Review Article

Role of Systemic Antibiotics in Preventing Epidermal Growth Factor Receptor: Tyrosine Kinase Inhibitors-induced Skin Toxicities

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ABSTRACT

The epidermal growth factor receptor (EGFR) is actively involved in the growth of multiple tumor types and has been found as an effective treatment target in various solid cancers, for example, lung cancer and head and neck cancer. Of effective drugs which target and inhibit EGFR functions, tyrosine kinase inhibitors have shown promising results, albeit at a cost of side effects, skin toxicity being the most common. This article provides an evidence-based strategy to oncology nurse practitioners in dealing with such toxicity.

Key words: Epidermal growth factor receptor, papulopustular rash, skin toxicity, tyrosine kinase inhibitors

Introduction

Epidermal growth factor receptor (EGFR), one of the versatile signaling units in cell biology, is involved in the regulation of cell proliferation, survival, and differentiation of a variety of cell types during development, tissue homeostasis, and tumorigenesis.[1] EGFR is expressed in many solid tumors such as nonsmall cell lung cancer (NSCLC), mostly adenocarcinoma, colon cancer, pancreatic cancer, renal cell carcinoma, hepatocellular cancer, and its blockade is beneficial in terms of its infinite effects on tumor growth and spread.[2] One of the strategies for targeting EGFR pathway involves small molecule tyrosine kinase inhibitors (TKIs) that completely block receptor phosphorylation.[3]

TKIs are unique class of drugs which are administered orally and they avoid many side effects caused by cytotoxic chemotherapeutic agents. However, as promising as the TKIs

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are, they do come with a variety of side effects. The most common adverse events (AEs) are gastrointestinal (diarrhea and stomatitis) and cutaneous (rash, dry skin, and paronychia).[4]

Cutaneous toxicities are the most common AEs associated with EGFR-TKI treatment. They occur in more than 50% of patients with Grade 3 or greater severity in 3%–20% of patients receiving these agents.[5,6] The proper functioning of the EGFR signaling pathway contributes to the normal development and maintenance of the skin (e.g., protection against ultraviolet (UV)-induced damage, wound healing). EGFR is highly expressed in the human skin within keratinocytes, follicular epithelium, sweat and sebaceous glands, and in dermal capillaries. Moreover, EGFR plays a critical role in keratinocyte activation.[2] Although the mechanisms underlying EGFR-TKI-related dermatologic toxicities are not fully understood, animal models suggest that inhibition of EGFR blocks downstream signaling pathways and prevents keratinocytes from maturing properly as they migrate to the outer stratum corneum.[2,7,8] This results in the thinning of the outermost layers of the epidermis and corneal layers, and subsequent loss of the skin's protective barrier that results in the increased sensitivity to UV radiation damage.[6]

The most common dermatological toxicity resulting from EGFR-TKI treatment is papulopustular eruption (PPE), also known as "acne-like rash" or "folliculitis."[9,10] Additional toxicities include nail changes, hair changes, ocular changes, pruritus, xerosis, and photosensitivity or erythema. The PPE may be localized to the face, arms, back, and chest region and occurs 2–3 days following the start of EGFR-TKI treatment and worsens within 1–3 weeks.[4] Several grading criteria have been developed to judge the rash severity. The primary goals of these grading criteria were to develop a uniform, common terminology for the assessment of rash severity and to help clinicians tailor therapy depending on the severity of the rash.[11]

EGFR-TKI-related skin side effects may be a surrogate marker of drug efficacy.[7,12] Therefore, early and intensive monitoring during treatment exposure remains a major concern for a careful toxicity management, as well as dose adaptation. These cutaneous toxicities may induce physical and psycho-social discomfort and can affect patients' quality of life (QoL), as well as compliance with treatment.[7,13] Hence, preventive and therapeutic strategies are important to ensure optimal therapeutic dosing and maximize patient outcomes, including improved survival and QoL.

The preventive and therapeutic measures to control skin toxicities include topical application of emollient, antibiotics, steroid creams, administration of systemic steroids and antibiotics, avoidance of sun exposure, and the use of high-protection factor sunscreens.[10,14]

There are various treatment measures suggested in literature for the prevention of EGFR-TKI-induced skin toxicities, but the level of evidence is not known.[15] Although EGFR-TKIs are associated with significant skin-related AEs, there are not many studies addressing the problem. Mostly, there are practice guidelines or expert consensus[5,11] which provide low level of evidence dealing with the issue, hence it is necessary to look for a robust data set, which addresses the EGFR-TKI-associated dermatological AEs.

