Case Series

Neoadjuvant T-DM1 for HER2-positive breast cancer used as a bridging strategy during COVID-19 pandemic: lessons learned—a case series

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Background: Coronavirus disease 19 (COVID-19) has played a pivotal role in changing medical care around the world. During the pandemic, the operating rooms (ORs) were closed to elective surgery. Since breast cancer surgery is not regarded as an emergent procedure, there was an adoption of treatment regimen modification due to delays in treatment. Therefore, a decision was made to bridge early-stage HER2-positive breast cancer patients with neoadjuvant treatment to postpone surgery. Consequently, to reduce the frequency of dosing and the number of visits, as well as avoid steroid premedication, these patients were treated with ado-trastuzumab emtansine (T-DM1) every three weeks as opposed to weekly taxol and herceptin (TH).

Case Description: Five patients with early-stage HER2-positive cancer were treated with neoadjuvant T-DM1 3.6 mg/kg IV every three weeks. Three of the five patients developed cancer progression identified by their physical exam and/or imaging. T-DM1 was discontinued, and all three patients underwent immediate surgery. The remaining two patients, 4 and 5, had a complete and partial pathological response, respectively. All five patients received adjuvant therapy after surgery, and currently, none of these patients show evidence of disease on follow-up.

Conclusions: Our findings underscore the obstacles and treatment challenges encountered during the COVID-19 pandemic while preventing the spread of the virus and cancer progression. Furthermore, the use of T-DM1 for neoadjuvant treatment remains controversial, particularly when T-DM1 is used as a bridge to surgery during critical times. Perhaps better patient selection or a different drug regimen could have resulted in a better outcome in our study.

Keywords: Breast cancer; ado-trastuzumab emtansine (T-DM1); neoadjuvant therapy; coronavirus disease 19 (COVID-19); case series

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Introduction

Breast cancer accounts for nearly 1/3rd of all cancer cases diagnosed in women (1). Early detection of breast cancer significantly influences mortality rates and treatment outcomes (2). Patients with HER2-positive tumors less than 2 cm are usually treated with de-escalation treatment options, such as upfront surgery, followed by adjuvant treatment with taxol and herceptin (TH) (3). However, because coronavirus disease 19 (COVID-19) caused the closure of operating rooms (ORs) for elective procedures, HER2-positive cancer patients who required surgery as first-line treatment faced a high risk of cancer progression. As New York City was considered an epicenter for the COVID-19 pandemic, only truly emergency surgeries were performed and almost no cancer surgery was considered emergent. The definition of emergency surgery was not universally adopted in areas of the country that were not as greatly affected. The patients in our case series would have not been considered for neoadjuvant therapy in a non-pandemic setting, but because ORs were closed to elective procedures indefinitely, the multidisciplinary team was concerned that their HER2-positive disease would progress. Therefore, a unanimous decision was made by the multidisciplinary tumor board at our institution to bridge early-stage breast cancer patients with neoadjuvant treatment to postpone surgery. Consequently, HER2-positive cancer patients were treated with ado-trastuzumab emtansine (T-DM1) as opposed to weekly TH to reduce the frequency of dosing, the number of patient visits, and avoid steroid premedication, which could increase risk of acquiring COVID-19. Additionally, due to the higher incidence of grade 3 neutropenia associated with docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP), which could have negatively affected the patients during COVID-19, the decision was made to use T-DM1 (4).

T-DM1 is an antibody-drug conjugate composed of a monoclonal antibody against HER2 combined with a thioether linker and the antimicrotubule chemotherapy moiety maytansine with the benefit of being administered every three weeks (5). It has also been studied as a treatment for HER2-positive breast cancer in the neoadjuvant setting (6). Therefore, we found it prudent to use T-DM1 as a bridging therapy to surgery which avoids weekly chemotherapy infusions, reduces hospital burden, and limits patient visits to control the spread of the virus while providing appropriate neoadjuvant treatment to decrease the risk of cancer progression. Thus, our non-consecutive retrospective single-center case series aims to highlight the outcomes of using T-DM1 as neoadjuvant therapy in HER2-positive breast cancer patients rather than the standard TH. We present this article in accordance with the AME Case Series reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-447/rc).

