Journal of
Cancer Science & Therapy

Alsabbak et al., J Cancer Sci Ther 2013, 5.12
DOI: 10.4172/1948-5956.1000236

Case Report Open Access

The Association of Adjuvant Trastuzumab (Herceptin) with Radiation Recall Dermatitis: A Case Study

Hassan Alsabbak[1]*, Zaid Aljuboori[2], Marnee Spierer[3] and Paula Klein[1]

[1]Department of Hematology-Oncology, Beth Israel Medical Center, USA
[2]Department of General Surgery, Bronx Lebanon Hospital, USA
[3]Department of Radiation Oncology, The Farber Center for Radiation Oncology, USA

Introduction

Radiation recall is an inflammatory reaction that occurs when an individual receives chemotherapy following radiation therapy for cancer [1]. Its estimated frequency is 8.8% [2]. This phenomenon was first described by D'Angio et al. in the 1950s with Actinomycin D [3].

Symptoms of radiation recall are due to inflammation in a region that was previously treated with radiation. The most common type of reaction is radiation recall dermatitis, a skin rash characterized by redness, swelling, and/or blistering of the skin. The rash is often painful and can have the appearance of severe sunburn [4].

The chemotherapy drugs most commonly associated with radiation recall include [5,6]:

Docetaxel (Taxotere)
Paclitaxel (Taxol)
Gemcitabine (Gemzar)
Capecitabine (Xeloda)
Doxorubicin (Adriamycin)

Treatment for a radiation recall reaction is primarily supportive care, eliminating the source of the reaction (for example, discontinuing the chemotherapy drug felt to be responsible) often as the first step. Medications such as corticosteroids and anti-inflammatory preparations may be used in some cases to decrease the inflammation [7].

Unfortunately, it is difficult to predict if someone will react to a particular chemotherapy drug after radiation therapy. Radiation recall does seem to be less common when the time interval between radiation therapy and chemotherapy is longer, but considerations other than radiation recall are often more important in decisions about timing of treatments.

Case

A 47 year old woman presented with a lump in her right breast, she underwent bilateral mammogram on June, 2012, which showed a suspicious mass corresponding to the palpable abnormality. Then a week later the patient underwent ultrasound-guided biopsy of a 3 o'clock axis right breast mass, which was positive for invasive ductal carcinoma HER2 positive (3+), weakly positive for ER (Estrogen receptor) (5 to 10%) and negative for PR (Progesterone receptor). Ki-67 was low at 1 to 4%. Patient was married with history of 2 pregnancies; one pregnancy was ended with elective abortion, and the other one the patient gave birth to full term baby at age of 42 years.

On July, 2012, the patient underwent right mastectomy and sentinel lymph node biopsy with DIEP (deep inferior epigastric perforators) flap reconstruction. Biopsy revealed two foci of infiltrating ductal carcinoma, moderately differentiated, in the right breast. The larger focus was reported to measure 2.0 cm in greatest dimension. Lymphovascular space invasion was identified. There was invasive carcinoma extending into the anterior surface of the junction of the upper inner and lower inner quadrants. Also there was invasive carcinoma 4 mm from inked retroalveolar margin. Two sentinel lymph nodes were negative for disease. The patient was considered to be stage T1cN0M0 invasive ductal carcinoma of the right breast.

Additionally multifocal DCIS (Ductal carcinoma insitu) was identified with central necrosis, high grade; with retrograde extension into the lobules. There was DCIS within a millimeter of the inked anterior surface of the lower inner quadrant. LCIS (lobular carcinoma insitu) was present. Prior biopsy site changes were seen. Additional upper inner quadrant excision was negative.

The patient was given six cycles of adjuvant chemotherapy TCH (Docetaxel + Carboplatin + Trastuzumab) between September, 2012 and January 2013. The patient was not able to undergo further surgery to achieve clear margins and was therefore recommended to undergo a course of adjuvant RT (radiation therapy). She received radiation therapy between February and April, 2013. In addition she received trastuzumab every three weeks during and after the radiotherapy because she was HER2 positive. She received 50Gy to her flap and an additional 14Gy to the area of positive margins. 9MeV electrons were used prescribed to the 90% isodose line using 1cm of bolus daily. RT side-effect timeline:

Weeks 2 – 3: Patient developed Grade 1 dermatitis (faint erythema); patient was using OTC skin moisturizer.

