Published in final edited form as:

Cancer Treat Commun. 2016 ; 7: 1–3. doi:10.1016/j.ctrc.2016.02.006.

Pigmentation of the Tongue with Lapatinib Treatment in a Patient with Advanced Breast Cancer: A Case Report

Matthew D. Bloom, Joseph M. Gibney, and Coy D. Heldermon^{\$}

University of Florida Department of Medicine, Box 100278, 1600 SW Archer Road, Gainesville, Florida, 32610

Matthew D. Bloom: mdbloom4@gmail.com; Joseph M. Gibney: josephmgibney@gmail.com

Keywords

lapatinib; EGFR; pigmentation; tongue

Introduction

Breast cancer is often associated with dysregulation of the Epidermal-growth-factor-receptor(EGFR)-mediated signaling pathways. HER-1 [EGFR/ErbB-1] overexpression is present in ~27%–30% of breast tumors and HER-2 [ErbB-2], an adverse prognostic marker for breast cancer, is overexpressed in ~20%–25% of breast tumors.^{1,2} Both HER-1 and HER-2 are members of the family of epidermal growth factor receptor (EGFR) tyrosine kinases (RTKs) that are involved in regulation of normal and aberrant cell proliferation and survival.²

Lapatinib, an oral receptor tyrosine kinase inhibitor, intracellularly targets both HER-1 and HER-2 receptors.^{2,3} Lapatinib is indicated for treatment of advanced or metastatic HER-2 positive breast cancers in combination with capecitabine or endocrine therapy. In trials with trastuzumab, lapatinib has demonstrated significant median OS advantage for patients with HER-2-positive metastatic breast cancers.^{4,5}

EGFR is inhibited by lapatinib not only on tumor cells, but also on keratinocytes.⁶ The dermatologic events from lapatinib and other EGFR inhibitors have already been well documented along with their management recommendations.^{6–9} Acneiform rash is the most common lapatinib cutaneous toxicity, with lesions usually occurring on the face, trunk, and extremities.¹⁰ Oral complications from lapatinib, such as taste alterations/dysgeusia, have also been reported.¹¹

Despite the various mucocutaneous adverse events reported for lapatinib and other epidermal growth factor receptor inhibitors (EGFRIs), in our review of the literature, this is

^{\$}Corresponding Author: Coy Heldermon coy.heldermon@medicine.ufl.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

the first case presenting drug-induced pigmentation of the tongue as a side effect while on lapatinib treatment.

Case Report

A 54-year-old woman was initially diagnosed with T1cN0, Gr II, ER+ PR– HER-2+ left breast cancer and underwent a lumpectomy and sentinel node biopsy followed by adjuvant chemotherapy (adriamycin and cyclophosphamide/taxol-trastuzumab) and radiotherapy (XRT).

After two years the patient presented with swollen lymph nodes and underwent an axillary lymph node dissection (ALND) (9 of 11 nodes positive) and a mastectomy and began treatment with docetaxel and trastuzumab. Carboplatin was also prescribed but was soon stopped for chest pain.

Follow up ten months later with review of PET/CT revealed lung and supraclavicular node involvement and docetaxel was replaced by capecitabine. She was referred to our facility.

We added lapatinib at a dose of 1,250 mg/day. A month later, her capecitabine was stopped in the setting of rising tumor markers and hand-foot syndrome. We replaced capecitabine with letrozole. Her drug regimen at this time included letrozole, lapatinib, trastuzumab, and denosumab.

Seven months later, the patient was observed to have developed black pigmentation of her tongue [figure 1]. The buccal mucosa, gingiva, hard palate, and lips were normal. The lesions were painless. She never had similar pigmentation in the past. She also complained of altered taste/dysguesia.

Other symptoms she was experiencing included increased lymphedema in her left arm; clavicle, sternal, and right chest pain; diarrhea; sleep disturbances; and left knee and hip pain. Other current medications included ergocalciferol, losartan, and lorazepam.

Upon discontinuation of lapatinib, the patient showed a resolution of tongue pigmentation back to normal.

Discussion

Targeted treatments for blocking HER-1 and HER-2 signaling include; [1] inhibition of the receptor intracellular kinase domain (lapatinib, erlotinib, gefitinib); and [2] monoclonal antibody targeting of the receptor extracellular domain (trastuzumab, cetuximab).^{11,12} The use of targeted therapies for HER-1 and HER-2, as well as other cellular targeted agents are growing rapidly.¹³ For many of these targeted therapies, the adverse effect profiles continue to emerge. These toxicities, especially dermatologic toxicities, seem to be associated with improved response to therapy.¹⁴