Highlight box

Key findings

- Neoadjuvant ado-trastuzumab emtansine (T-DM1) led to suboptimal response in our patients with small HER2-positive breast cancers unable to access surgery during the Coronavirus disease 19 pandemic, with 3 of 5 patients progressing on treatment.
- Patients who responded poorly were HER2-positive based on fluorescence in situ hybridization, but not immunohistochemistry.

What is known and what is new?

- In stage II–III HER2-positive breast cancers, neoadjuvant T-DM1 plus pertuzumab led to inferior pathologic complete response rates, but less neutropenia and infection, than standard of care (SOC) neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab. SOC for stage I HER2-positive breast cancer involves surgery followed by adjuvant taxol and herceptin, which requires weekly treatment visits and steroid premedication.
- Neoadjuvant T-DM1 was postulated to be safer regimen for Stage I HER2-positive breast cancer patients unable to obtain surgery during the pandemic but did not lead to adequate response.

What is the implication, and what should change now?

- Frequent monitoring should be employed if using T-DM1 as a bridge to surgery during critical times.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case series and accompanying images was not obtained from the patients or the relatives after all possible attempts were made.

Case No. 1

A 61-year-old woman presented with a 1.3 cm mass in the 10:00 position in the right breast on a screening mammogram. The mass was 1.1 cm on ultrasound (*Figure 1*). Biopsy revealed an invasive ductal carcinoma (IDC) clinical stage I T1 (1.1 cm) N0 M0 grade 3, estrogen receptor (ER)/progesterone receptor (PR)-negative [ER 2+ on

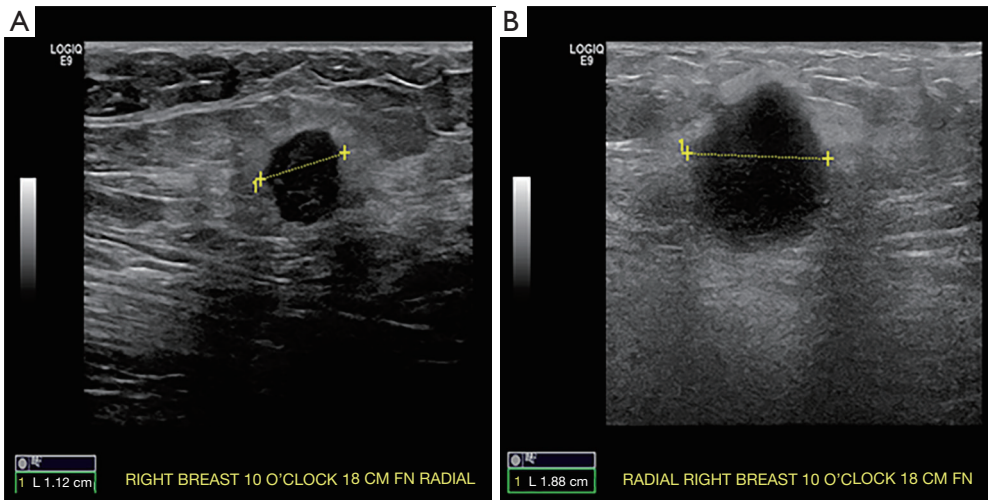

Figure 1 Ultrasound imaging before and after neoadjuvant treatment with T-DM1 for Patient 1. (A) Before: right breast 10:00 18 cm from the nipple is a 1.1 cm mass. (B) After: right breast 10:00 18 cm from nipple there is a hypoechoic mass now measuring maximally 1.8 cm previously measured maximally 1.12 cm. T-DM1, ado-trastuzumab emtansine.

