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Clinical Response to T-DM1 Plus Tucatinib in Pre-treated HER2-Positive Metastatic Breast Cancer: A Case Series

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Abstract

Background: HER2-positive breast cancer accounts for approximately 15–20% of all breast cancers and carries a historically aggressive clinical course. Real world evidence for T-DM1 plus tucatinib in elderly patients. Ado-trastuzumab emtansine (T-DM1) (UJVIRA®, Zydus Lifesciences Ltd.), is the second-line standard after pertuzumab-trastuzumab-based first-line therapy. Tucatinib (TUKAVO®, Zydus Lifesciences Ltd.), a highly selective HER2-directed tyrosine kinase inhibitor, improved survival in HER2-positive metastatic breast cancer in the HER2CLIMB trial. The phase III HER2CLIMB-02 trial showedthat adding tucatinib to T-DM1 significantly prolongs progression-free survival compared with T-DM1 monotherapy in previously treated patients.

Case Presentations: We report three patients with HER2-positive (IHC 3+) de novo or previously treated metastatic breast cancer who received T-DM1 plus tucatinib after progression on pertuzumab-trastuzumab-docetaxel and T-DM1. Two patients were 78 years old; one was 62 years old. All patients had high-volume nodal disease. After only three cycles of T-DM1 plus tucatinib, repeat PET-CT demonstrated near-complete or major partial metabolic responses in all three patients, with significant reduction in FDG-avid nodal, pulmonary, and skeletal disease. Toxicity was manageable across all cases, with grade 1 diarrhea being the most common adverse effect. No grade ≥3 toxicity, cardiac events, or dose reductions were required in the initial cycles.

Conclusion: T-DM1 plus tucatinib can induce rapid and deep metabolic responses in heavily pretreated HER2-positive metastatic breast cancer, including in elderly patients. These findings are hypothesis-generating and require validation in larger cohorts. The cases support the clinical utility of this regimen beyond its established efficacy in clinical trials and underscore the persistence of HER2 pathway addiction across multiple lines of therapy.

Keywords: HER2-positive breast cancer; Tucatinib; T-DM1; Ado-trastuzumab emtansine; HER2CLIMB-02; Metabolic response, biosimilar

Introduction

HER2-positive breast cancer, defined by HER2 gene amplification or protein overexpression, constitutes approximately 15–20% of all invasive breast cancers and has historically been associated with aggressive clinical

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behavior and reduced survival [1,2]. The advent of targeted anti-HER2 therapies has dramatically altered the natural history of this disease. Dual antibody blockade with pertuzumab and trastuzumab combined with docetaxel (THP) is established as the first-line standard of care in metastatic HER2-positive disease, producing a median overall survival exceeding 56 months in the phase III CLEOPATRA trial [3,4]. Following progression on THP, ado-trastuzumab emtansine (T-DM1) (UJVIRA®, Zydus Lifesciences Ltd.), an antibody-drug conjugate delivering the cytotoxic maytansinoid DM1 directly to HER2-overexpressing cells, is the established standard second-line agent, based on the EMILIA trial, which demonstrated significantly improved progression-free and overall survival compared with lapatinib plus capecitabine [5].

Tucatinib (TUKAVO®, Zydus Lifesciences Ltd.) is a highly selective, oral small-molecule inhibitor of the HER2 tyrosine kinase domain, with minimal off-target EGFR inhibition, conferring a differentiated tolerability profile compared with less selective HER2 tyrosine kinase inhibitors [6]. The pivotal HER2CLIMB trial demonstrated that tucatinib added to trastuzumab and capecitabine significantly improved progression-free survival (HR 0.54) and overall survival (median 24.7 vs. 19.2 months) in patients previously treated with trastuzumab, pertuzumab, and T-DM1, including those with brain metastases [7, 8]. Building on this, the phase III HER2CLIMB-02 trial evaluated the addition of tucatinib to T-DM1, demonstrating a statistically significant improvement in median progression-free survival (9.5 vs. 7.4 months; HR 0.76) compared with T-DM1 alone in patients previously treated with trastuzumab and a taxane, including patients with brain metastases [9, 10]. Despite advances in HER2-directed therapy, real-world evidence for T-DM1 plus tucatinib remains limited, particularly in heavily pretreated and elderly patients and in settings using biosimilar/generic formulations. This series highlights early PET-based metabolic responses observed within three cycles in routine practice. In this case series, biosimilar T-DM1 (UJVIRA®, Zydus Lifesciences Ltd.) and generic tucatinib (TUKAVO®, Zydus Lifesciences Ltd.) were used. These observations suggest that clinically meaningful responses can be achieved in routine practice, while acknowledging the small sample size and descriptive nature of this report.

