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Dermatologic Adverse Events Associated with use of Adjuvant Lapatinib in Combination with Paclitaxel and Trastuzumab for HER2 positive Breast Cancer: A Case Series Analysis

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Keywords

Lapatinib; rash; toxicity; HER2 positive breast cancer

Introduction

Lapatinib (L) is a dual tyrosine kinase inhibitor that has been shown to be effective in combination therapy against HER2 positive breast cancer in both the metastatic and neoadjuvant setting.¹⁻⁵ The incorporation of lapatinib into common adjuvant treatment regimens for HER2 positive breast cancer has been limited by the high rates of adverse events found in previous trials. The typical adverse events noted were all grades, but particularly grade 3 diarrhea.⁶⁻⁸ For many of the adjuvant studies with lapatinib, diarrhea was the most common adverse event and the most frequent cause of dose reduction or discontinued treatment.⁶⁻⁸ The largest trial examining this is the global multi-center BIG 2-06; NCCTG [Alliance] N063D (ALTTO) trial. They compared lapatinib alone, trastuzumab (H) alone, and combination of both with chemotherapy in 4 different arms.⁷ In a study by Dang et al, looking at dose-dense doxorubicin and cyclophosphamide followed by weekly paclitaxel (T) with trastuzumab and lapatinib in HER2 positive breast cancer, 88% of patients experienced diarrhea, 29% of the diarrhea was grade 3, and 43% required dose reduction in lapatinib, mostly secondary to diarrhea. Due to high rate of dose reduction, the study was closed early and the combination of dose-dense doxorubicin, cyclophosphamide, followed by paclitaxel, trastuzumab and lapatinib was deemed to not be feasible. On the contrary, the rates of all grade and grade 3 rashes in these patients were 27% and 3%, respectively; rates of all grade and grade 3 acneiform rashes were 16% and 2%, respectively.⁸ In an additional ongoing clinical trial, the COMPLETE trial (NCT00667251) comparing taxane based chemotherapy in combination with lapatinib compared to

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combination with trastuzumab. Overall reported adverse events have been about equal for lapatinib versus trastuzumab groups, 97% versus 99%, respectively, however the amount of diarrhea was much greater in the lapatinib group, 78.8% versus 37.8%, as was rash, 57.76% versus 34.7%.⁹ In another study, RC0639, lapatinib was reduced from 1000mg to 750mg with weekly paclitaxel, and trastuzumab (after doxorubicin and cyclophosphamide) and also showed a high rate of grade 3 diarrhea of 39%. It also showed a high incidence of grades 1-2 acneiform rash of 55.9%.⁶ Despite the increased incidences of diarrhea, one study of health related quality of life measured in patients treated with adjuvant lapatinib versus placebo did not show a significant difference, indicating that there may still be some role for adjuvant lapatinib in certain clinical situations.¹⁰

Although there was a small proportion of rash compared to diarrhea in the above studies, dermatologic adverse events have been well reported with lapatinib as well as with many other tyrosine kinase inhibitors (TKIs).¹¹⁻¹³ The mechanism of rash associated with lapatinib use is related to the expression of the HER family of epidermal growth factors in the dermis and epidermis. Particularly, EGFR inhibition can prevent keratinocyte migration and EGFR blockade can also induce keratinocyte apoptosis.¹⁴ In addition, the modulation of cytokine release caused by EGFR blockade in keratinocytes has been found to lead to the influx of inflammatory cells into the dermis and epidermis resulting in the prototypical acneiform rash that is predominantly inflammatory versus infectious in nature.¹⁵

Dermatologic adverse events are typically graded using the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), which grades based on percentage body surface area. Grade 1 is <10% BSA, grade 2 10-30% BSA, and grade 3 is >30% BSA.¹⁶ In a review by Lacouture et al, which included data from five metastatic breast cancer trials, skin rash was the most common dermatologic adverse event (DE). Skin rash occurred in 43% of patients treated with lapatinib and of those, 4% were grade 3. In the group of lapatinib plus paclitaxel, 76% of patients experienced DEs, compared to 58% of those treated with lapatinib as a monotherapy. Overall, 66% of patients on lapatinib + paclitaxel experienced grade 1 and 2 DEs, and 10% experienced grade 3.¹⁷ These findings were reflected in our recent phase II trial of dose dense paclitaxel (every other week dosing) with trastuzumab and lapatinib for early node negative HER2 positive breast cancer. In this study patients were assigned to receive paclitaxel every other week x4 cycles and weekly trastuzumab and daily oral lapatinib were initiated concurrently (THL phase, cycles 1-4). After the completion of the THL portion, patients received HL for up to one year; each cycle was every 3 weeks (cycles 5-19). In this study, all grades and grades 2 and 3 rash were found in 18/19 (95%), 7/19 (37%), and 2/19 (11%) of patients. Here we highlight the course of the 9 patients with grade 2 and 3 dermatologic lesions.¹⁸

Cases

The patients' demographic and initial tumor information is summarized in Table 1.