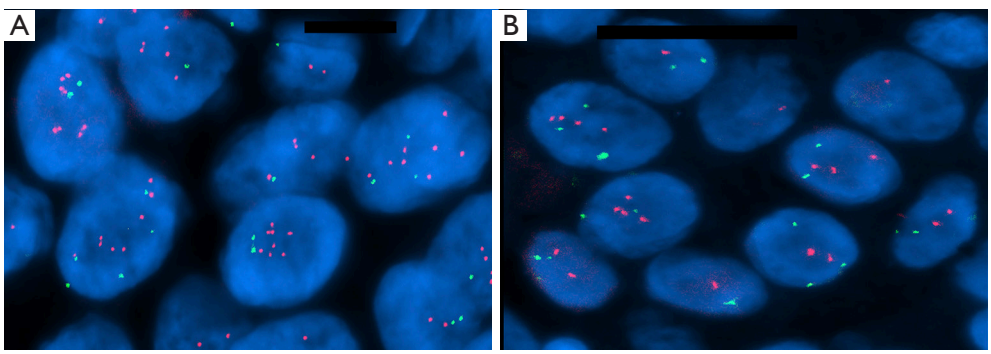

Figure 2 FISH analysis before and after neoadjuvant therapy with T-DM1 for Patient 1 (×1,000). (A) Before: FISH analysis of a breast tissue FFPE specimen with dual color DNA probes: D17Z1 (control; Centromere 17—Green) and ERBB2 (aka *HER2* gene of 17q12—red). Results: *HER2* gene amplified. (B) After: FISH analysis of a breast tissue FFPE specimen with dual color DNA probes: D17Z1 (control; Centromere 17—green) and ERBB2 (aka *HER2* gene of 17q12—Red). Results: *HER2* gene not amplified. FISH, fluorescence in situ hybridization; T-DM1, ado-trastuzumab emtansine.

immunohistochemistry (IHC)], and HER2-equivocal on IHC (2+), but confirmed positive on fluorescence in situ hybridization (FISH) analysis (signal ratio of 2.14 and a copy number of 6.3) (*Figure 2*). A lumpectomy with sentinel lymph node biopsy (SLNB) was scheduled, but due to the pandemic, the surgery was postponed. During the multidisciplinary meeting, the patient's case was discussed, and a decision was made to offer neoadjuvant T-DM1 3.6 mg/kg IV every three weeks for six cycles.

Due to adverse side effects, it was collectively decided that the T-DM1 dose should be reduced from 3.6 to 3.0 mg/kg. A repeat ultrasound five months after the 5th cycle of T-DM1 revealed a 1.8 cm mass in the 10:00 position, which was initially measured at 1.1 cm (*Figure 1*). Due to cancer progression, the patient underwent surgery with lumpectomy and SLNB.

Histology confirmed the presence of a 2.8 cm grade 3, IDC that was ER/PR-negative, HER2-negative by FISH (signal ratio of 1.63 and a copy number of 3.9) (*Figure 2*) and HER2-equivocal on IHC (2+). The patient was started on TCHP along with prophylactic pegfilgrastim therapy every three weeks followed by 11 cycles of maintenance

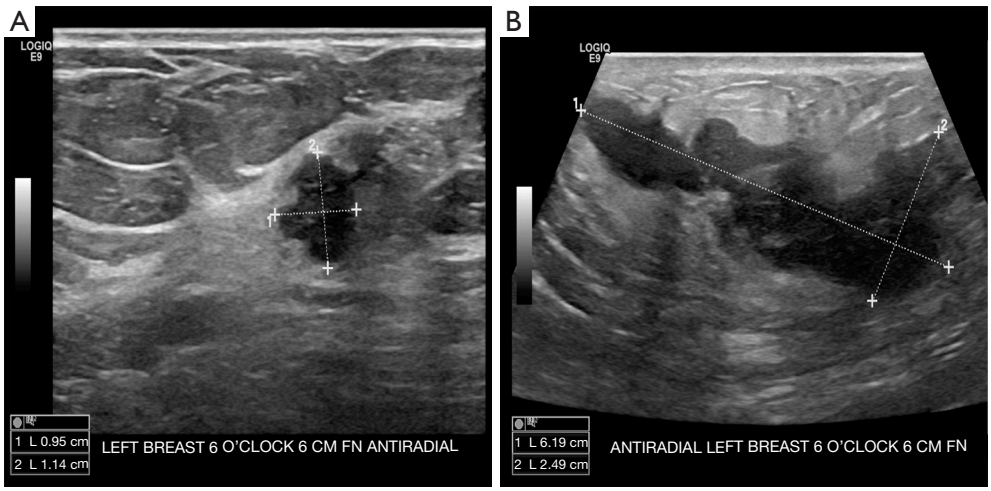

Figure 3 Ultrasound imaging before and after neoadjuvant treatment with T-DM1 for Patient 3. (A) Before: left breast 6:00 6 cm from the nipple there is a 1.1 cm mass correlates with the mammographic finding. (B) After: the previously identified mass in the 6:00 axis 6 cm from nipple has grown in size. It measures 6.1 cm × 2.4 cm in transverse and anteroposterior dimension. Previously 1.1 cm × 0.9 cm. T-DM1, ado-trastuzumab emtansine.

therapy with trastuzumab and pertuzumab. The patient also underwent adjuvant radiotherapy to the whole breast, receiving a cumulative dose of 52.4 Gy. Currently, the patient is showing no evidence of disease on follow-up.