Case Presentation

Case 1

A 78-year-old woman presented to the outpatient clinic with a 4-month history of a progressively enlarging left breast mass, increasing fatigue, dry cough, and 5 kg of unintentional weight loss. Examination revealed a 4–5 cm, irregular mass in the upper outer quadrant with skin tethering, nipple retraction, matted left axillary nodes, and a 1.5 cm supraclavicular node. Eastern Cooperative Oncology Group (ECOG) performance status was 1. Core biopsy confirmed grade 3 invasive ductal carcinoma, immunohistochemistry showed estrogen receptor (ER) positivity at 5%, progesterone receptor (PR) negative, HER2 IHC 3+ (confirmed by FISH), and Ki-67 45%. Positron Emission Tomography-Computed Tomography (PET-CT) revealed extensive FDG-avid nodal involvement in the axillary, supraclavicular, mediastinal, and abdominal nodal disease with bilateral pulmonary nodules, indicative of de novo metastatic HER2-positive breast cancer. The patient underwent six cycles of pertuzumab, trastuzumab, and docetaxel, followed by maintenance dual HER2 blockade, this treatment regimen yielded substantial disease control for approximately 14 months during maintenance pertuzumab-trastuzumab therapy. At progression, a re-biopsy of supraclavicular node showed the tumor had converted to ER 0% and PR 0%, with persistent HER2 3+ overexpression with a Ki-67 of 60%. Second-line T-DM1 was administered with initial disease stabilization; however, after six months, PET-CT demonstrated progressive nodal disease. T-DM1 was then continued with the addition of tucatinib. The combination treatment was well tolerated, and the only notable toxicity was Grade 1 diarrhoea, which was successfully managed with dietary changes and loperamide. Transient grade 1 transaminase elevation resolved spontaneously. No grade ≥3 adverse events, clinically significant thrombocytopenia or cardiac events were observed. Subsequent assessments showed stable laboratory parameters and the LVEF was 55%. After three treatment cycles, PET-CT demonstrated nearly complete metabolic response, along with clinical improvement and a maintained ECOG performance status of 1. Baseline and follow-up PET-CT maximum intensity projection images demonstrated marked interval metabolic response after treatment with tucatinib plus T-DM1 (Figure 1).

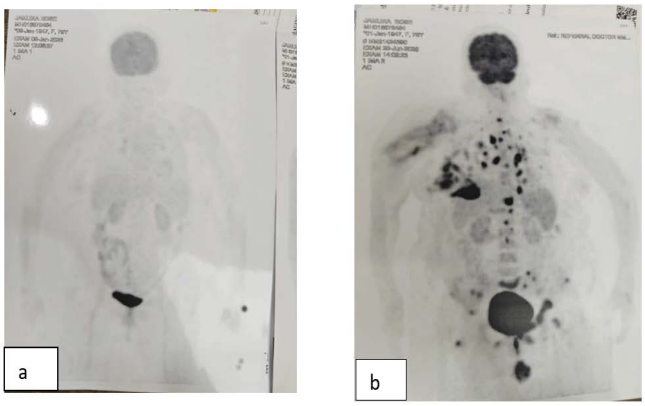

Figure 1: Baseline and follow-up PET-CT images in Case 1 showing marked metabolic response after tucatinib plus T-DM1.