Weeks 3 – 4: Grade 2 dermatitis (moderate erythema with moderate swelling). Patient continued OTC skin moisturizer.

Week 5: Grade 2 dermatitis with small areas of grade 3 dermatitis (moderate erythema with moist desequamation). Patient was given prescription for Silvadene (Silver sulfadiazine) to reduce the severity of radiation-induced skin injury [8].

3 days after completing RT: Larger area of moist desquamation. Some areas encrusted. Given gel petals to apply to skin. Felt immediate relief. Continued Silvadene.

2 weeks after completing RT: Markedly improved with remnant

***Corresponding author:** Hassan Alsabbak, Clinical Trials Coordinator, Beth Israel Medical Center, Hematology-Oncology, 325 West 15th street, New York, New York 10011, USA, Tel: 7328011641; E-mail: hassan.alsabbak@yahoo.com

Received October 04, 2013; **Accepted** December 13, 2013; **Published** December 18, 2013

Citation: Alsabbak H, Aljuboori Z, Spierer M, Klein P (2013) The Association of Adjuvant Trastuzumab (Herceptin) with Radiation Recall Dermatitis: A Case Study. J Cancer Sci Ther 5: 427-429. doi:10.4172/1948-5956.1000236

small areas of Grade 3 dermatitis. Gel petals gave great relief. Continued Silvadene to open areas.

4 weeks after completing RT: Continued improvement with Grades 1 and 2 dermatitis. Silvadene discontinued.

Six weeks after completing RT the patient described an "itchy" feeling while receiving trastuzumab, and 2 weeks after that cycle of trastuzumab (8 weeks after completing RT), she noticed rash on her reconstructed breast mound. Nine weeks after completing RT, patient presented for her scheduled dose of trastuzumab, with worsening of the dermatitis covering the majority of the treatment portal; most prominent in the area of the boost (upper inner and lower inner quadrants). The rash was wholly contained within the radiation portal (Figure 1).

She did not get that scheduled dose of trastuzumab. She was treated with over-the-counter benadryl cream and over-the-counter steroid cream with eventual resolution of both the rash and the accompanying pruritis. She received her next cycle of trastuzumab as planned without incident.

Discussion

Trastuzumab (Herceptin) is a monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 proteins, HER2. Based on the established improved overall survival and disease control with adjuvant trastuzumab after primary breast cancer therapy, adjuvant trastuzumab has been included into the standard management of HER2 positive early stage breast cancer [9].

The most common adverse reactions with trastuzumab include fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity [10].

There have been few documented cases of trastuzumab-associated radiation recall reaction with the first report was by Shrimali et al in 2009, the patient in that report started her trastuzumab 42 days after completing post-mastectomy radiation therapy. She developed erythema before the second cycle of trastuzumab which was contained within the radiation portal (Figure 2). She was treated with IV steroids with continuation of trastuzumab, the rash completely resolved with steroids [11]. Chung et al reported radiation recall dermatitis in a patient who began her trastuzumab four weeks after completing radiation therapy. This patient had a known latex allergy, which may have increased the possibility of a hypersensitivity reaction, triggering radiation recall. Additionally, in this patient, trastuzumab was given in the ipsilateral arm to which she received radiation therapy [12]. Moon et al reported the occurrence of radiation recall dermatitis in a woman who was receiving trastuzumab during radiation therapy; the patient developed an acute rash, which was well demarcated within the border of her radiation field (Figure 3). A skin biopsy was done. Pathology revealed epidermal atrophy and superficial and deep perivenular lymphocytic infiltration compatible with radiation recall dermatitis. The rash resolved completely after 7 days without any medication [13].

Our patient did give a history of having "very sensitive skin" and had a history of a penicillin allergy which might have contributed to the development of the recall dermatitis. In her case, the trastuzumab was given in the contralateral arm and she did receive trastuzumab during and after radiation therapy. Skin biopsy was not done. She was given Silvadene (Silver sulfadiazine) which was shown to reduce the severity of radiation-induced skin injury in clinical trials [8] but it did not lead to complete resolution of her symptoms. Later she was given OTC Benadryl cream and OTC steroid cream which resulted in complete resolution of her symptoms and upon re-challenging her with the trastuzumab, the dermatitis did not occur.