Case No. 2

A 76-year-old woman presented with a lump in her left breast, and a diagnostic mammogram revealed two 10 mm spiculated masses in the 11:00 and 1:00 positions. Biopsy of the lesions showed clinical stage I T1 (1.0 cm) N0 M0 grade 3 IDC, ER-positive (1%, weakly positive), PR-negative, HER2-equivocal on IHC (2+), and HER2-positive on FISH analysis (signal ratio of 3.74 and a copy number of 9.9) for the 11:00 lesion. Similarly, a biopsy of the 1:00 lesion revealed the same histology. Surgery was postponed due to the COVID-19 pandemic, and the case was discussed in a multidisciplinary tumor board.

As a bridging strategy to surgery, 3.6 mg/kg IV T-DM1 was administered every three weeks for seven cycles. By cycle five, the patient's bilirubin levels had risen, necessitating a dose reduction of T-DM1 to 3 mg/kg. The mass became evidently larger upon physical examination (thus imaging was forgone) and a left mastectomy with SLNB was performed after cycle seven of neoadjuvant T-DM1. Surgical pathology determined disease progression by showing five grossly distinct tumors, ranging in size from 5 mm to 1.4 cm. All of these masses were grade 3 ductal carcinoma in situ (DCIS) and had the same morphology, being ER/PR-negative and HER2-positive (3+ on IHC) with pathological stage I.

Since there was a progression of disease during neoadjuvant treatment, the patient was started on 11 cycles of taxol, herceptin, and pertuzumab. The patient completed treatment and is disease-free.

Case No. 3

A 68-year-old female presented with a 1.7 cm mass at 6:00 position in the left breast mass on a routine mammogram. The mass was 1.1 cm on ultrasound (*Figure 3*). Ultrasound-guided biopsy showed a clinical stage I T1 (1.7 cm) N0 M0 IDC that was ER/PR-negative, and HER2-equivocal on IHC (2+) but positive on FISH (signal ratio of 1.47 and a copy number of 6.4). During the multi-disciplinary tumor board meeting, it was decided to offer the patient 3.6 mg/kg neoadjuvant T-DM1 every three weeks for six cycles to delay surgery.

On follow-up, physical examination of the left breast demonstrated palpable evidence of disease progression. Follow-up imaging prior to the sixth cycle of treatment revealed an increase in the tumor size from 1.1 cm × 0.9 cm to 6.1 cm × 2.4 cm (*Figure 3*). A repeat biopsy of the left breast mass confirmed IDC upstaged to clinical stage III

T3 N1 M0 with a positive left axillary lymph node, ER/PR-negative, HER2-equivocal on IHC (2+), and HER2-positive on FISH (signal ratio of 1.75 and a copy number of 11.7).

The patient underwent a mastectomy with axillary lymph node dissection (ALND). Surgical pathology revealed a 6 cm IDC, ER/PR-negative, HER2-equivocal on IHC (2+), HER2-positive by FISH (signal ratio of 1.47 and a copy number of 6.4), and stage III T3 N1 M0 grade 3 with 3/10 nodes positive along with extra-nodal extension and negative tumor margins. Adjuvant TCHP was given to the patient for six cycles, followed by radiotherapy with cumulative dose of 42.4 Gy. The patient completed targeted therapy, and the most recent imaging revealed no evidence of local or metastatic disease.

Case No. 4

A 62-year-old female on screening mammogram was found to have calcifications in the 12:00 axis of the right breast. Stereotactic biopsy of the breast showed several foci of IDC, along with high-grade DCIS, clinical stage I T1 (0.8 cm) N0 M0 tumor that was ER-positive (1%, weakly positive), PR-negative, and HER2-positive (3+ on IHC). The case was discussed at a multi-disciplinary tumor board, and the decision to begin neoadjuvant 3.6 mg/kg T-DM1 every three weeks for six cycles of treatment as a bridging strategy to surgery was made.