Patient 1

Patient was a 52 year old Caucasian woman with a history of rosacea and hypothyroidism and was diagnosed with stage IA ductal carcinoma. After her first cycle, she developed

grade 2 acneiform rash on the face, chest, back and was referred to the Dermatology service. She was initially recommended treatment with clindamycin topical lotion and triamcinolone 0.1% cream daily. The patient did not use the prescribed creams, and her rash worsened and spread to her trunk and legs. At that time she was reevaluated by the dermatologist and was considered to have grade 2 acneiform rash and grade 2 maculopapular rash. She was then prescribed a methylprednisolone dose pack in addition to triamcinolone cream, which she was encouraged to use daily. Her rash did improve slowly; however by cycle 3, the patient had also developed grade 2 diarrhea as well as fatigue related to her cancer therapy, and ultimately lapatinib was stopped. The patient continued with paclitaxel and trastuzumab for her breast cancer.

Patient 2

Patient was a 74 year old Caucasian woman with a history of psoriasis and was diagnosed with stage IIA ductal carcinoma. After cycle 1, she developed a papular erythematous rash on her face as well as grade 1 diarrhea. The patient also developed an infusion reaction with facial flushing during her second cycle of paclitaxel, which resolved with diphenhydramine. Also during cycle 2, her rash progressed to grade 2 maculopapular involving the face, thighs, abdomen, and back. She did not see a dermatologist. On cycle 5 lapatinib dose was decreased to 750mg daily. Shortly afterwards, she was diagnosed with multiple myeloma (unrelated to breast cancer therapy) and was taken off lapatinib and study.

Patient 3

Patient was a 46 year old Asian woman with stage IIA invasive ductal carcinoma. After cycle 2, patient reported that she had a full body rash, which resolved on its own by the time she was assessed. She did, however, have a grade 1 acneiform rash on her face at the time of assessment. She also experienced grade 1 diarrhea that was managed with loperamide. By cycle 3, the acneiform rash had progressed to grade 2. It was generalized to the torso, back, arms, legs, and was pruritic. She was prescribed cetirizine and diphenhydramine cream by her oncologist and her rash improved to grade 1. She continued to do well on trastuzumab and lapatinib after paclitaxel was completed, with continued improvement in her rash and diarrhea, and she was able to complete her maintenance lapatinib and trastuzumab.

Patient 4

Patient was a 36 year old Hispanic woman with stage IA invasive ductal carcinoma. After cycle 1, she developed an acneiform rash on her face. During cycle 2, the rash worsened involving the neck and scalp as well. She was referred to the Dermatology service. There she was determined to have grade 2 acneiform rash and was prescribed alcometasone cream as well as clindamycin cream. The rash improved with this treatment regimen and she was successfully able to complete the protocol.

Patient 5

Patient was a 41 year old African American woman with a history of fibrocystic breast disease and was diagnosed with stage IA invasive ductal carcinoma. During cycle 4 when she developed right chest wall cellulitis which was appropriately treated; this was considered

a grade 3 dermatologic adverse event. During cycle 6, she developed a grade 1 periorbital erythematous rash and pruritus of her face. She also had maculopapular erythematous grade 1 rash, as well as dry skin with brittle fingernails, which was treated symptomatically with hydrocortisone cream. She was able to complete protocol successfully.

Patient 6

Patient was a 49 year old Caucasian woman with stage IA invasive ductal carcinoma. During cycle 1, she developed grade 2 acneiform rash on her face and upper torso which resolved with holding lapatinib for two weeks. At cycle 3, the patient developed pustular lesions on the face and scalp, and was referred to the Dermatology service. On dermatologic evaluation, she was found to have grade 1 acneiform rash on her face and scalp for which she was prescribed clindamycin cream. The facial rash was thought to be secondary to lapatinib, whereas the scalp rash was deemed to be secondary to paclitaxel. She also had grade 2 pruritus and dry skin for which she was prescribed triamcinolone 0.1% cream. However, she ultimately came off study due to persistent grade 1 diarrhea. She was continued on trastuzumab alone but was also started on tamoxifen.

