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Case Report

Radiation dermatitis in patients treated with concurrent trastuzumab emtansine (T-DM1)

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ABSTRACT

Trastuzumab Emtansine (T-DM1) improves outcomes for patients with HER2+ breast cancer, and is given concurrently with radiation. We have noted increased radiation dermatitis in these patients, which may have been underreported on the KATHERINE clinical trial, and call for clinicians to remain vigilant of unexpected toxicities with newly approved therapies.

1. Introduction

Modern multi-modality therapy for non-metastatic breast cancer has yielded improved outcomes, with 5-year survival rates over 90% [1]. In particular, improvements in treatments in the era of molecular characterization may help optimally match therapies to patients, identifying opportunities for both escalation and de-escalation of treatment.

As more therapy has shifted to the neo-adjuvant setting, pCR rates have increased and residual disease at the time of surgery has been identified as a negative prognostic factor in some biologic subtypes [2,3], associated with higher risk for disease recurrence. New therapeutic strategies are focused on treatment intensification for these high-risk patients. Importantly, there are now options for both triple negative and HER2 positive patients [4,5]. The landmark KATHERINE clinical trial randomized women with pathologic residual disease after neoadjuvant therapy to standard adjuvant trastuzumab versus adjuvant trastuzumab emtansine (T-DM1), an antibody–drug conjugate of trastuzumab and the microtubule inhibitor emtansine. Radiation therapy, when indicated, was given concurrently with T-DM1.

Interim analysis of the KATHERINE trial published February 2019 demonstrated a remarkable 50% relative reduction in the risk of recurrence or death in patients who received T-DM1 [5]. While treatment toxicities were higher in the TDM-1 arm as compared with trastuzumab, treatment was generally well tolerated, and adjuvant T-DM1 has been adopted as a standard of care for patients with pathologic evidence of residual disease after neo-adjuvant chemotherapy [6,7].

As new systemic therapies are developed and integrated into treatment, concurrently or sequentially with radiation therapy, the radiation oncology community will need to monitor for unexpected frequency or magnitude of toxicity with radiation. Within our growing experiences across two academic medical centers with TDM-1 administered concurrently with radiotherapy, we have noted what appears to be heightened skin toxicity in several patients, with one example described below.

2. Case

In January 2019, a 55 year-old previously healthy female was diagnosed with a large multifocal cT2N0 ER+ PR- HER2+ grade 2 invasive ductal carcinoma of the right breast. After multidisciplinary evaluation, she initiated neoadjuvant systemic therapy with pertuzumab, trastuzumab, and docetaxel (THP), followed by skin sparing mastectomy and SLN biopsy. Final pathology yielded two foci of micrometastasis within 1 of 2 sentinel nodes. Based on residual disease after surgery, adjuvant TDM-1 was recommended along with radiotherapy to the chest wall and regional lymph nodes without further axillary surgery. Given the recommendation for regional nodal coverage including internal mammary nodes, she was treated with proton therapy to reduce heart and lung dose. The radiation dose was 50 Gy delivered in 25 fractions over 32 total days, without a boost. No bolus was used. D90% of the skin, as defined by the 3mm rind of tissue below the external surface, was 93.9%. D1cc of the skin was 101% (50.5 Gy).

Radiation dermatitis was noted in the second week of treatment, with skin findings felt to be more significant than expected based on skin dose. Topical prophylactic film was in place over the breast mound for the duration of her treatment, a standard

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within our practice, with no apparent reduction in dermatitis [8]. Uncovered areas were initially managed with topical steroids when desquamation developed. During the final week of treatment, she developed dry desquamation in the right inframammary fold, which was managed with vinegar soaks and silver sulfadiazine cream (Fig. 1a). She returned to clinic for a skin check five days after completing radiation, at which time moist desquamation was noted throughout the breast mound (Fig. 1b). This was assessed as Grade 3 radiation dermatitis at the peak of toxicity. In the following weeks, her skin recovered as expected. At her 3 month follow-up appointment, her dermatitis had completely resolved.

