Letters

RESEARCH LETTER

Association of Antibiotic Resistance With Antibiotic Use for Epidermal Growth Factor Receptor Inhibitor–Related Papulopustular Eruption

Papulopustular eruption (PPE) develops in up to 90% of patients with cancer treated with epidermal growth factor receptor (EGFR) inhibitors.[1] Consensus recommendations for management include emolliation, sunscreen, topical corticosteroids, and topical and systemic antibiotics, which effectively decrease severity of EGFR inhibitor-related PPE.[2] Although the initial EGFR inhibitor-related PPE is sterile, secondary infection increases the severity and duration of PPEs. Higher-grade, refractory cases may show antibiotic-resistant bacterial infection on wound culture.[3] This study investigated whether use of topical clindamycin and/or oral tetracyclines during management of EGFR inhibitor-related PPE is associated with antibiotic-resistant bacterial infection.

Methods | We conducted a retrospective medical record review of the Stanford Cancer Institute Research Database. All patients were screened for inclusion and provided a waiver of consent. Patients included in the cohort were enrolled in the database from January 1, 2012, to July 31, 2016, diagnosed with at least grade 1 EGFR inhibitor-related PPE,[4] and had a subsequent wound culture of the PPE that yielded bacterial organ-

Table 1. Demographic Characteristics of 71 Patients With Positive Bacterial Wound Culture Results From Papulopustular Eruptions Secondary to EGFR Inhibitor Therapy[a]

Characteristic	Wound Culture Without Antibiotic-Resistant Bacterial Secondary Infection of PPE (n = 41)[b]	Wound Culture With Antibiotic-Resistant Bacterial Secondary Infection of PPE (n = 30)[b]	*P* Value
Sex			
Female	15 (36.6)	10 (33.3)	.78
Male	26 (63.4)	20 (66.7)	
Age at start of EGFR inhibitor treatment, mean (SD), y[c]	62.7 (13.5)	61.9 (12.5)	.79
Cancer			
Head and neck	20 (48.8)	13 (43.3)	.16
Breast	4 (9.8)	0	
Colorectal	6 (14.6)	3 (10.0)	
Lung	10 (24.4)	14 (46.7)	
Other	1 (2.4)	0	
EGFR inhibitor			
Afatinib	1 (2.4)	1 (3.3)	.34
Afatinib and cetuximab	0	1 (3.3)	
Cetuximab	22 (53.7)	13 (43.3)	
Erlotinib	9 (22.0)	12 (40.0)	
Trastuzumab and pertuzumab	3 (7.3)	0	
Panitumumab	5 (12.2)	3 (10.0)	
Lapatinib	1 (2.4)	0	
Topical clindamycin use			
None	26 (63.4)	8 (26.7)	<.001
1-28 d	10 (24.4)	3 (10.0)	
≥4 wk	5 (12.2)	19 (63.3)	
Oral tetracycline use			
None	36 (87.8)	12 (40.0)	<.001
1-28 d	4 (9.8)	4 (13.3)	
≥4 wk	1 (2.4)	14 (46.7)	
No. of antibiotics used			
None	23 (56.1)	4 (13.3)	<.001
1 (Clindamycin or tetracycline)	16 (39.0)	12 (40.0)	
2 (Clindamycin and tetracycline)	2 (4.9)	14 (46.7)	

Abbreviations: EGFR, epidermal growth factor receptor; PPE, papulopustular eruption.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Resistant to clindamycin and/or tetracycline in wound culture resistance report.

[c] Age was compared by the 2-sided, unpaired *t* test; all other variables were analyzed by the χ^2 or Fisher exact test as appropriate.

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ism. We collected dates of EGFR inhibitor therapy, time and duration of antibiotic exposure to topical clindamycin and/or oral tetracyclines, and bacterial wound culture results, including antibiotic susceptibility testing. Patients concurrently treated with antiseptics or with no antibiotic duration reported were excluded. The study was approved by the Stanford University Administrative Panel on Human Subjects in Medical Research under the extended approval process. All data were deidentified.

To compare patients whose wound culture yielded antibiotic-resistant bacteria with those whose wound culture did not, age was compared with an unpaired *t* test. Categorical variables were compared by χ^2 or Fisher exact test as appropriate. Cox proportional hazards regression was performed to determine whether time from EGFR inhibitor therapy start to first positive wound culture result was associated with antibiotic exposure. Antibiotic exposures were treated as time-dependent variables. All tests were 2-sided, and $P < .05$ was considered to be statistically significant. All statistical analyses were conducted with SAS statistical software, version 9.4 (SAS Institute Inc).