Patient 7

Patient was a 41 year old Caucasian woman with stage IA invasive ductal carcinoma. During cycle 1, the patient developed a grade 2 acneiform rash on the face, chest, and hands, which progressed and became more generalized. She saw a dermatologist, and cultures of the lesions were taken. The cultures from her pustular facial lesions grew staphylococcus aureus. She was recommended treatment with cefadroxil 500mg twice daily in addition to alclometasone cream applied to face. She was also instructed to hold lapatinib for cycle 2. However, the patient develop another maculopapular rash that had spread to the chest, arms, and back and it was considered grade 3 (See Figure 1). Subsequently, she was taken off study. She was then started on vinorelbine with trastuzumab and also began radiation therapy.

Patient 8

Patient was a 38 year old Hispanic woman with stage IA invasive ductal carcinoma. After cycle 1, the patient developed grade 2 erythematous and pruritic facial rash. The rash was treated with emollients and clindamycin topical. Following cycle 2, the rash worsened and became more pustular. She was started on minocycline orally as well as a methylprednisolone taper for the pruritus (which was also classified as grade 2). Concurrently, the patient also suffered from grade 2 diarrhea which was treated with loperamide. The rash and pruritus improved with the methylprednisolone pack, although it was still at grade 1. Treatment for the rash was continued with a topical steroid, hydrocortisone. The rash improved, especially after completion of paclitaxel. However the pruritus persisted. She was given cetirizine and ultimately hydroxyzine to alleviate the pruritus. Erythematous patches on the face waxed and waned. Eventually, the pruritus was controlled to grade 1 and also fluctuated. About two months later, the patient also developed dry fingertips and cracking of the finger nails which was treated with urea containing moisturizer with gloves at night. Ultimately, all of her dermatologic issues resolved and she was able to successfully complete the protocol.

Patient 9

Patient was a 56 year old Caucasian woman with a history of acne and seborrheic keratosis with stage IA invasive ductal carcinoma. Following cycle 1, the patient developed a grade 2 acneiform rash on her face. Two days after beginning to take lapatinib, she noticed erythematous, painful, pruritic, oozing pustular lesions on her face. She was referred to the Dermatology service and was treated with alcometasone and clindamycin gel. This treatment did improve her lesions. However she also had a hypersensitivity reaction to her second cycle of paclitaxel and came off study. She was subsequently treated with vinorelbine with trastuzumab as well as radiation therapy to the left breast followed by tamoxifen maintenance.

A summary of the skin manifestations described in the patients above can be found in Table 2.

Discussion

Lapatinib in combination with paclitaxel and trastuzumab was not feasible due to high rate of incompleteness of the THL phase, with one of the causes being high incidence of rash. The cases presented above represent the patients that experienced significant dermatologic adverse events. Almost all of the patients that developed lapatinib associated skin lesions developed them during the first cycle of treatment (6/9 or 67%). One patient even reported noticing facial lesions two days after starting lapatinib. Another important discovery on closer inspection of these cases is that several of the patients that ultimately went off study (5/9 or 56%), only 2 (22%) did so due to rash, the other 3 (33%) did so secondary to other reasons.

In terms of rash and diarrhea, the results of our findings (of every 2-weekly T with HL) are in contrast to those found in a prior study of dose-dense doxorubicin/cyclophosphamide followed by weekly T with HL.⁸ The incidence of grade 3 diarrhea was lower with every 2-weekly T and HL in the order of 16 %, as opposed to 29% with weekly T and HL. This may have allowed for an increased absorption of lapatinib, leading to higher incidence of skin rash. Interestingly, although dermatologic side effects have been well documented with TKIs, lapatinib compared to other TKIs has been shown to characteristically cause fewer rashes. Lapatinib, as a dual EGFR (HER1)/HER2 inhibitor, has been shown to cause increased pAKT expression in the epidermis as well as decreased p27 expression, which leads to less keratinocyte apoptosis compared to EGFR only inhibitors.¹⁴ The high incidence of rash seen in this study was an unexpected result. Perhaps, the dermatologic events seen in these patients are related to an interaction between lapatinib, paclitaxel, and trastuzumab. Other studies examining the efficacy of lapatinib combined with paclitaxel in the metastatic setting showed similar results. Guan et al specifically noted an increase in grade 3 rash with paclitaxel and lapatinib together compared to paclitaxel alone.¹⁹ Di Leo et al showed similar results, with an increase in grade 3 rash from 0% to 4% with the addition of lapatinib to paclitaxel.²⁰ Kaklamani et al demonstrated similar findings in the neoadjuvant setting. In this study using nab-paclitaxel and lapatinib 66% of patients with combination nab-paclitaxel and lapatinib had all grade rash versus 58% with lapatinib alone. This further

supports the claim that adding a taxane to lapatinib may increase the risk of dermatologic adverse events.²¹