3. Discussion

Within the KATHERINE trial, review of toxicities relevant to radiation demonstrated a numerical increase in the low rate of pneumonitis in patients receiving T-DM1, at 1.5% compared with 0.7%. Any grade of "Radiation related skin injury" was reported in 25.4% of patients on the T-DM1 arm, compared to 27.6% on the trastuzumab arm. Grade 1 and 2 radiation-related skin injury were significantly more common than Grade 3 toxicity, which was noted in 10 patients (1.4%) on the T-DM1, compared to 7 (1%) on the trastuzumab arm. Per CTCAE Version 4.0, Grade 1 radiation dermatitis is defined as "faint erythema or dry desquamation." In practice, acute radiation dermatitis is an expected toxicity of breast radiation, with nearly all patients experiencing grade 1–2 toxicity, and in some series, more than half of post mastectomy patients experiencing moist desquamation [9]. The low rates reported on the trial suggest that the reporting mechanisms or time points may not have been sensitive enough to capture acute dermatitis during breast radiation.

While limited anecdotes of heightened skin toxicity may reflect simple chance, there is mechanistic feasibility for T-DM1 to heighten radiation toxicities. T-DM1 is comprised of trastuzumab conjugated to emtansine, a microtubule inhibitor. Other microtubule inhibitors, including taxanes and vinca alkaloids, are known radiation sensitizers, potentially increasing the risk radiation-related toxicities including dermatitis and pneumonitis [10].

This case highlights the important role of radiation oncologists in monitoring treatment toxicities as novel systemic agents are incorporated into multimodality treatment. Radiation oncologists should be included in the study design of trials that incorporate multimodality therapy, and these studies should carefully evaluate the potential for synergy in acute and late radiotherapy-related toxicities. Additionally, per the National Cancer Institute, phase 4 clinical trials, also called post-marketing surveillance trials, "study the side effects caused over time by a new treatment after it has been approved and is on the market. These trials look for side effects that were not seen in earlier trials..." [11]. In the absence of these data, the onus of detecting treatment-related toxicity caused by newly introduced therapeutics falls to the adopting clinicians. Going forward, we will continue to use concurrent T-DM1 when indicated, and continue to monitor skin reactions in patients who receive concurrent T-DM1.

If, upon further evaluation, it is found that T-DM1 concurrent with radiation increases rates of dermatitis or other toxicities, the clear benefits of T-DM1 and other effective new targeted therapies should not be ignored. Instead, strategies to mitigate these toxicities, such as reducing the aggressiveness of bolus, may be considered on an individual basis. We bring this single example to the readers' attention in order to point out that in the modern era, the techniques and toxicities of radiotherapy must be continually re-evaluated within the ever-changing landscape of multimodality cancer care. For the welfare of our patients, radiation oncologists must play a leading role in this effort.

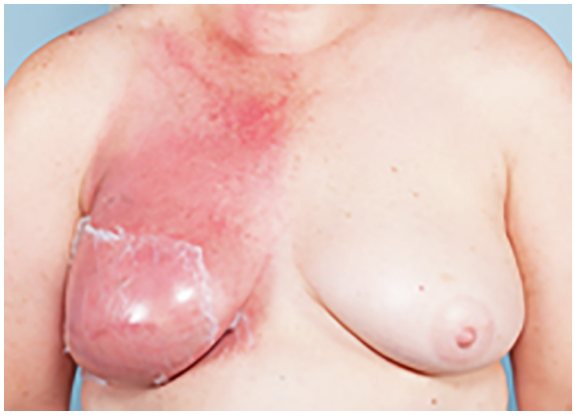

Fig. 1. a) Photographs after 23 of 25 fractions of radiation and b) five days after completing radiation. The topical prophylactic film is partially removed at the time of photography.

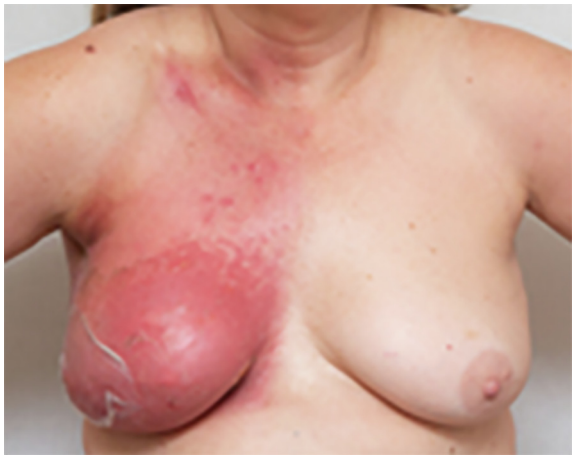

Fig. 1 (*continued*)

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None.

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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