The clinical presentation in our patient and in the previously mentioned case reports [11-13] was similar to the presentations of radiation recall dermatitis following administration of drugs more commonly known to be associated with this reaction which

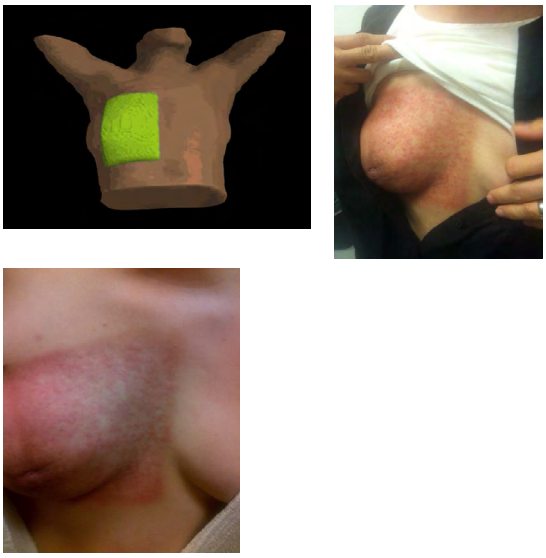

Figure 1: The 50Gy dose color wash from the patient's radiation plan, displayed alongside the photo showing the radiation recall dermatitis.

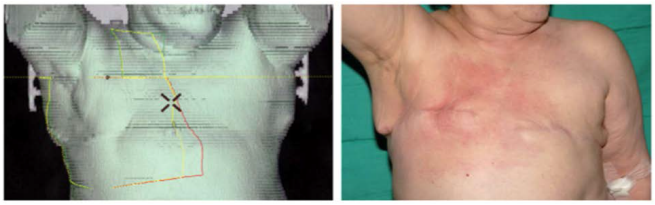

Figure 2: The digitally reconstructed photographs from the patient's radiation plan, displayed alongside the photo showing the radiation recall dermatitis [13].

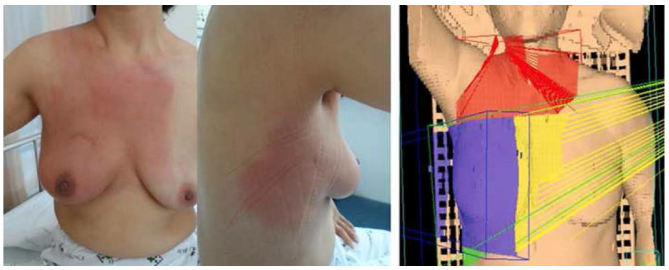

Figure 3: The digitally reconstructed photographs from the patient's radiation plan, displayed alongside the photo showing the radiation recall dermatitis [8].

can be characterized by: Rapid onset of the erythema and vesicular rash with swift resolution of symptoms. The clinical distribution of the rash completely contained within the borders of the radiation portal. Symptoms can occur just a few days after radiation therapy is completed, or years later. Median time between conclusion of radiation treatment and onset of radiation recall dermatitis was found to be 39 days in a review of the literature, and the dose of radiation widely ranged between 10 and 61 Gy [5]. Some exceptions were reported where recall dermatitis occurred as long as 15 years after radiotherapy [14].

Re-challenging the patients with the recall-triggering drug carries a small risk of triggering the same reaction again, which raise the question whether chemotherapy should be continued after the first manifestation of radiation recall dermatitis, especially if there is a limited choice of available drugs. The decision should consider the benefits and potential risks of re-challenge with the same drug [15].

Several hypotheses regarding the pathophysiology of recall dermatitis have been proposed including epithelial stem cell deficiency, vascular damage, drug hypersensitivity, or epithelial stem cell sensitivity [16,17] but still the exact pathophysiology of this phenomenon remains poorly understood. From several *in vitro* studies, there is evidence that radiation can produce stable long-term changes in the cell phenotype [17]. The p53-mediated signal transduction pathway activates the cellular response to DNA damage produced by ionizing radiation. Smith et al. [18], have revealed, using immunohistochemical staining, that cumulative p53 mutations may play some, but not the major, role in the pathogenesis of radiation recall dermatitis. In their opinion, mitochondrial dysfunction probably has a more important role in these eruptions [18].