Prophylactic dermatologic intervention is important. In our series, only 5/9 (56%) received care from a dermatologist, and of those, two of them saw the dermatologist after they had already been taken off study. Of note, 3/9 (33%) of patients had a prior history of skin disorders, which may suggest a predisposition. Several predictors of rash development with TKIs have been proposed such as the planned total dose of lapatinib, the presence of brain metastasis, and concomitant use of 5HT3 anti-emetics, which were all found to be associated with a higher incidence of grade 2 rash.^{22,23} Besides being able to predict which patients may be at higher risk for rash, many prophylactic regimens have been proposed as well.^{24,25} According to a set of clinical practice guidelines determined by a multidisciplinary group, patients with EGFR inhibitor-related acneiform rash may benefit from prophylaxis with hydrocortisone 0.1% cream (level IIC evidence).²⁵ Other recommendations included prophylaxis with minocycline or doxycycline (level IIA evidence).²⁴⁻²⁶ Prophylaxis with other agents such as pimecrolimus and tazarotene have been showed to be ineffective in clinical trials.²⁵⁻²⁷ In terms of treatment recommendations, the standard options are alclometasone and clindamycin cream which were prescribed to 5/9 (56%) of the patients mentioned here who saw a dermatologist.^{27,28} Another choice for either treatment or prophylaxis may include vitamin K based creams.^{29,30} This underscores the importance of having the Dermatology service involved as an interdisciplinary approach to prevention and treatment of DEs. It is important to also consider that the trials used to determine these guidelines were with other TKIs (most notably cetuximab) and not lapatinib. Further studies looking specifically at prophylaxis during lapatinib treatment are warranted.

Conclusion

In conclusion, although the phase II trial of lapatinib in addition to dose dense paclitaxel and trastuzumab was terminated early for excessive toxicity, dermatologic adverse events may not be the most important deterrent to this regimen. Despite a high incidence of rash in the study patients, many of them were able to complete the protocol with improvement of their symptoms. Further studies need to be conducted which focus on including dermatologic prophylaxis and involvement of dermatology services from the onset of treatment in order to prevent or effectively manage DEs to allow therapeutic potential.

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References

1. Baselga J, Bradbury I, Eidtmann H, Di Cosimo S, de Azambuja E, Aura C, Gómez H, Dinh P, Fauria K, Van Dooren V, Aktan G, Goldhirsch A, Chang TW, Horváth Z, Coccia-Portugal M, Domont J, Tseng LM, Kunz G, Sohn JH, Semiglazov V, Lerzo G, Palacova M, Probachai V, Pusztai L, Untch M, Gelber RD, Piccart-Gebhart M, NeoALTTO Study Team. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2012; 379(9816):633–40. [PubMed: 22257673]

