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Acute skin radiation toxicity seen with concurrent T-DM1: A single institutional report of 35 patients

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ABSTRACT

Trastuzumab emtansine (T-DM1) is a novel therapeutic for HER2+ breast cancer patients with residual disease after neoadjuvant chemotherapy. Concurrent radiotherapy (RT) is offered to a subset of patients based on results from the KATHERINE trial which showed a favorable safety profile. With emerging therapies that necessitate concurrent RT, we must closely follow rates of skin toxicity. Our first 35 patients who underwent concurrent T-DM1 treatment with breast/chest wall (CW) ± nodal irradiation are reported. Most patients (22/35) had grade 2+ toxicity and 3 patients had grade 3 toxicities. We add our experience with radiation dermatitis and concurrent T-DM1 to contribute to existing reports.

1. Introduction

Over recent years, the therapeutic landscape of breast cancer has expanded significantly to include novel systemic therapies including immune checkpoint inhibitors, targeted therapies, and antibody-drug conjugates. In particular, several therapies are under investigation or have recently been FDA-approved for breast cancer that overexpresses Human Epidermal Growth Factor Receptor 2 (HER2) [1–4]. The treatment paradigm for early-stage HER2 amplified breast cancer often involves neoadjuvant systemic therapy. Trastuzumab, a monoclonal antibody against HER2, has transformed the natural history of HER2+ breast cancer and has historically been continued for one year in individuals who receive neoadjuvant therapy [1,5–8]. In 2013, T-DM1 or Kadcyla, emerged as a treatment option for patients with metastatic breast cancer. T-DM1 is an antibody/drug conjugate that combines trastuzumab with emtansine (DM1), a chemotherapy which inhibits microtubule activity [7,9]. In the phase III KATHERINE clinical trial, patients with HER2+ breast cancer who had residual invasive early breast cancer after neoadjuvant therapy had a 50% reduction in risk of recurrence or death with adjuvant T-DM1 versus trastuzumab [10,11]. Notably, no new safety concerns were raised in their report. The KATHERINE study findings were practice-changing for patients with HER2+ breast cancer who had residual cancer following neoadjuvant chemotherapy.

It is important to note that when patients complete neoadjuvant chemotherapy, the majority qualify for adjuvant radiation therapy (RT). Limited data exist regarding the toxicity from concurrent T-DM1 and radiation, as we await large meta-analyses examining toxicities associated with this combination. Herein, we report our institutional experience in the first 35 patients treated with concurrent T-DM1 and radiation to the breast/chest wall (CW) ± nodes.

2. Methods

Following institutional review board approval, medical records from 2019 to 2021 of all patients who received concurrent T-DM1 (within 14 days of the start of RT) + RT to the breast/CW ± regional nodes were retrospectively reviewed using the electronic medical record. The primary endpoint was radiation-induced skin toxicity within the radiation portal using the Common Terminology Criteria for Adverse Events version 5.0 criteria for radiation dermatitis. Assessments for toxicity were made during routine weekly on-treatment visits by the treating physician and at follow-up visits and were recorded in the electronic medical record. Radiation plans were reviewed and confirmed to be within institutional guidelines and did not have outliers with regards to hot spots, skin dose, and volume of radiation.

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Table 1
Cancer staging, radiation treatment, and toxicity details for the 35 patients treated with concurrent RT + T-DM1. 34 patients with neoadjuvant chemo and post-operative pathologic staging as well as one patient with neoadjuvant chemo and intact breast (clinically staged) are presented in this table. Time to peak acute skin toxicity is denoted by @[fraction number]. Of note, peak toxicity refers to the number of fractions completed before the patient reached their highest recorded grade of skin toxicity. Abbreviations are defined as follows: CW = chest wall, VMAT= Volumetric Modulated Arc Therapy, IMRT= Intensity-Modulated Arc Therapy, 3D CRT= Three-dimensional Conformal Radiation Therapy, R = right-sided, L = left-sided, Rad = radical, DIBH = Deep inspiratory breath hold (used for many left-sided cases), C1/C2 denotes radiation course number for the patient's radiation history. For staging purposes: IDC = invasive ductal carcinoma, G = grade of disease on histopathologic review, ER = Estrogen Receptor, PR= Progesterone receptor, SLNBx = sentinel lymph node biopsy, ALND = axillary lymph node dissection, SCLV = supraclavicular nodes, fx = fractions. The word "portal" refers to the radiation portal when using 3DCRT.