Tongue hyperpigmentation has been associated with several medications. These include; antineoplastic agents, including adriamycin, capecitabine, cyclophosphamide, tegafur¹⁵, minocycline¹⁶, and combination treatment with interferon-alpha and ribavirin.¹⁵ Imatinib,

another tyrosine kinase inhibitor, has reported cases of mucosal pigmentation of the hard palate¹⁷ and erlotinib, an EGFR tyrosine kinase inhibitor, has reported association with black hairy tongue.¹⁸ Medication-associated pigmentation of the oral cavity has also been seen with clofazamine, antimalarials, such as chloroquine, hydroxychloroquine, amodiaquine, and quinacrine, and conjugated estrogen.¹⁷

In most cases of hyperpigmentation, the underlying pathogenesis is not well understood and is likely to be different depending on the administered drug.¹⁹ In our case, the mechanism is unknown. Possible causes for drug-induced hyperpigmentation of the oral cavity include: [1] drug stimulation of melanin synthesis; [2] drug metabolites chelated with iron; or [3] direct products from breakdown of the drug.¹⁷

Targeted agents are frequently administered in combination with or following conventional anticancer therapies. It can be challenging to identify the toxicities of targeted agents because they can combine with or accentuate toxicities from conventional therapies.¹³ For this reason, toxicities from targeted agents may be underreported.

Druginformers lists 9 reports of lapatinib related tongue discoloration from the Federal Drug Administration's AERS database from 2007 to 2012. The patients range in age from 34 to 80 and range in dosage of lapatinib from 250 mg to 1250 mg.²⁰

As mentioned above, tongue pigmentation from capecitabine use has been described as a rare side effect. In reported cases of capecitabine induced tongue pigmentation, the discoloration was resolved after capecitabine therapy was discontinued. Complete resolution of hyperpigmented macules in one patient was seen on the tongue after 10 week cessation of the drug.¹⁹ In other instances, the pigmented macules faded or showed a resolution of hyperpigmentation after completion of therapy.^{21,22} Our patient had previously taken capecitabine for approximately 2 months which was discontinued due to chemotherapy toxicity and disease progression 7 months prior to observation of her tongue pigmentation.

The co-administration of drugs that are CYP3A inhibitors can result in increased risk of lapatinib related toxicity, as elimination of lapatinib is primarily metabolized by the cytochrome P450 enzymes CYP3A4/5.¹² To our knowledge, our patient was not on any CYP3A inhibitors.

The pigmentation on our patient's tongue resolved after cessation of lapatinib. The lesions were painless and did not require delay or dose reduction. Systematic evaluation of the oral cavity of patients on lapatinib is not a routine clinical practice so cases may be underreported.

Conclusion

Pigmentation of the tongue while on lapatinib treatment is a potential finding of which clinicians and health care workers in oncology should be aware.

Acknowledgments

We would like thank the financial support for CDH provided by the University of Florida Gatoraid Fund and K08 DK085141.