a) Baseline scan showing multiple hypermetabolic metastatic lesions

b) Follow-up scan showing marked interval reduction in metabolic activity

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Case 2

A 62-year-old woman presented to the outpatient clinic with anorexia, progressive exertional dyspnea, dry cough, right supraclavicular swelling, and 6 kg weight loss over 2 months. Examination revealed a 3 cm mass in the right breast, right axillary lymphadenopathy, a 2 cm right supraclavicular node, and reduced right basal air entry. ECOG performance status was 1. The biopsy results confirmed grade 3 invasive ductal carcinoma, characterized by ER 10% weak positive, PR negative, and HER2 3+ confirmation by FISH. Baseline PET-CT demonstrated extensive FDG-avid axillary, supraclavicular, mediastinal, and abdominal lymph node involvement, along with bilateral pulmonary nodules, consistent with de novo metastatic HER2-positive breast cancer. The patient underwent six cycles of pertuzumab, trastuzumab, and docetaxel, followed by maintenance therapy with dual HER2 blockade. This regimen yielded substantial disease control for 13 months. Following disease progression, a re-biopsy revealed ER/PR negativity (0%), sustained HER2 3+ overexpression, and a Ki-67 of 65%. Second-line T-DM1 resulted in initial stabilization; however, after 7 months, PET-CT demonstrated marked progression with bulky mediastinal nodes and worsening pulmonary and skeletal disease. T-DM1 with tucatinib was administered owing to persistent HER2+ positivity. The treatment combination was well tolerated. Grade 1 diarrhoea was managed effectively with loperamide. No ≥3 neutropenia, thrombocytopenia, or significant hepatotoxicity were reported. Serial echocardiography confirmed preserved LVEF of 57%. After three cycles, repeat PET-CT demonstrated a near-complete metabolic regression with resolution of previously hypermetabolic cervical, mediastinal, hilar, and abdominal nodal clusters, near-complete disappearance of pulmonary FDG uptake, and markedly decreased skeletal activity. Clinically, the cough resolved, supraclavicular nodes regressed, and the ECOG performance status was maintained at 0–1.

Case 3

A 78-year-old postmenopausal woman presented with 4-5 months of progressive left breast swelling, mild pain, and unintentional weight loss. Physical examination revealed a 4–5 cm hard, irregular mass in the upper outer quadrant with ipsilateral axillary lymphadenopathy. ECOG performance status at presentation was 1–2. Core biopsy confirmed grade 3 invasive ductal carcinoma characterized by HER2 IHC 3+ and elevated Ki-67. Baseline PET-CT demonstrated FDG-avid primary disease with mediastinal and abdominal nodal metastases and visceral involvement, staged as de novo metastatic (Stage IV). The patient was initiated on first-line therapy with weekly paclitaxel and trastuzumab, achieving initial clinical response; however, follow-up PET-CT revealed disease progression with increased FDG uptake in mediastinal and abdominal nodes. Second-line therapy consisting of T-DM1 combined with tucatinib was then initiated. PET-CT after three cycles demonstrated marked reduction in FDG avidity of mediastinal nodes, significant decrease in abdominal nodal disease, reduced visceral metabolic activity, and no new lesions, thereby indicating a major partial metabolic response. This response was accompanied by clinical improvement, including improved appetite, reduced fatigue, and a stable performance status.

Table 1: Summary of baseline characteristics, prior treatment, response, and toxicity

Parameter	Case 1	Case 2	Case 3
Age	78	62	78
Disease setting	De novo metastatic	De novo metastatic	De novo metastatic
Hormone receptor status	Initial ER 5%, PR negative; re-biopsy ER/PR 0%	Initial ER 10% weak positive, PR negative; re-biopsy ER/PR 0%	Not fully specified
HER2 status	IHC 3+, FISH confirmed	IHC 3+, FISH confirmed	IHC 3+
Prior therapies	THP ×6, maintenance pertuzumab + trastuzumab, then T-DM1	THP ×6, maintenance pertuzumab + trastuzumab, then T-DM1	Weekly paclitaxel + trastuzumab
Line at which T-DM1 + tucatinib used	After progression on THP and T-DM1	After progression on THP and T-DM1	Second line
Sites of metastasis	Axillary, supraclavicular, mediastinal, abdominal nodes; bilateral pulmonary nodules;	Axillary, supraclavicular, mediastinal, abdominal nodes; bilateral pulmonary nodules;skeleton	Mediastinal, abdominal nodes; visceral;
Best early response (after 3 cycles)	Nearly complete metabolic response on PET-CT	Near-complete metabolic regression on PET-CT	Major partial metabolic response on PET-CT
Duration of responses (months)	6+ ongoing	5+ ongoing	4+ ongoing
Key toxicity	Grade 1 diarrhea; transient grade 1 transaminase elevation	Grade 1 diarrhea	No major toxicity reported
Cardiac status	LVEF 55%, no cardiac event	LVEF 57%, preserved	Stable, no

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Discussion

This case series reports three patients with HER2-positive metastatic breast cancer, including two elderly patients aged 78 years, who achieved near-complete or major partial metabolic responses after three cycles of T-DM1 plus tucatinib. The findings are hypothesis-generating and highlight several clinically relevant observations. First, all three patients demonstrated sustained HER2 pathway dependency across multiple lines of therapy. Re-biopsy at progression confirmed persistent HER2 3+ overexpression in both cases in which repeat biopsy was performed, with progressive elevation of Ki-67 suggesting ongoing clonal evolution within a HER2-driven tumor biology. This mirrors the HER2CLIMB-02 patient population, in which prior dual antibody blockade did not eliminate HER2 dependency [9]. The importance of repeat biopsy at progression to confirm receptor status and guide subsequent therapy sequencing is reinforced by these observations.