When the ORs reopened, the patient had a right breast lumpectomy and SLNB. Pathology after surgery revealed no residual carcinoma and negative nodes, indicating pathologic complete response (pCR). In addition, the patient received radiotherapy (40 Gy), trastuzumab 6 mg/kg IV every three weeks for 11 cycles, and anastrozole 1 mg daily as adjuvant treatment. The patient is currently on anastrozole and shows no evidence of disease.

Case No. 5

A 75-year-old woman presented with a self-palpated lump in the upper outer quadrant of the right breast. Subsequent mammography revealed a 1.5 cm hypoechoic mass with calcifications. Core biopsy of the mass showed a poorly differentiated IDC grade 3, ER/PR-negative, and HER2-positive (3+ on IHC). A mutual decision at the tumor board was made to begin neoadjuvant 3.6 mg/kg T-DM1 every three weeks for six cycles of treatment to delay surgery.

When ORs reopened, the patient underwent a lumpectomy with SLNB after enduring six cycles of T-DM1. Histology showed the presence of residual disease stage I T1 (≤0.1 cm) N0 M0 focus of microinvasion with few foci of DCIS, and ER/PR-negative, and HER2-positive (3+ on IHC). T-DM1 was decided to be continued as an adjuvant treatment for a total of 17 cycles, along with radiotherapy (52.5 Gy), to treat the microinvasive disease. Currently, the patient on follow-up shows no evidence of disease.

Discussion

Anti-HER2 therapy has played a vital role in improving patient outcomes with HER2-positive disease. For patients with HER2-positive early-stage breast cancer, neoadjuvant treatment has become a popular choice of management compared to adjuvant therapy because it offers a similar survival benefit to adjuvant therapy. Additionally, neoadjuvant therapy has the advantage of downstaging both the primary tumor and the axilla, resulting in a more conservative surgery, as well as the ability to tailor the adjuvant treatment based on the pathologic response obtained at surgery (7). Chemotherapy combined with anti-HER2 therapy, such as TCHP, is the most effective neoadjuvant treatment option in patients with HER2-positive early-stage breast cancer (8). While TCHP has shown significant results in terms of pCR, it has also been associated with significant side-effects such as neutropenia, diarrhea, febrile neutropenia, and anemia (6). These complications are minimized using T-DM1, an alternative chemotherapy-free drug that has reported a lower grade ≥3 adverse effects when compared to other anti-HER2 therapies used for breast cancer treatment (9-11). Initially, T-DM1 was approved for metastatic settings since it demonstrated a better safety profile and improved overall survival, as highlighted in the EMILIA and TH3RESA trials (10,11). Based on the EMILIA trial, which compared T-DM1 *vs.* lapatinib plus capecitabine in patients previously treated with trastuzumab and a taxane, there was a 3.6 month improvement in median progression-free survival (PFS) [hazard ratio (HR) 0.65; 95% confidence interval (CI): 0.55–0.77; P<0.001] and median overall survival of 5.8 months (HR 0.68; 95% CI: 0.55–0.85; P<0.001) (9). Similarly, the TH3RESA trial highlighted that the overall survival was significantly longer with T-DM1 (22.7 months; 95% CI: 19.4–27.5) as opposed to physician's choice [15.8 (13.5–18.7) months; HR 0.68; 95% CI: 0.54–0.85, P=0.0007] (11). Following the EMILIA trial, the Food and Drug Administration (FDA) approved T-DM1 in 2013 for use as a second-line adjuvant treatment for patients who

had previously received trastuzumab and a taxane (12). To evaluate the role of T-DM1 as an adjuvant treatment option, the KATHERINE trial was conducted in patients with early-stage HER2-positive disease, which demonstrated the superiority of T-DM1 over traditional trastuzumab therapy and increased invasive disease-free survival (iDFS) in patients that had residual disease after neoadjuvant systemic chemotherapy plus single or dual HER2-directed therapy (HR 0.50; 95% CI: 0.39–0.64) (13). Thereafter, multiple trials have been conducted to assess the potential role of T-DM1 in de-escalation strategies (14,15).