References

1. Moy B, Goss PE. Lapatinib: current status and future directions in breast cancer. *Oncologist*. 2006; 11(10):1047–1057.10.1634/theoncologist.11-10-1047 [PubMed: 17110623]
2. Bilancia D, Rosati G, Dinota A, Germano D, Romano R, Manzione L. Lapatinib in breast cancer. *Ann Oncol*. 2007; 18(suppl 6):vi26–vi30.10.1093/annonc/mdm220 [PubMed: 17591827]
3. Spector NL, Xia W, Burris H, et al. Study of the biologic effects of lapatinib, a reversible inhibitor of ErbB1 and ErbB2 tyrosine kinases, on tumor growth and survival pathways in patients with advanced malignancies. *J Clin Oncol*. 2005; 23(11):2502–2512.10.1200/JCO.2005.12.157 [PubMed: 15684311]
4. Blackwell KL, Burstein HJ, Storniolo AM, et al. 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):2585–2592.10.1200/JCO.2011.35.6725 [PubMed: 22689807]
5. Lin NU, Guo H, Yap JT, et al. Phase II Study of Lapatinib in Combination With Trastuzumab in Patients With Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer: Clinical Outcomes and Predictive Value of Early [18F]Fluorodeoxyglucose Positron Emission Tomography I. *J Clin Oncol*. 2015; 33(24):2623–2631.10.1200/JCO.2014.60.0353 [PubMed: 26169615]
6. Galimont-Collen AFS, Vos LE, Lavrijsen APM, Ouwkerk J, Gelderblom H. Classification and management of skin, hair, nail and mucosal side-effects of epidermal growth factor receptor (EGFR) inhibitors. *Eur J Cancer*. 2007; 43(5):845–851.10.1016/j.ejca.2006.11.016 [PubMed: 17289377]
7. Gutzmer, R.; Becker, J.; Enk, A. [Accessed June 7, 2015] Management of cutaneous side effects of EGFR inhibitors: recommendations from a German expert panel for the primary treating physician. *JDDG J der ....* 2011. <http://onlinelibrary.wiley.com/doi/10.1111/j.1610-0387.2010.07561.x/full>
8. Lacouture, M.; Laabs, S. [Accessed June 7, 2015] Analysis of dermatologic events in patients with cancer treated with lapatinib. *Breast cancer Res ....* 2009. <http://link.springer.com/article/10.1007/s10549-008-0020-7>
9. Agero ALC, Dusz SW, Benvenuto-Andrade C, Busam KJ, Myskowski P, Halpern AC. Dermatologic side effects associated with the epidermal growth factor receptor inhibitors. *J Am Acad Dermatol*. 2006; 55(4):657–670.10.1016/j.jaad.2005.10.010 [PubMed: 17010747]
10. Metzger Filho O, Saini KS, Azim HA, Awada A. Prevention and management of major side effects of targeted agents in breast cancer. *Crit Rev Oncol Hematol*. 2012; 84(Suppl 1):e79–e85.10.1016/j.critrevonc.2010.07.014 [PubMed: 20817545]
11. Watters AL, Epstein JB, Agulnik M. Oral complications of targeted cancer therapies: a narrative literature review. *Oral Oncol*. 2011; 47(6):441–448.10.1016/j.oraloncology.2011.03.028 [PubMed: 21514211]
12. de, GC., Jr; Awada, A. [Accessed June 7, 2015] Side effects of anti-cancer molecular-targeted therapies (not monoclonal antibodies). *Curr Opin Oncol*. 2006. http://journals.lww.com/co-oncology/Abstract/2006/07000/Side_effects_of_anti_cancer_molecular_targeted.2.aspx
13. Parkhill, A. [Accessed June 7, 2015] Oral Mucositis and Stomatitis Associated with Conventional and Targeted Anticancer Therapy. *J Pharmacovigil*. 2013. <http://esciencecentral.org/journals/oral-mucositis-and-stomatitis-associated-with-conventional-and-targeted-anticancer-therapy-2329-6887.1000112.pdf>
14. Azim HA, Agbor-Tarh D, Bradbury I, et al. Pattern of rash, diarrhea, and hepatic toxicities secondary to lapatinib and their association with age and response to neoadjuvant therapy: analysis from the NeoALTTO trial. *J Clin Oncol*. 2013; 31(36):4504–4511.10.1200/JCO.2013.50.9448 [PubMed: 24248687]

15. Casamiquela, K.; Cohen, P. [Accessed June 7, 2015] Chemotherapy-associated tongue hyperpigmentation and blue lunula. J drugs dermatology .... 2013. <http://europepmc.org/abstract/med/23377398>
16. Imafuku, K.; Natsuga, K. [Accessed June 7, 2015] Mucosal hyperpigmentation from prophylactic minocycline for EGFR inhibitor. J .... 2015. <http://onlinelibrary.wiley.com/doi/10.1111/jdv.12978/abstract>
17. Li C-C, Malik SM, Blaeser BF, et al. Mucosal pigmentation caused by imatinib: report of three cases. Head Neck Pathol. 2012; 6(2):290–295.10.1007/s12105-011-0325-4 [PubMed: 22209988]
18. Jeong JS, Lee JY, Kim MK, Yoon TY. Black hairy tongue associated with erlotinib treatment in a patient with advanced lung cancer. Ann Dermatol. 2011; 23(4):526–528.10.5021/ad.2011.23.4.526 [PubMed: 22148027]
19. Zekri, J.; Abdel-Ghany, E. [Accessed June 7, 2015] Hyperpigmentation of the tongue, palms and soles: Rare side effect of capecitabine. J Cancer Res Ther. 2013. <http://www.nobleresearch.org/Journals/JCRT/Article/Volume1/JCRT13-10025.aspx>
20. [Accessed June 7, 2015] Lapatinib Ditosylate Tongue Discolouration Reports - DrugInformer. http://www.druginformer.com/search/side_effect_details/lapatinibditosylate/tonguediscolouration.html
21. Vasudevan B. An unusual case of capecitabine hyperpigmentation: Is hyperpigmentation a part of hand-foot syndrome or a separate entity? Indian J Pharmacol. 2010; 42(5):326–328.10.4103/0253-7613.70401 [PubMed: 21206630]
22. Villalón, G.; Martín, J.; Pinazo, M. [Accessed June 7, 2015] Focal acral hyperpigmentation in a patient undergoing chemotherapy with capecitabine. Am J .... 2008. <http://europepmc.org/abstract/med/19489659>

Clinical Practice Points

- Clinicians should assess skin, hair, nail, and mucosal side effects from epidermal growth factor receptor inhibitors (EGFRIs), such as lapatinib.
- Oncologists should recognize the possible occurrence of pigmentation of the tongue associated with lapatinib treatment.

Figure 1.
Tongue discoloration on lapatinib.