Different EGFR-TKIs share common toxicities although with some variance in severity. For example, four TKIs are approved for NSCLC so far, namely, gefitinib, erlotininb, afatinib, and osimertinib. Diarrhea is more common with afatinib as compared to erlotinib or gefitinib. Similarly, all grades or Grades 3–4 skin rash is more commonly associated with afatinib.[16,17]

Methods

Inclusion and exclusion criteria

This review aims to analyze the current available evidences about the role of systemic antibiotics for EGFR-TKIs-induced dermatologic toxicity. In pursuance of required answer, a set of inclusion and exclusion criteria was established. Studies that enrolled adult cancer patients treated with EGFR-TKIs for any cancer and have developed cutaneous toxicity were included in the review. These inclusion and exclusion criteria are presented in Table 1.

Search strategy

The search focused on identifying all the relevant literature. The research question was broken down into its components, identifying the population (adult cancer

Table 1: Inclusion and exclusion criteria

Criteria	Item
Inclusion criteria	English language
	Until November 2015
	Studies from different countries
	Published studies
	Studies addressing the role of systemic antibiotics for EGFR-TKI-associated skin toxicity
Exclusion criteria	Studies not published in English
	Review article
	Consensus reports
	Editorials
	Studies addressing skin toxicity associated only with monoclonal antibodies (e.g., cetuximab, panitumumab)
	Studies only focusing on topical treatment or other systemic intervention other than systemic antibiotics

EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitor

patients treated with EGFR-TKI), the intervention (systemic antibiotics), the comparison (placebo), and the outcome measure (skin toxicity results and QoL). For each part of the question, key terms and synonyms were identified [Table 2].

A comprehensive search of electronic databases was executed. Two electronic databases, SCOPUS and MEDLINE, were searched to identify published articles in an attempt to assess the efficacy of systemic antibiotics. All articles focusing on the effects of the preventive or curative treatment of EGFR-TKI-associated dermatologic toxicities were selected. The study references and related review article references were analyzed during the search for additional studies. Searches were carried out until November 2015 with no limit on previous dates.

Literature identified

With the use of all possible keywords [Table 3], more than 1048 hits were identified. All titles were examined for relevance to study question and 66 titles were found meeting the study inclusion criteria. Citation lists of all these articles were reviewed to ensure exhaustive literature search. Four completely reported randomized control trials (RCTs), an abstract of phase III RCT with large sample size, and two retrospective studies with interesting findings, which met the inclusion and exclusion criteria, were included in this review [Figure 1 and Table 4].

Table 2: Facet analysis of the question

Population	Intervention	Comparison	Outcome
Adult cancer patients (not specified in the search) treated with EGFR-TKI	Tetracycline OR Minocycline OR Doxycycline OR Azithromycin	Placebo (not specified in the search	Cutaneous toxicity OR Skin rash OR Acneiform rash OR Folliculitis

Table 3: Keywords used for literature search

Keywords
TKI
EGFR inhibitor
Skin rash
Cutaneous toxicity
Rash
Folliculitis
Papulopustular rash
Dermatologic
Toxicity
Rash
Papulopustular rash
Cutaneous toxicity
Skin rash
Acneiform rash
Minocycline
Doxycycline
Erlotinib
Afatinib

TKI: Tyrosine kinase inhibitor, EGFR: Epidermal growth factor receptor

Results

Important findings of all included studies are described according to the treatment agent used in this section and are also shown in Table 4.

Tetracycline

The first North Central Cancer Treatment Group (NCCTG) study was a randomized, placebo-controlled, phase III trial (N03CB), conducted in the USA. It included 61 cancer patients (31 lung, 16 colorectal cancer, and 15 other malignancies) being treated with an EGFR-targeted agent (cetuximab, gefitinib, and others). Participants were randomized to receive either tetracycline (500 mg/bid for 28 days) or placebo. Patients were evaluated at the end of weeks 4 and 8 for performance status, AEs, and rash according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. There was no difference in the incidence of physician-reported rash within 4 weeks (70% in tetracycline vs. 76% in placebo arm). Although patient-reported symptoms were similar within 4 weeks, patients treated with tetracycline reported less itching, burning, stinging, and skin irritation.[18]

A confirmatory NCCTG supplementary randomized N03CB trial was conducted on 65 patients (33 in the tetracycline arm and 32 in the placebo arm). More than 50% of patients had gastrointestinal cancers and >60% received cetuximab. The similar dose of tetracycline was used as the last trial. This study failed to explain any benefit from tetracycline in terms of incidence or severity of rash.[20]

In a prospective, open-label trial by O. Arrieta *et al.*,[23] ninety patients taking afatinib for NSCLC were randomly