Patient	Age (years)	Post-chemo staging	Radiation details	CTCAE v5.0 reported skin toxicity; onset of highest G toxicity	Treatment(s)/Skin care used
1	40	IDC- ypT1c(m), pN0 (i+) (sn), cM0, G2, ER+, PR+, HER2+, s/p L mastectomy	proton beam; C1 L CW + regional nodes, 50.4 Gy in 28 fx	G 2; sclv @ 14/28 fx	Aquaphor
2	45	IDC-ypT1c (2), pN2a (sn), cM0, G3, ER+, PR+, HER2+, s/p R mastectomy	proton beam; C1 R CW + regional nodes, 50.4 Gy in 28 fx + 10 Gy boost in 5 fx, 33 fx total	G 2; skin folds @ 20/33 fx	Aquaphor
3	32	IDC- ypT1a, pN1a, cM0, G1, ER+, PR+, HER2+, s/p R mastectomy w/implant	proton beam; C1 R CW + regional nodes, 50.4 Gy in 28 fx	G 2 skin folds @ 10/28 fx	Coconut oil + triamcinolone
4	60	IDC-ypT2 (6), pN0, cM0, G3, ER+, PR+, HER2+, s/p L mastectomy	proton beam; C1 L CW + flap + regional nodes, 50.4 Gy in 28 fx	G 2; low neck @ 20/28 fx	Eucerin
5	42	IDC-ypT1c(m), pN0 (sn), cM0, ER+, PR+, HER2+, s/p L mastectomy w/ implant	proton beam; C1 R CW + regional nodes, 50.4 Gy in 28 fx	G 2; skin folds@22/28 fx	Aquaphor + triamcinolone
6	64	IDC-ypT1c ypN2a, cM0, G3, ER-,PR-, HER2+, s/p Lumpectomy + ALND	VMAT; C1 L breast + nodes, 50 Gy in 25 fx + 10 Gy boost regional node+ 6 Gy inv. node boost, 33 fx total	G 2; left axilla @ 25/33 fx	Aquaphor and triamcinolone
7	37	IDC-ypT0, pN1mi (sn), cM0, GX, ER+, PR+, HER2+, s/p mast w/flap + SLNBx	VMAT; C1 R CW + nodes, 50.4 Gy in 28 fx	G 2; skin folds @ 28/28 fx	Aquaphor + Vaseline
8	36	IDC-ypT1a, N0c, M1a, ER+,PR-, HER2+, s/p bilateral mastectomy w/ implant	3DCRT; C1 R CW + nodes (sclv and axilla only); 50 Gy in 25 fx	G 1; radiation portal; @ 11/25 fx	Eucerin
9	56	IDC-ypT1c, pN0, cM0, G3, ER+, PR-, HER2+, s/p lumpectomy	3DCRT; C1 R breast, prone, 42.56 Gy + 10 Gy boost to 52.56 Gy, 20 fx total	G 1; radiation portal @ 8/20 fx	Aquaphor
10	66	IDC-ypT1c, pN1a, cM0, G1, ER+, PR+, HER2+, s/p mastectomy	3DCRT; C1 R breast + nodes, 50.5 Gy R CW + nodes in 28 fx	G 1; portal @ 18/28 fx	Aquaphor
11	81	IDC-ypT1b, pN0, cM0, G3, ER-, PR-, HER2+, s/p lumpectomy + SLNBx	3DCRT; C1 R breast, 42.56 Gy + 10 Gy boost to 52.56 Gy, 20 fx total	G 1; crease @ 15/20 fx	Aquaphor + Nystatin
12	69	IDC-ypT1c ypN0 (i+).cM0, ER-,PR-, HER2+, s/p mastectomy + SLNBx	3DCRT; C1 L CW + nodes, 50 Gy, DIBH, in 25 fx	G 1; portal; @ 13/25 fx	Aquaphor
13	47	IDC-ypT1c(m), pN1mi, cM0, G2, ER-, PR-, HER2+, s/p rad mastectomy	3DCRT; C1 L CW + nodes, 50.40 Gy, DIBH, in 28 fx	G 1; portal@ 8/28 fx	Aquaphor
14	43	IDC-ypT1c, pN0 (sn), cM0, G2, ER+, PR+, HER2+, s/p lumpectomy + SLNBx	3DCRT; C1 R breast + nodes, 50 Gy in 25 + 10 Gy boost in 5 fx to lump cavity, 30 fx total	G 1; portal@ 8/30 fx	Aquaphor
15	55	IDC-ypT1N0 cM0, G2, ER+, PR-, HER2+, s/p mastectomy + SLNBx	3DCRT; C1 L CW + nodes, 50 Gy 25 fx + 10 Gy in 5 fx boost, 30 fx total	G 1; portal@ 12/30 fx	Medichoice + Aquaphor