2. O'Sullivan CC, Smith KL. Therapeutic Considerations in Treating HER2-Positive Metastatic Breast Cancer. *Curr Breast Cancer Rep*. 2014; 6(3):169–182. [PubMed: 25285186]
3. Blackwell KL 1, Burstein HJ, Storniolo AM, Rugo HS, Sledge G, Aktan G, Ellis C, Florance A, Vukelja S, Bischoff J, Baselga J, O'Shaughnessy J. Overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer: final results from the EGF104900 Study. *J Clin Oncol*. 2012; 30(21):2585–92. [PubMed: 22689807]
4. de Azambuja E, Holmes AP, Piccart-Gebhart M, Holmes E, Di Cosimo S, Swaby RF, Untch M, Jackisch C, Lang I, Smith I, Boyle F, Xu B, Barrios CH, Perez EA, Azim HA Jr, Kim SB, Kuemmel S, Huang CS, Vuylsteke P, Hsieh RK, Gorbunova V, Eniu A, Dreosti L, Tavarikiladze N, Gelber RD, Eidtmann H, Baselga J. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. *Lancet Oncol*. 2014; 15(10):1137–46. [PubMed: 25130998]
5. Robidoux A 1, Tang G, Rastogi P, Geyer CE Jr, Azar CA, Atkins JN, Fehrenbacher L, Bear HD, Baez-Diaz L, Sarwar S, Margolese RG, Farrar WB, Brufsky AM, Shibata HR, Bandos H, Paik S, Costantino JP, Swain SM, Mamounas EP, Wolmark N. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2013; 14(12):1183–92. [PubMed: 24095300]
6. Moreno-Aspitia A, Dueck AC, Ghanem-Cañete I, Patel T, Dakhil S, Johnson D, Franco S, Kahanic S, Colon-Otero G, Tenner KS, Rodeheffer R, McCullough AE, Jenkins RB, Palmieri FM, Northfelt D, Perez EA. RC0639: phase II study of paclitaxel, trastuzumab, and lapatinib as adjuvant therapy for early stage HER2-positive breast cancer. *Breast Cancer Res Treat*. 2013; 138(2):427–35. [PubMed: 23479422]
7. Piccart-Gebhart MJ, Holmes AP, Baselga J, et al. First results from the phase III ALTTO trial (BIG 2-06; NCCTG [Alliance] N063D) comparing one year of anti-HER2 therapy with lapatinib alone, trastuzumab alone, their sequence, or their combination in the adjuvant treatment of HER2-positive early breast cancer. ASCO Annual Meeting. Abstract LBA4. Presented June 1, 2014.
8. Dang C, Lin N, Moy B, Come S, Sugarman S, Morris P, Abbruzzi A, Chen C, Steingart R, Patil S, Norton L, Winer E, Hudis C. Dose-dense doxorubicin and cyclophosphamide followed by weekly paclitaxel with trastuzumab and lapatinib in HER2/neu-overexpressed/amplified breast cancer is not feasible because of excessive diarrhea. *J Clin Oncol*. 2010; 28(18):2982–2988. [PubMed: 20479410]
9. National Institutes of Health ClinicalTrials.gov. Chemotherapy and Lapatinib or Trastuzumab in Treating Women with HER2/Neu-Positive Metastatic Breast Cancer. <http://www.clinicaltrials.gov/ct2/show/NCT00667251>
10. Boyle FM, Smith IE, O'Shaughnessy J, Ejlersen B, Buzdar AU, Fumoleau P, Gradishar W, Martin M, Moy B, Piccart-Gebhart M, Pritchard KI, Lindquist D, Amonkar M, Huang Y, Rappold E, Williams LS, Wang-Silvanto J, Kaneko T, Finkelstein DM, Goss PE, TEACH investigators. Health related quality of life of women in TEACH, a randomised placebo controlled adjuvant trial of lapatinib in early stage Human Epidermal Growth Factor Receptor (HER2) overexpressing breast cancer. *Eur J Cancer*. 2015; 51(6):685–96. [PubMed: 25752740]
11. Nardone B, Nicholson K, Newman M, Guitart J, Gerami P, Talarico N, Yang XJ, Rademaker A, West DP, Lacouture ME. Histopathologic and Immunohistochemical Characterization of Rash to Human Epidermal Growth Factor Receptor 1 (HER1) and HER1/2 Inhibitors in Cancer Patients. *Clin Cancer Res*. 2010; 16(17):4452–4460. [PubMed: 20732960]
12. Hu JC, Sadeghi P, Pinter-Brown LC, Yashar S, Chiu M. Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. *J Am Acad Dermatol*. 2007; 56:317–26. [PubMed: 17141360]
13. Belum VR, Fontanilla Patel H, Lacouture ME, Rodeck U. Skin toxicity of targeted cancer agents: mechanisms and intervention. *Future Oncol*. 2013; 9(8):1161–70. [PubMed: 23902247]
14. Rodeck U, Jost M, Kari C, et al. EGF-R dependent regulation of keratinocyte survival. *J Cell Sci*. 1997; 110:113–21. [PubMed: 9044042]