Results | Among 71 patients (mean [SD] age, 62.4 [13.1] years; 46 [64.8%] male) with positive bacterial wound culture results, the incidence of clindamycin-resistant infection was highest among patients who received topical clindamycin therapy for greater than 4 weeks (n = 19 [63.3%]) vs no treatment (n = 8 [26.7%]) and treatment for less than 4 weeks (n = 3 [10.0%]). The incidence of tetracycline-resistant infection was highest among patients who received oral tetracycline therapy for greater than 4 weeks (n = 14 [46.7%]) vs no treatment (n = 12 [40.0%]) and treatment for less than 4 weeks (n = 4 [13.3%]) (**Table 1** and **Table 2**). The risk of antibiotic-resistant bacterial infection was greater with increased treatment time for patients with history of oral tetracycline use (hazard ratio, 3.15; 95% CI, 1.45-6.85; $P = .004$) or prior topical clindamycin use (hazard ratio, 1.94; 95% CI, 0.83-4.50; $P = .12$).

Discussion | In this study, patients who received topical clindamycin or oral tetracycline for management of EGFR inhibitor-related PPEs had a higher incidence of secondary skin infection with antibiotic-resistant bacteria compared with patients without prior antibiotic exposure, a finding that reached statistical significance with exposure to oral tetracyclines. A greater incidence of resistant infections was seen in patients with greater than 4 weeks of exposure to either antibiotic, suggesting that longer duration of antibiotic use is associated with increased risk of developing antibiotic resistance.

Our findings are consistent with a previous study[5] in acne vulgaris, which found that antibiotic use without concurrent antiseptic therapy was associated with development of antibiotic-resistant bacteria. Guidelines for EGFR inhibitor-related PPE management understandably recommend against using benzoyl peroxide because of potential exacerbation of EGFR inhibitor-related xerosis and skin irritation.[3,6] Given the finding that patients with a history of antibiotic monotherapy for EGFR inhibitor-related PPE may develop antibiotic-resistant skin infections, we suggest consideration of concurrent antiseptic therapy (eg, benzoyl peroxide, dilute bleach baths, or chlorhexidine) during topical or oral antibiotic therapy for EGFR inhibitor-related PPE.

Table 2. Positive Bacterial Wound Culture Results From 71 Patients[a]

Wound Culture Result	No. (%) of Patients
MSSA	
Clindamycin and tetracycline susceptible	20 (28)
Clindamycin resistant	11 (15)
Tetracycline resistant	4 (6)
Clindamycin and tetracycline resistant	6 (8)
MRSA	
Clindamycin and tetracycline susceptible	2 (3)
Clindamycin resistant	3 (4)
Tetracycline resistant	1 (1)
Clindamycin and tetracycline resistant	1 (1)
Enterococcus species[b]	2 (3)
Serratia species	1 (1)
Tetracycline-resistant *Serratia* species	4 (6)
Other gram-negative bacteria[c]	28 (39)

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.

[a] One wound culture from papulopustular eruptions per patient was included. If patients had multiple wound cultures, the wound culture with a positive result was taken. Among 71 patients with positive bacterial wound culture results, 83 total strains of bacteria were reported because some patients had polymicrobial skin infections.

[b] Antibiotic susceptibility profiles did not include clindamycin or tetracycline susceptibilities.

[c] Other gram-negative bacteria found included *Enterobacter, Klebsiella, Pseudomonas, Moraxella, Proteus*, *Citrobacter*, *Elizabethkingia*, *Raoultella*, and *Stenotrophomonas* species and uncharacterized gram-negative bacteria.

Limitations to this study include the sample size and single-center design. Lifetime exposure to antibiotics, which may result in permanent changes to skin flora, was not assessed. Patient adherence to antibiotic use may have been variable. The effect of concurrent antiseptic therapy on reducing the incidence of antibiotic-resistant bacterial infections has not yet been determined. The risk of xerosis and skin irritation with concurrent antiseptic therapy in this patient population has not yet been determined; however, in our institutional experience, antiseptic-related xerosis can be effectively managed with diligent emolliation. We look forward to future studies that investigate whether the addition of topical antiseptics during management of EGFR inhibitor-related PPE may lead to reduction of antibiotic resistance and, subsequently, improved outcome and quality of life in this susceptible patient population.

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1. Li T, Perez-Soler R. Skin toxicities associated with epidermal growth factor receptor inhibitors. *Target Oncol*. 2009;4(2):107-119. doi:10.1007/s11523-009-0114-0

2. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al; 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):1079-1095. doi:10.1007/s00520-011-1197-6

3. Eilers RE Jr, Gandhi M, Patel JD, et al. Dermatologic infections in cancer patients treated with epidermal growth factor receptor inhibitor therapy. *J Natl Cancer Inst*. 2010;102(1):47-53. doi:10.1093/jnci/djp439

4. Common Terminology Criteria for Adverse Events v5.0 (CTCAE). https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed July 4, 2018

5. Cunliffe WJ, Holland KT, Bojar R, Levy SF. A randomized, double-blind comparison of a clindamycin phosphate/benzoyl peroxide gel formulation and a matching clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris. *Clin Ther*. 2002;24(7):1117-1133. doi:10.1016/S0149-2918(02)80023-6

6. Potthoff K, Hofheinz R, Hassel JC, et al. Interdisciplinary management of EGFR-inhibitor-induced skin reactions: a German expert opinion. *Ann Oncol*. 2011;22(3):524-535. doi:10.1093/annonc/mdq387

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