues treatment with immunotherapy along with systemic trastuzumab/pertuzumab and letrozole/leuprolide.

- Restaging CT TAP and bone scan from 3/21/25 continue to show liver metastasis resolution, stable bone metastasis and post-treatment changes of the left breast. Diminished left breast mass. Clinically patient is doing well without pain, or limitations in activities of daily living.

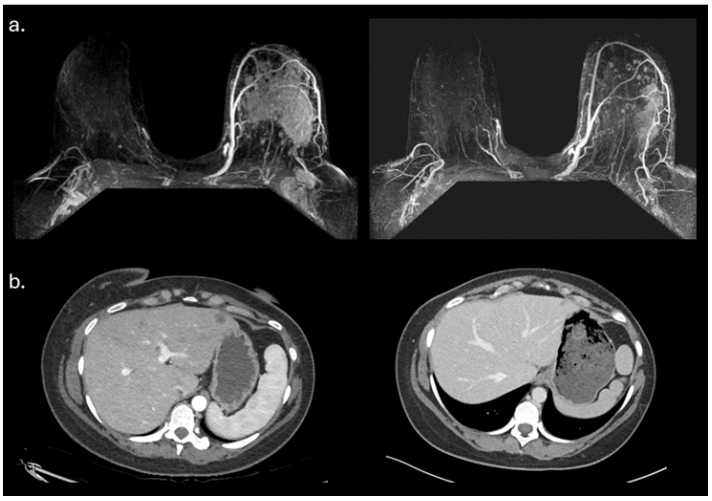

Figure 2: Patient 2: **(a)** Breast MRI pre-(left) and post-treatment (right) with cDC1 immunotherapy. Post-treatment MRI demonstrates decrease in size of the known malignant diffuse non-mass enhancement and axillary lymph node bulk. **(b)** CT Abdomen pre-(left) and post-treatment (right) with cDC1 immunotherapy. Post-cDC1 immunotherapy CT demonstrates a decrease in hepatic metastasis.

Discussion

Survival of de novo metastatic BC, although modestly better than recurrent/metastatic, still has substantial mortality [5, 6], highlighting the urgent need to integrate novel therapeutic strategies to reduce mortality. Surgical resection of the primary tumor has not been shown to be of significant benefit to reduce mortality [7, 8]. As such, we have taken the opportunity to use a novel immunotherapy to attempt to immunoablate the primary tumor and eliminate distant metastasis.

Cancer immunotherapy, particularly in the treatment of HER2 positive BC, has gained significant interest due to its potential to harness the immune system to target and destroy cancer cells. The introduction of monoclonal antibodies, such as trastuzumab and pertuzumab, has revolutionized treatment, improving outcomes for many patients [9]. However, a notable portion of patients still experience recurrence post-treatment. Research has shown that anti-HER2 CD4+ T helper cell (Th1) immunity plays a crucial role in effective cancer therapy, with weak Th1 responses being indicative of poor prognosis and treatment outcomes [10]. This is because CD4+ T helper cells are pivotal in mediating both innate and adaptive immune responses to tumors. They exhibit direct cytotoxic activity, modify antitumor cytokine responses, and enhance long-term immunologic memory, making them critical in combating tumor progression and recurrence [11]. They have

strong capacity to induce interferon gamma production, which eliminates HER2 expression on the surface and synergizes with anti-HER2 antibodies to cause senescence and apoptosis of HER2 BC [12].