15. Abdullah SE, et al. Dermatologic Toxicities from Monoclonal Antibodies and Tyrosine Kinase Inhibitors against EGFR: Pathophysiology and Management. *Chemother Res Pract.* 2012; doi: 10.1155/2012/351210
16. US Department of Health and Human Services. National Institute of Health. National Cancer Institute; 2009. Common Terminology Criteria for Adverse Events (CTCAE) v4.0. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
17. Lacouture ME, Laabs SM, Koehler M, Sweetman RW, Preston AJ, Di Leo A, Gomez HL, Salazar VM, Byrne JA, Koch KM, Blackwell KL. Analysis of dermatologic events in patients with cancer treated with lapatinib. *Breast Cancer Res Treat.* 2009; 114(3):485–493. [PubMed: 18600445]
18. Iyengar NM, Fornier MN, Sugarman SM, Theodoulou M, Troso-Sandoval T, D'Andrea G, Drullinsky PR, Fasano J, Gajria D, Goldfarb SB, Comen EA, Lake DE, Modi S, Traina TA, Lacouture ME, Chen MF, Patil S, Baselga J, Norton L, Hudis CA, Dang CT. Phase II feasibility study of paclitaxel (T) with trastuzumab (H) and lapatinib (L) for node-negative, HER2-positive breast cancer (BC). *J Clin Oncol.* 2014; 32:5s. (suppl; abstr 633).
19. Guan Z, Xu B, DeSilvio ML, Shen Z, Arpornwirat W, Tong Z, Lorvidhaya V, Jiang Z, Yang J, Makhson A, Leung WL, Russo MW, Newstat B, Wang L, Chen G, Oliva C, Gomez H. Randomized trial of lapatinib versus placebo added to paclitaxel in the treatment of human epidermal growth factor receptor 2-overexpressing metastatic breast cancer. *J Clin Oncol.* 2013; 31(16):1947–53. [PubMed: 23509322]
20. Di Leo A, Gomez HL, Aziz Z, Zvirbule Z, Bines J, Arbushites MC, Guerrero SF, Koehler M, Oliva C, Stein SH, Williams LS, Dering J, Finn RS, Press MF. Phase III, double-blind, randomized study comparing lapatinib plus paclitaxel with placebo plus paclitaxel as first-line treatment for metastatic breast cancer. *J Clin Oncol.* 2008; 26(34):5544–52. [PubMed: 18955454]
21. Kaklamani VG, Siziopikou K, Scholtens D, Lacouture M, Gordon J, Uthe R, Meservey C, Hansen N, Khan SA, Jeruss JS, Bethke K, Cianfrocca M, Rosen S, Von Roenn J, Wayne J, Parimi V, Jovanovic B, Gradishar W. Pilot neoadjuvant trial in HER2 positive breast cancer with combination of nab-paclitaxel and lapatinib. *Breast Cancer Res Treat.* 2012; 132(3):833–842. [PubMed: 21359953]
22. Dranitsaris G, Lacouture ME. Development of prediction tools for diarrhea and rash in breast cancer patients receiving lapatinib in combination with capecitabine. *Breast Cancer Res Treat.* 2014; 147(3):631–638. [PubMed: 25216762]
23. Jatoi A, Green EM, Rowland KM Jr, et al. Clinical predictors of severe cetuximab-induced rash: observations from 933 patients enrolled in north central cancer treatment group study N0147. *Oncology.* 2009; 77:120–123. [PubMed: 19622902]
24. Lacouture ME, Anadkat MJ, Bensadoun RJ, Bryce J, Chan A, Epstein JB, Eaby-Sandy B, Murphy BA, MASCC Skin Toxicity Study Group. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. *Support Care Cancer.* 2011; 19(8):1079–95. [PubMed: 21630130]
25. Jatoi A, Rowland K, Sloan JA, Gross HM, Fishkin PA, Kahanic SP, Novotny PJ, Schaefer PL, Johnson DB, Tschetter LK, Loprinzi CL. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). *Cancer.* 2008; 113(4):847–53. [PubMed: 18543329]
26. Boone SL, Rademaker A, Liu D, Pfeiffer C, Mauro DJ, Lacouture ME. Impact and management of skin toxicity associated with anti-epidermal growth factor receptor therapy: survey results. *Oncology.* 2007
27. Balagula Y, Garbe C, Myskowski P, Hauschild A, Rapoport B, Boers-Doets CB, Lacouture ME. Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. *Int J Dermatol.* 2011; 50:129–146. [PubMed: 21244375]
28. Ocivirk J, Heeger S, McCloud P, Hofheinz RD. A review of the treatment options for skin rash induced by EGFR-targeted therapies: Evidence from randomized clinical trials and a meta-analysis. *Radiol Oncol.* 2013 Jun; 47(2):166–175. [PubMed: 23801914]
29. Chanprapaph K, Vachiramon V, Rattanakaemakorn P. Epidermal Growth Factor Receptor Inhibitors: A Review of Cutaneous Adverse Events and Management. *Dermatol Res Pract.* 2014; 2014:734249. [PubMed: 24723942]

30. Ocuvir J, Rebersek M. Treatment of cetuximab-associated cutaneous side effects using topical application of vitamin K1 cream. *J Clin Oncol*. 2009; 27 supplement 5087.