Second, the depth and speed of metabolic response achieved with T-DM1 plus tucatinib in these cases were notable. Because metabolic changes on FDG PET-CT may precede anatomical response, these early findings provide supportive evidence of treatment activity. Near-complete PET-CT metabolic responses were observed after just three cycles in two of three patients, with a major partial response in the third. This is consistent with the mechanism of action of this combination: tucatinib selectively blocks HER2 kinase signalling, potentially overcoming downstream resistance pathways to T-DM1, while T-DM1 retains direct HER2-targeting and delivery of a cell-killing agent directly inside HER2-positive cells. Preclinical data have demonstrated synergistic activity of tucatinib and T-DM1 in HER2-positive models [9]. The HER2CLIMB-02 trial demonstrated a statistically significant median progression-free survival benefit of 9.5 versus 7.4 months with tucatinib plus T-DM1 versus T-DM1 alone (HR 0.76), with a more pronounced benefit in patients with brain metastases [9, 10]. Although CNS disease was not present in this series, tucatinib's known intracranial activity adds broader clinical relevance to this combination in HER2-positive metastatic breast cancer. equivalent clinical benefit.

Third, tolerability in elderly patients is a significant clinical concern when escalating to combination targeted therapy. Both 78-year-old patients tolerated T-DM1 plus tucatinib without grade ≥3 adverse events, dose reductions, or cardiac compromise. Grade 1 diarrhea, managed conservatively with dietary modification and loperamide, was the most consistent toxicity. This is consistent with the HER2CLIMB-02 safety profile, in which the combination did not introduce new safety signals relative to T-DM1 alone, though treatment discontinuation rates were somewhat higher in the tucatinib arm [9]. The HER2CLIMB trial similarly demonstrated that tucatinib was well tolerated, with diarrhea and transient transaminase elevations as the most notable but generally manageable adverse effects [7].

The preserved LVEF observed in all cases is particularly relevant given the historical concern surrounding cumulative cardiotoxicity from prolonged HER2-directed therapy. Cardiac safety of T-DM1-based regimens has been demonstrated in large trials [5], and tucatinib's relative selectivity for HER2 over EGFR inhibition may further limit off-target cardiac effects. These cases add to a growing body of real-world evidence supporting the feasibility of HER2-directed intensification in older patients who are often underrepresented in clinical trials. While the current second-line standard of care has shifted toward trastuzumab deruxtecan (T-DXd) based on the DESTINY-Breast03 trial demonstrating superiority over T-DM1 [11], T-DM1 plus tucatinib represents a clinically relevant and affordable alternative, particularly for patients with T-DXd contraindications (e.g., significant interstitial lung disease risk), those with brain metastases where tucatinib's CNS penetration offers an additional advantage, or in settings where T-DXd access is limited. HER2CLIMB-02 provides level I evidence supporting this combination, and these cases demonstrate translatable clinical benefit. The use of biosimilar T-DM1 and generic tucatinib adds practical real-world relevance, particularly in settings where access and affordability influence treatment choice. However, these findings should be interpreted as descriptive and hypothesis-generating, and not as evidence of equivalence to originator products.

Conclusions

This case series suggests that T-DM1 plus tucatinib produced rapid, clinically meaningful metabolic responses with manageable toxicity in three heavily pretreated HER2-positive metastatic breast cancer cases, including elderly patients. These findings are hypothesis generating and require validation in larger cohorts. They support the real-world feasibility of this regimen, particularly where access to newer Antibody Drug Conjugates may be limited.

Ethics Statement

Written informed consent was obtained from all patients for publication of clinical details and accompanying images. Institutional Ethics Committee approval was waived as this is a retrospective case series involving anonymized clinical data and images, with no prospective intervention beyond routine clinical care.

Conflict of Interest

The authors declare that there is no conflict of interest with the content of this article.

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