16	53	IDC-ypT1c, pN1a, cM0, G3, ER+, PR+, HER2+, s/p L mast w/expander + ALND	3DCRT; C1 L CW + nodes, 50.4 Gy, DIBH, in 28 fx	G 1; portal @ 13/28 fx	Aquaphor
17	51	IDC-cT4cN3 (prechemoIMN) M1 (liver), ER-/PR-, HER2+, intact	3DCRT; C2 L breast only- 10 fx, 30 Gy palliative RT to fungating mass	G 2; skin folds @ 10/10 fx	Aquaphor + lidocaine + hydrocortisone
18	58	IDC- ypT1, cN0, cM0, ER+, PR+, HER2+, s/p lumpectomy	3DCRT; C1 R breast + nodes, 50 Gy in 25 fx breast + nodes + 10 Gy boost in 5 fx, 30 fx total	G 2; skin folds @ 26/30 fx	Aquaphor + lidocaine + silvadene
19	70	IDC-ypT1b, pN0 (sn), cM0, G3, ER+, PR-, HER2+), s/p lumpectomy + SLNBx	3DCRT; C1 R breast, whole breast, 42.56 Gy in 16 fx +12.5 Gy boost in 5 fx, 21 fx total	G 2; skin folds @ 13/21 fx	Aquaphor
20	55	IDC-ypT2, pN0 (i+) (sn), cM0, G2, ER+, PR-, HER2+), s/p R mastectomy	3DCRT; C1 R breast + regional nodes, 50 Gy in 25 fx	G 2; skin folds@22/25 fx	Aquaphor
21	50	IDC-ypT1a, pN0, cM0, G3, ER-, PR-, HER2+), s/p lumpectomy + SLNBx	3DCRT; C1 R breast, 42.56 Gy + 10 Gy boost to 52.56 Gy, 20 fx total	G 2; skin folds @ 17/20 fx	Mometasone + silvadene
22	51	IDC-rcT0, pN1, cM0, GX, ER+, PR+, HER2+, s/p mastectomy + SLNBx	3DCRT; C2 R axilla, 50 Gy axillary and sclv nodes, no CW, in 25 fx	G 2; portal @ 25/25 fx	Aquaphor
23	41	IDC-ypT1a, pN0 (i+), G3, ER+, PR+, HER2+, s/p lumpectomy + SLNBx	3DCRT; C2 R breast + nodes, 50 Gy to breast + regional nodes + 5 Gy boost, 25 fx total	G 2; skin folds + sclv @19/25 fx	Aquaphor
24	38	IDC-ypT2, pN1a, cM0, G2, ER+, PR+, HER2+), s/p mast w/expander + ALND	3DCRT; C1 L CW (with expander)+nodes, 50.4 Gy, DIBH, in 28 fx	G 2; portal/central@ 25/28 fx	Aquaphor
25	71	IDC-ypT0 N1mi, ER+, PR+, HER2+, s/p mastectomy + ALND	3DCRT; C1 R CW + nodes, 50 Gy in 25 fx	G 2; portal @ 25/25 fx	Lindi roll
26	42	IDC-ypT1b, pN1a, cM0, G3, ER-, PR-, HER2+, s/p bilat. mast + ALND	3DCRT; C1 R breast + nodes, 50 Gy in 25 fx	G 2; portal @ 25/25 fx	Aquaphor + calendula
27	54	IDC-ypT1a (m2) N1a cM0, ER+, PR+, HER2+, s/p lumpectomy + ALND	3DCRT; C1 L breast + SCLV nodes, initial 50 Gy in 25 fx, 10 Gy boost in 5 fx, 30 fx total	G 2; crease; @ 27/30 fx	Aquaphor
28	54	IDC-ypTis (DCIS), pN1a, cM0, ER-, PR-, HER2+, s/p rad mastectomy	3DCRT; C1 L CW + nodes, 50.40 Gy in 28 fx	G 2; portal@ 15/28 fx	Aquaphor
29	56	IDC-ypT1c ypN1a (sn) cM0, G3, ER+, PR+, HER2+, s/p lumpectomy + SLNBx	3DCRT; C1 L breast + nodes, 50.4 Gy initial+ 10 Gy boost in 5 fx, 33 fx total	G 2; portal @19/33 fx	Silvadene
30	44	IDC-ypT1mi, pN0, cM0, GX, ER-, PR-, HER2+, s/p, s/p mastectomy + ALND	3DCRT; C1 R CW + nodes, 50.4 Gy in 28 fx	G 2; portal @ 25/28 fx	Coconut oil
31	47		3DCRT; C1 R CW + nodes, 50.4 Gy in 28 fx	G 2; portal @ 28/28 fx	