Treatment of this condition is mainly through discontinuation of the responsible drug which usually results in resolution of radiation dermatitis. Steroids and antihistamines can be used to control pruritus and pain.

Conclusion

Despite its first description in the late 1950s, radiation recall dermatitis remains a challenge for clinicians. While it has been most commonly reported in the drugs listed previously [5,6]. Now there are several case reports of its occurrence with newer and different drugs like trastuzumab. Also it has been reported in cancer patients using herbal remedies like hypericin (St. John's wort) [19], which further could complicate the clinical picture. Considering the increased use of combination radiotherapy and chemotherapy in the treatment of malignant disease, clinicians need improved knowledge of radiation recall dermatitis and its management.

Consent

Informed consent was obtained from the patient for being included in the case report.

References

1. Azria D, Magné N, Zouhair A, Castadot P, Culine S, et al. (2005) Radiation recall: a well recognized but neglected phenomenon. Cancer Treat Rev 31: 555-570.
2. Kodym E, Kalinska R, Ehringfeld C, Sterbik-Lamina A, Kodym R, et al. (2005) Frequency of radiation recall dermatitis in adult cancer patients. Onkologie 28: 18-21.
3. D'ANGIO GJ, FARBER S, MADDOCK CL (1959) Potentiation of x-ray effects by actinomycin D. Radiology 73: 175-177.
4. Burris HA 3rd, Hurtig J (2010) Radiation recall with anticancer agents. Oncologist 15: 1227-1237.
5. Camidge R, Price A (2001) Characterizing the phenomenon of radiation recall dermatitis. Radiother Oncol 59: 237-245.
6. Alley E, Green R, Schuchter L (2002) Cutaneous toxicities of cancer therapy. Curr Opin Oncol 14: 212-216.
7. Caloglu M, Yurut-Caloglu V, Cosar-Alas R, Saynak M, Karagol H, et al. (2007) An ambiguous phenomenon of radiation and drugs: recall reactions. Onkologie 30: 209-214.
8. Hemati S, Asnaashari O, Sarvizadeh M, Motlagh BN, Akbari M, et al. (2012) Topical silver sulfadiazine for the prevention of acute dermatitis during irradiation for breast cancer. Support Care Cancer 20: 1613-1618.
9. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, et al. (2005) Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 353: 1659-1672.
10. John PC (2010) "Herceptin (Trastuzumab) Drug Information: Side Effects and Drug Interactions - Prescribing Information at RxList." RxList.
11. Shrimali RK, McPhail NJ, Correa PD, Fraser J, Rizwanullah M (2009) Trastuzumab-induced radiation recall dermatitis--first reported case. Clin Oncol (R Coll Radiol) 21: 634-635.
12. Chung C, Stuart D, Keyes M (2009) Radiation recall reaction induced by adjuvant trastuzumab (herceptin). Case Rep Med 2009: 307894.
13. Moon D, Koo JS, Suh CO, Yoon CY, Bae J, et al. (2013) Radiation recall dermatitis induced by trastuzumab. Breast Cancer .
14. Burdon J, Bell R, Sullivan J, Henderson M (1978) Adriamycin-induced recall phenomenon 15 years after radiotherapy. JAMA 239: 931.
15. RistiÄ‡ B (2004) Radiation recall dermatitis. Int J Dermatol 43: 627-631.
16. Hureaux J, Le Guen Y, Tuchais C, Savary L, Urban T (2005) Radiation recall dermatitis with pemetrexed. Lung Cancer 50: 255-258.
17. Camidge R, Price A (2001) Characterizing the phenomenon of radiation recall dermatitis. Radiother Oncol 59: 237-245.
18. Smith KJ, Germain M, Skelton H (2002) Histopathologic features seen with radiation recall or enhancement eruptions. J Cutan Med Surg 6: 535-540.
19. Putnik K, Stadler P, Schäfer C, Koelbl O (2006) Enhanced radiation sensitivity and radiation recall dermatitis (RRD) after hypericin therapy -- case report and review of literature. Radiat Oncol 1: 32.