While cDC1 used as a systemic vaccine has had success in causing a HER2-directed response to ductal carcinoma in situ (DCIS), invasive breast cancer elimination has been unremarkable when cDC1 has been used as a vaccine systemically [13]. We have subsequently demonstrated that delivery of large numbers of these cells directly into the tumor combined with anti-HER2 antibodies leads to dramatic resolution of tumors in preclinical models and regression of distant lesions as well [2]. This has been tested in early HER2 positive BC prior to initiation of THP therapy with substantial success causing regressions of primary tumors in 75% of patients [3,14]. This has emerged as a promising approach to augment the immune response in HER2 positive BC. This cDC1 intratumoral immunotherapy enhances lymphocyte infiltration, particularly CD4+ and CD8+ T cells, into cancerous regions, leading to disease elimination in approximately 30% of treated patients before surgical resection [3]. There is also a critical influx of non-conventional T cells such as NKT and γδ T cells, which may transform the inhibitory tumor microenvironment to enhance effectiveness. Moreover, cDC1 intratumoral therapy has been associated with long-lasting immunity, maintaining their efficacy even when patients subsequently undergo chemotherapy and trastuzumab treatment [3].

The safety of cDC1 therapy has been validated through multiple studies involving patients with DCIS and HER2 positive early-stage invasive BC [3,13,14]. Over 250 patients have been treated with cDC1 therapy without significant cardiac toxicity. Known side effects are typically mild (grade I or II), including injection site soreness, fatigue, fever, chills, muscle aches, headaches, and nausea, all of which are short-lasting and manageable with common medications like acetaminophen [3, 14].

Further supporting the efficacy of cDC1 immunotherapy, research has highlighted their role in inducing a robust anti-HER2 Th1 response. This response is critical for improving treatment outcomes, as demonstrated by studies showing that patients with higher levels of tumor-infiltrating lymphocytes (TILs) have better prognoses, as well as higher rates of pathological complete response (pCR) following chemotherapy [15, 16]. Specifically, high levels of CD8+ T-lymphocytes have been strongly correlated with positive clinical outcomes [17]. Additionally, CD4+ T cells play a significant role in enhancing the functionality of CD8+ T cells and maintaining adaptive immunity [18, 19].

We present this novel therapeutic approach that combines intratumoral cDC1 therapy with concurrent HER2-targeted and endocrine therapies in three young women diagnosed with de novo HER2-positive metastatic breast cancer. All patients demonstrated favorable tolerability and encouraging clinical responses. Imaging revealed significant tumor regression and signs of metastatic healing prior to the initiation of chemotherapy. Additionally, peripheral blood ELISPOT analyses showed robust immune activation, supporting the immunogenicity of this cDC1 approach in this setting. In addition, recent evidence suggests this therapy can eliminate disseminated cancer cells and may help to prevent continuous recurrence of further distant metastasis [20]. The positive impact of this immunotherapy on these stage four de novo patients suggests a trial using intratumoral cDC1 therapy with anti-HER2 antibodies is warranted to improve the mortality of these patients.

In conclusion, the integration of cDC1 intratumoral therapy into treatment protocols for HER2-positive BC represents a significant advancement in cancer immunotherapy. Moving forward continued research and clinical trials are warranted to optimize these protocols, identify biomarkers for patient selection, and explore combination therapies to further enhance treatment efficacy. By enhancing the body's immune response to tumors, this therapy offers a promising avenue for improving patient outcomes, reducing recurrence rates, and achieving long-lasting immunity.

Statements

Statement of Ethics: Treatment with cDC1 immunotherapy was obtained and approved through single patient investigational new drug application (INDs) with the FDA. The patients provided written informed consent prior to initiation of treatment. Informed patient consent was also obtained for publication of the data and images contained in these case reports.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions

Eliana Burgos[1], Paige Aiello[2], Amy Aldrich[2], Jared Weinfurtner[2], Brian J Czerniecki[2], Aixa E Soyano Muller[2].

1. University of South Florida, Tampa, FL, USA

2. H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

Contributions

EB, PA, AA, BC and AS contributed to data collection,

interpretation, literature searching, and manuscript drafting. JW contributed to data collection and interpretation. BC contributed to data interpretation, and critical review of the manuscript. All authors approved the final manuscript draft.

Data Availability Statement: All the data supporting the findings in this case report are contained within the text. Further enquiries can be directed to the corresponding author.

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