(*continued on next page*)

Table 1 (*continued*)

Patient	Age (years)	Post-chemo staging	Radiation details	CTCAE v5.0 reported skin toxicity; onset of highest G toxicity	Treatment(s)/Skin care used
		IDC-ypT2 N0, cM0, ER-, PR-, HER2+), s/p rad mastectomy			Miaderm, Aquaphor/ lidocaine, cortisone, Lindi roll
32	34	ILC-ypT1b, N0, cM0, G2, ER+, PR+, HER2 +, s/p mastectomy + SLNBx	3DCRT; C1 R breast + nodes, 50.4 Gy in 28 fx	G 2; portal@ 23/28 fx	Silvadene
33	38	IDC-ypT1c, pN1a, cM0, G3, ER+, PR+, HER2+, s/p lumpectomy + SLNBx	3DCRT; C1 R breast + nodes, 50 Gy in 25 fx + 10 Gy boost in 5 fx to lump cavity, 30 fx total	G 3; portal @ 30/30 Fx	Aquaphor
34	44	IDC-ypT4d, pN0 (sn), pM1, G3, ER-, PR+, HER2+, s/p rad mastectomy	3DCRT; C1 L CW + nodes, 50.4 Gy initial+ 10 Gy boost in 5 fx, 33 fx total	G 3; portal @ 33/33 fx	Aquaphor + Eucerin + Hydrocortisone, Silvadene
35	65	IDC-ypTxN1miM0, G3, ER-, PR-, HER2+, s/p mastectomy + SLNBx	3DCRT; C1 L breast + nodes, 50.40 Gy in 28 fx	G 3; sclv@ 20/28 fx	Aquaphor; A + D ointment

3. Results

Thirty-five patients were identified who received concurrent T-DM1+ RT to the breast/CW ± regional nodes. Relevant patient data are summarized in Table 1. Median age was 51 (range 32–81 years). All patients were female and had a performance status of 0–1. Treatment plans varied as follows: 5 proton-based, 2 VMAT/IMRT, 28 3D-CRT. Fourteen patients had left-sided treatment. Fractionation schemes ranged from 10 to 33 fractions. Median delivered RT dose was 50 Gy (range 30–60.4 Gy). Radiation fields included breast alone, breast with nodal irradiation as well as CW alone and CW + nodal irradiation. Nodal irradiation ranged from axilla alone to full regional nodal irradiation including supraclavicular and IMN fields. This was the first course of radiation for 32 of 35 patients and no patients underwent overlapping re-irradiation. At the median follow up of 20 months, 2 patients died: one of metastatic disease and the other of sepsis after cholestasis (ages 44 and 81, respectively).

With regards to skin toxicity, 35/35 (100%) patients had at least grade 1 skin toxicity reported during their treatment. Most patients reported grade 2 skin toxicity (n = 23, 66%). Three patients (9%) experienced grade 3 toxicity (all received 3D-CRT). No grade 4–5 skin toxicities were reported. No patients had long-term dermatologic complaints. Median time to developing peak recorded toxicity was 20 fractions (range 8–33). For those patients who developed skin toxicity, all responded well to conventional management of skin toxicity.