Although previous studies have evaluated the use of T-DM1 as an adjuvant treatment option in patients with HER2-positive breast cancer, fewer have elucidated its outcomes in the neoadjuvant setting with early-stage HER2-positive disease (4,6,15,16). In addition, many studies were conducted with patients that had higher stage disease than our cohort, as well as T-DM1 part of a polytherapy instead of a monotherapy in the neoadjuvant setting. The KRISTINE trial, which randomized 444 patients and compared neoadjuvant TCHP *vs.* T-DM1 plus pertuzumab, is the largest randomized trial to investigate the role of T-DM1 as neoadjuvant therapy in patients with HER2-positive early breast cancer (6). According to the trial, when compared to TCHP in a neoadjuvant setting, the pCR achieved by T-DM1 plus pertuzumab was subpar 44% *vs.* 56% (absolute difference –11.3 percentage points, 95% CI: –20.5 to –2.0; P=0.016); however, T-DM1 plus pertuzumab superseded in terms of safety (6). In the same trial, patients in the T-DM1 plus pertuzumab arm experienced locoregional recurrence prior to surgery (6.7% *vs.* 0%), and 66.7% of those patients had HER2 IHC 2+, suggesting that patients with HER2 heterogeneity may experience locoregional progression on T-DM1 (6). Furthermore, a 3-year follow-up from the same trial revealed a higher risk of event-free survival in the T-DM1 *vs.* TCHP (HR 2.61; 95% CI: 1.36–4.98); however, no significant differences were found in iDFS (HR 1.11; 95% CI: 0.52–2.40) nor overall survival (HR 1.21; 95% CI: 0.37–3.96) after surgery (4). The MARIANNE study demonstrated non-inferiority of PFS with T-DM1 therapy when compared to trastuzumab plus taxane (stratified HR for T-DM1 *vs.* trastuzumab plus taxane, 0.91; 97.5% CI: 0.73–1.13; P=0.31) (17). The study also showed non-inferiority of PFS for patients that received T-DM1 with pertuzumab *vs.* T-DM1 alone (17). Additionally, the ATEMPT trial demonstrated excellent 3-year iDFS when comparing T-DM1 *vs.* TH in the adjuvant setting (97.8%, 95% CI: 96.3–99.3; P<0.0001) and was not associated with less clinical relevant toxicities (CRTs) (46% *vs.* 47%; P=0.83) (14). While the trial's results were released after ORs reopened to elective surgeries, TH requiring steroid premedication during the pandemic was taken into consideration. Overall, these trials lead the interdisciplinary team at our institution to the decide on T-DM1 alone instead of T-DM1 with pertuzumab or TH as the neoadjuvant treatment in our patients. After ORs reopened to elective surgeries, the PREDIX HER2 trial compared T-DM1 *vs.* docetaxel, trastuzumab, and pertuzumab in the neoadjuvant setting and found the pCR was similar between the 2 groups (43.9% *vs.* 45.5%) (16). In conclusion, the multifactorial benefits of having low adverse effects during the pandemic, being non-inferior with no difference in overall survival, coupled with the additional benefit of being administered every 3 weeks without steroid premedication instead of weekly, supported our decision to use T-DM1 in the neoadjuvant setting during the pandemic while ORs were closed to elective surgeries.

In our single institution study, 3 of the 5 patients demonstrated disease progression after neoadjuvant T-DM1 (*Table 1*). Similarities between the patients included age, non-Caucasian race, and pre-operative pathology of intraductal carcinoma and tumor size less than 2 cm with clinical staging T1N0M0. A major difference between the patients was receptor status and which molecular test determined HER2 positivity. Currently, there is no consensus on the use of T-DM1 in the neoadjuvant setting for patients with HER2-positive breast cancer and their subsequent hormone receptor status. Prior literature has demonstrated that patients with HER2-positive and hormone receptor-negative disease had a higher chance of achieving a pCR; however, two of three patients in our study who had disease progression after T-DM1 therapy were hormone-receptor negative (4,6). In contrast, patients in the phase 2 West German Study Group Adjuvant Dynamic marker-Adjusted Personalized Therapy (WSG-ADAPT) study demonstrated a pCR of more than 40% in HER2-positive and hormone receptor-positive patients, thus highlighting the need for consensus on guidelines for the use of T-DM1 in different hormone receptor status cases (16). Furthermore, all the patients in our study received adjuvant therapy following surgery and currently exhibit no evidence of disease on follow-up. Moreover, our patients who responded to neoadjuvant T-DM1 had 3+ IHC for HER2. The patients who demonstrated disease progression had 2+ IHC despite being positive on FISH, which is similar to the results highlighted in