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Clinical Practice Points

Lapatinib, a dual HER1/2 inhibitor has been approved for use against HER2 positive breast cancer in the metastatic setting. Several studies have examined the use of lapatinib in combination with other treatments in the adjuvant setting. These trials were limited by a high incidence of adverse events, the most notable of these being high incidence of rash and diarrhea. A recent phase II trial of lapatinib with dose dense paclitaxel and trastuzumab was terminated early due to a 95% incidence of rash. This series describes the course of 9 patients from the trial who experienced grade 2 and 3 rash. Several observations can be made by examining these cases in more detail. One such observation is that onset of rash occurs early on usually within the first cycle of treatment. In addition, only 56% of these patients were referred to the Dermatology service, many of them being referred late in the course of the rash. Moreover, of the 5 patients who ultimately came off study, 3 of them had other concomitant serious adverse reactions. Thus, this case series highlights several important areas for further research including the use of prophylactic dermatologic treatment for breast cancer patients being treated with lapatinib.

Figure 1. Patient 7 with grade 3 maculopapular rash generalized to face, chest, abdomen, back. This high grade rash also resulted in the patient being taken off study.

Demographic data including; age, race, stage, size of initial tumor, surgical intervention, and receptor positivity for patients with grade 2 and 3 rash.

Table 1

Patient #	AGE	RACE	STAGE	TUMOR SIZE	SURGERY	RECEPTORS
1	52	Caucasian	IA	0.24cm	Bilateral Mastectomies	ER+, PR+, HER2/neu+
2	74	Caucasian	IIA	2.5cm	Left Lumpectomy	ER+, PR+, HER2+
3	46	Asian	IIA	2.1cm and 0.4cm	Bilateral Mastectomies	ER-, PR-, HER2/neu+
4	36	Hispanic	IA	1.5cm	Left Lumpectomy	ER+, PR+, HER2/neu+
5	41	African American	IA	0.55cm	Bilateral Mastectomies	ER+, PR+, HER2/neu+
6	49	Caucasian	IA	1.6cm	Right Lumpectomy	ER+, PR+, HER2/neu+
7	41	Caucasian	IA	0.5cm (multiple foci)	Left Lumpectomy	ER-, PR-, HER2/neu+
8	38	Hispanic	IA	1.4cm	Left Lumpectomy	ER+, PR+, HER2/neu+
9	56	Caucasian	IA	0.6cm	Left Lumpectomy	ER+, PR+, HER2/neu+

Table 2

This table summarizes characteristics of the rashes experienced by the patients in the phase II trial. Prior skin related history, the cycle of chemotherapy during which the rash occurred, the type of rash, its locations, grade, and how the rash was treated is included.

Patient #	History of Skin Disorder	Cycle	Rash Type	Rash Site	Grade	Treatment
1	Rosacea	1 and 2	Acneiform (1) and Maculopapular (2)	Face, chest back	2	Clindamycin topical and Triamcinolone 0.1% (not used by patient) then given Medrol dose pack and triamcinolone (used by patient)
2	Psoriasis	1	Maculopapular	Face, thighs, abdomen, back	2	N/A
3	No	2	Acneiform	Face, torso, back, arms, legs	2	Zyrtec, diphenhydramine cream, Eucerin cream
4	No	2	Acneiform	Face, neck, scalp	2	Acemetasone and clindamycin cream
5	No	4 and 6	Cellulitis Erythematous rash	Breast Face	3 2	Antibiotics Hydrocortisone cream
6	No	1	Acneiform	Face, torso	2	Clindamycin topical and hydrocortisone cream
7	No	1	Rash NOS and acneiform	Face, chest hands	2 and 3	Cefadroxil 500mg bid, acemetasone
8	No	1	Pustular	Face	2	Minocycline 100mg bid and Medrol dose pack
9	Acne	1	Acneiform	Face	2	Alcometasone and Clindamycin topical