4. Discussion

Herein we report the largest real-world cohort experience of acute radiation dermatitis from concurrent post-neoadjuvant T-DM1 with radiation. Specifically, we found that the majority of patients in this cohort experienced grade 1 (100%) and grade 2 (66%) skin toxicity, while no patients experienced grade 4/5 skin toxicity. Moreover, these toxicities were well-managed with conventional supportive skin care with no long-term sequelae. These data add the toxicity literature, thus far informed by large clinical trials of adjuvant T-DM1 (KATHERINE, ATEMPT) [12].

The landmark KATHERINE trial made T-DM1 standard in patients with HER2+ residual disease after neoadjuvant therapy [10]. Of the patients who received concurrent RT in KATHERINE, however, radiation details were not reported. KATHERINE reported grade 3 or greater skin toxicity in 1.4% with T-DM1 (1% in the trastuzumab arm, not significant) and concluded that T-DM1 was safe and effective [10,13]. In contrast, our retrospective shows 9% grade 3 toxicity. Moreover, in KATHERINE, any grade of skin toxicity was reported in 25.4% of patients in the T-DM1 arm, while in our series, 100% of patients reported any grade of skin toxicity and most, 75%, had grade 2+ dermatitis. We note that our results suggest there may be a higher rate of dermatitis in patients with concurrent T-DM1 than reported in the KATHERINE trial.

Concurrent RT + T-DM1 was also studied in the ATEMPT trial, which evaluated adjuvant T-DM1 for patients with low-risk stage I HER2+ disease [14,15]. ATEMPT reported rates of grade 2+ dermatitis to be 33.9% and showed that T-DM1 (over trastuzumab, 23.2%, P = 0.11) did not meet its endpoint of fewer clinically-relevant toxicities compared with trastuzumab although efficacy was excellent [15]. ATEMPT demonstrated safety in the delivery of concurrent RT + T-DM1, however their rate of grade 2+ toxicity of 33.9% was again notably lower than our reported toxicity of 75%.

Following KATHERINE and ATEMPT, the use of concurrent RT + T-DM1 therapy has become standard in select HER2+ patients and we will likely see many patients with varied dosing and fractionations. There remains a lack of data on various radiation modalities and fractionations even taking in the approximately 2000 patients on the combined KATHERINE and ATEMPT studies [10,14]. Interestingly, grade 2+dermatitis is generally accepted to be somewhere between 30 and 50% without concurrent therapy, which is notably higher than what was reported in the KATHERINE and ATEMPT trials, yet lower than what was seen in our cohort [16–19]. Factors that affect acute skin toxicity are multifactorial and range from breast size to radiation dosing, modality, and fractionation, to skin care alone. It is difficult to attribute the clear difference in acute radiation dermatitis seen in our cohort to any one of the factors that affect acute skin toxicity.

There are several smaller studies reporting their experience on skin toxicity with concurrent RT + T-DM1, although none have reported grade 3 dermatitis or comparable rates of any grade dermatitis. Zolcak et al. published their cohort of 14 patients, and reported 2/14 (14%) with grade 2 toxicity and 12/14 (86%) with grade 1 toxicity. There was no grade 3 acute radiodermatitis [20]. Becherini et al. reported on a series of 25 patients with concurrent T-DM1 and RT and showed no grade 3 events, and grade 1–2 in 80% of patients [21]. Lastly, Corbin et al. published a single example of grade 3 skin toxicity with concurrent T-DM1 given 50 Gy/25fx and urged providers to be mindful of increased radiation dermatitis in patients on T-DM1, noting that mechanistically, the use of a microtubule inhibitor may act as a radiation sensitizer and increase likelihood of developing radiation dermatitis [22].

5. Conclusion

We report the largest series to date of patients undergoing concurrent RT + T-DM1 outside of the KATHERINE and ATEMPT clinical trials, and find clinically significant rates of skin toxicity associated with concurrent T-DM1 and radiation. Providers should be attentive to the possibility of skin toxicity with concurrent RT/T-DM1. We present our findings to contribute to the toxicity data for further meta-analyses.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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