Table 1 Chart review of five patients who received T-DM1 neoadjuvant therapy at our institution

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	61	76	68	62	75
Race	Declined	Black/African-American	Black/African-American	Other	Other
Ethnicity	Spanish/Hispanic/Latino	Not-Spanish/Hispanic/Latino	Not-Spanish/Hispanic/Latino	Spanish/Hispanic/Latino	Spanish/Hispanic/Latino
BMI (kg/m^2)	29.88	20.6	30.4	29.1	28.1
Pre-op pathology	IDC	IDC	IDC	IDC	IDC
Pre-op tumor size (mm)	11	10	17	8	12
Multifocal	No	Yes	No	Yes	No
Pre-op clinical stage	cT1(c)N0M0	cT1(c(m))N0M0	cT1(c)N0M0	cT1(b)N0M0	cT1(c)N0M0
Pre-op receptor status	- ER-negative	- ER-weakly positive (1%)	- ER-negative	- ER-weakly positive (1–10%)	- ER-negative
	- PR-negative	- PR-negative	- PR-negative	- PR-negative	- PR-negative
	- HER2-positive (FISH signal ratio 2.4, copy number 6.3; IHC 2+ equivocal)	- HER2-positive (FISH signal ratio 3.74, copy number 9.9; IHC 2+ equivocal)	- HER2-positive (FISH signal 1.75, copy number 11.7; IHC 2+ equivocal)	- HER2-positive (IHC 3+)	- HER2-positive (IHC 3+)
Neoadjuvant therapy	T-DM1, 5 cycles	T-DM1, 7 cycles	T-DM1, 5 cycles	T-DM1, 6 cycles	T-DM1, 6 cycles
Post-op pathology	IDC	IDC	IDC	pCR	Single focus of microinvasion with multiple foci of DCIS
Post-op tumor size (mm)	28	14	60	pCR	≤1
Post-op pathology stage	ypT2N0M0	ypT1(c(m))N0M0	ypT3N1M0	pCR	ypT1(mi) + DCIS
Post-op receptor status	- ER-negative	- ER-negative	- ER-negative	pCR	N/A
	- PR-negative	- PR-negative	- PR-negative		
	- HER2-negative (FISH signal ratio 1.63, copy number 3.9; IHC 2+ equivocal)	- HER2-positive (IHC 3+)	- HER2-positive (FISH signal ratio 1.47, copy number 6.4)		
Response	Progression	Progression	Progression	Complete response	Partial response
Adjuvant chemotherapy	TCHP, 6 cycles	TCHP, 5 cycles	TCHP, 3 cycles	Trastuzumab, 9 cycles	T-DM1, 11 cycles
HER2 maintenance therapy	Trastuzumab + pertuzumab	Trastuzumab + pertuzumab	Trastuzumab + pertuzumab	N/A	N/A

Table 1 *(continued)*

Table 1 *(continued)*

Variables	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Adjuvant radiation therapy	WBRT	N/A	WBRT	WBRT	WBRT
Recurrence	No	No	No	No	No

T-DM1, ado-trastuzumab emtansine; BMI, body mass index; pre-op, pre-operative; IDC, invasive ductal carcinoma; ER, estrogen receptor; PR, progesterone receptor; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; post-op, post-operative; pCR, pathologic complete response; DCIS, ductal carcinoma in situ; TCHP, docetaxel, carboplatin, trastuzumab + pertuzumab; WBRT, whole brain radiation therapy; N/A, not available.

the KRISTINE trial, where 6.7% of the patients had locoregional recurrence prior to surgery, of which 66.7% were 2+ IHC (6). Therefore, HER2 heterogeneity may be a predictor of response to neoadjuvant T-DM1, with higher IHC positivity corresponding to greater tumor response. With this, neoadjuvant T-DM1 perhaps can be a targeted therapy in the neoadjuvant setting for optimal patients that meet selection criteria of HER2-positive on IHC. In regard to selection criteria, is it to be noted that patients that are younger and with more advanced diseases may be less advisable to this treatment and surgery should be urgent, if possible. Overall, our study highlights the suboptimal response to T-DM1 as a form of neoadjuvant treatment. Future studies specifically analyzing clinical stage I and T-DM1 are required to support our observation.

Our study has several limitations, firstly, our sample size was limited to only five patients. Secondly, all patients in our study were clinical stage I, as opposed to existing data that utilized T-DM1 as a neoadjuvant treatment for stage II and higher, limiting the support for the chosen treatment regimen. Lastly, our study fails to examine the both long and short-term implications of the use of T-DM1 in our patient group because of the small sample size and possible heterogeneity of clinicopathologic features.

Conclusions

Our findings underscore the obstacles and treatment challenges encountered during the COVID-19 pandemic while preventing the spread of the virus and cancer progression. In addition, the use of T-DM1 for neoadjuvant treatment remains controversial, particularly when T-DM1 is used as a bridge to surgery during critical times. Furthermore, if neoadjuvant therapy is used in the context of ORs closing to elective surgeries, more thorough physical exam and possibly ultrasound during treatment visits may be advised to monitor for rapidly growing cancers that would require urgent surgery to prevent progression. Lastly, perhaps better patient selection or a different drug regimen could have resulted in a better outcome in our study.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-447/rc

Peer Review File: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-447/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-447/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent for publication of this case series and accompanying images was not obtained from the patients or the relatives after all possible attempts were made. The article has been sufficiently anonymized to cause no harm to the patient or their family.

References

1. Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33.
2. Vanni G, Pellicciaro M, Materazzo M, et al. Lockdown of Breast Cancer Screening for COVID-19: Possible Scenario. In Vivo 2020;34:3047-53.
3. Tolaney SM, Guo H, Pernas S, et al. Seven-Year Follow-Up Analysis of Adjuvant Paclitaxel and Trastuzumab Trial for Node-Negative, Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer. J Clin Oncol 2019;37:1868-75.
4. Hurvitz SA, Martin M, Jung KH, et al. Neoadjuvant Trastuzumab Emtansine and Pertuzumab in Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer: Three-Year Outcomes From the Phase III KRISTINE Study. J Clin Oncol 2019;37:2206-16.
5. Isakoff SJ, Baselga J. Trastuzumab-DM1: building a chemotherapy-free road in the treatment of human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol 2011;29:351-4.
6. Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2018;19:115-26.
7. Caparica R, Lambertini M, Pondé N, et al. Post-neoadjuvant treatment and the management of residual disease in breast cancer: state of the art and perspectives. Ther Adv Med Oncol 2019;11:1758835919827714.
8. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30:1674.
9. Verma S, Miles D, Gianni L, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012;367:1783-91.
10. Diéras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:732-42.
11. Krop IE, Kim SB, Martin AG, et al. Trastuzumab emtansine versus treatment of physician's choice in patients with previously treated HER2-positive metastatic breast cancer (TH3RESA): final overall survival results from a randomised open-label phase 3 trial. Lancet Oncol 2017;18:743-54.
12. Vega Cano KS, Marmolejo Castañeda DH, Escrivá-de-Romaní S, et al. Systemic Therapy for HER2-Positive Metastatic Breast Cancer: Current and Future Trends. Cancers (Basel) 2022;15:51.
13. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med 2019;380:617-28.
14. Tolaney SM, Tayob N, Dang C, et al. Adjuvant Trastuzumab Emtansine Versus Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer (ATEMPT): A Randomized Clinical Trial. J Clin Oncol 2021;39:2375-85.
15. Arecco L, Blondeaux E, Damassi A, et al. Moving trastuzumab emtansine (T-DM1) to the early setting of breast cancer treatment. Ann Palliat Med 2020;9:512-6.
16. Hatschek T, Foukakis T, Bjöhle J, et al. Neoadjuvant Trastuzumab, Pertuzumab, and Docetaxel vs Trastuzumab Emtansine in Patients With ERBB2-Positive Breast Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol 2021;7:1360-7.
17. Perez EA, Barrios C, Eiermann W, et al. Trastuzumab Emtansine With or Without Pertuzumab Versus Trastuzumab Plus Taxane for Human Epidermal Growth Factor Receptor 2-Positive, Advanced Breast Cancer: Primary Results From the Phase III MARIANNE Study. J Clin Oncol 2017;35:141-8.

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