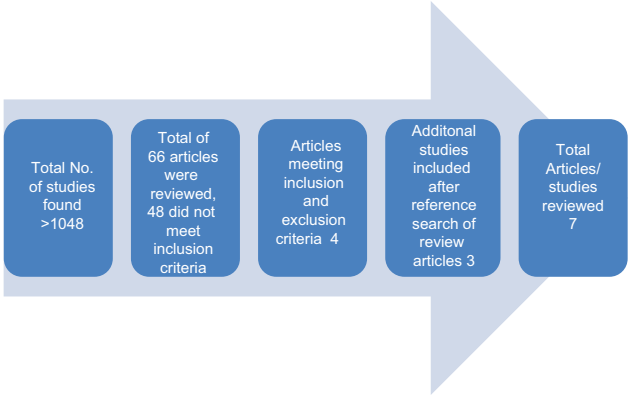

Figure 1: Reviewed studies

Table 4: Characteristics of included studies

Reference	Study design	Patients (*n*)	Patient characteristics	Antibiotic and dose (additional agents)	Duration of skin treatment	End point	Assessment tools	Skin toxicity results	Skin-related QoL
NCCTG N03CB[18]	Placebo-controlled, double-blind trial	61	Patients with lung/ gastrointestinal/other diseases treated with gefitinib, cetuximab, erlotinib/other investigational agents	Tetracycline (500 mg/bid)	4 weeks	Incidence of Grade >2 skin rash, QoL	NCI-CTCAE version 3.0, Skindex-16	76% versus 70% (P=0.61) developed a rash, Grade 2, 55% versus 17%, (P=0.009) at week 4	Less skin irritation, burning, or stinging (Skindex-16) in tetracycline arm (83% versus 50%, P=0.005)
Deplanque *et al*.,[19]	Open-label, randomized	147	NSCLC patients on erlotinib	Doxycycline (100 mg/day)	4 months	Incidence and severity of folliculitis	NCI-CTCAE version 3.0	Incidence: 68% versus 82%, Severity: Grade ≥2 reduced from 82% to 39%, (P<0.001), also significant decrease in other cutaneous AEs	NA
Supplementary NCCTG N03CB									
Jatoi *et al*.[20]	Randomized, double-blinded, placebo-controlled trial	65	Patients with lung/ gastrointestinal/other diseases treated with gefitinib, cetuximab, erlotinib/other investigational agents	Tetracycline (500 mg/bid)	4 weeks	Incidence and severity of skin rash, QoL	NCI-CTCAE version 3.0, Skindex-16 and LASA scales	82% versus 75% (P=0.056), Grade 2, 52% versus 44% (P=0.62)	No difference in intervention and placebo arm (Skindex-16)
Nikolaou *et al*.[21]	Retrospective study	20	Patients with NSCLC, pancreatic cancer, HNSCC, and CRC who received cetuximab, panitumumab, erlotinib	Azithromycin (500 mg/day) 3 days a week (19/20 patients used topical agent)	2 weeks	Efficacy and safety of azithromycin in the treatment of papulopustular eruption	NCI-CTCAE, version 3.0	55% of patients had complete and 35% had partial resolution of rash	NA
Shinohara *et al*.[22]	Retrospective study	96	Pancreatic cancer patients treated with erlotinib plus gemcitabine	Minocycline (200 mg/day) (heparinoids and steroid creams)	6 weeks	Incidence of acneiform rash and xerosis (prophylaxis vs. deferred treatment)	NCI-CTCAE, version 4.0	Rash incidence: 47.7% versus 80.8%; (P =0.001), Grade ≥2, 20.5% versus 28.8%, (P=0.34), Incidence of xerosis, 2.3% versus 19.2%; (P=0.01)	NA
Arrieta *et al*.[23]	Open-label, randomized control trial	90	Patients with NSCLC treated with afatinib	Tetracycline (250 mg/bid) (dermatologic-al measures)	4 weeks	Incidence of skin toxicities such as rash and paronychia	NCI-CTCAE, version 4.0	Incidence: 75.5% versus 44.5% (P=0.046), Grade ≥2, 35.6% versus 15.5% (P=0.03)	NA
Melosky and Hirsh[24]	Open-label, randomized, 3-arm trial	150	Patients with NSCLC treated with erlotininb	Minocycline (100 mg/twice a day)	Continuous	Incidence of skin rash and self-limiting effect of erlotinib-induced rash	NCI-CTCAE, version 3.0 and grading system developed by Perez-Soler *et al*.	Overall incidence 82% versus 84% (P=0.8769)	No difference in intervention and control arm (P=0.3904)

CRC: Colorectal cancer, HNSCC: Head and neck squamous cell cancer, LASA: Linear analog self-assessment, NCCTG: North Central Cancer Treatment Group, NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events, NSCLC: Nonsmall cell lung cancer, QoL: Quality of life, AEs: Adverse events, NA: Not available

assigned to receive tetracycline (250 mg/bid for 4 weeks) or dermatological recommendations. The control group had a rash incidence of 75.5% vs. 55.5% in the intervention group ($P = 0.005$) and Grade 2 or above severe rash was 35.6% vs. 15.6%, respectively. There was a decrease in the incidence of paronychia in the experimental group (28.9% vs. 44.4%). Although preemptive tetracycline reduced the incidence and rash severity, no difference was found between the two arms with regard to afatinib dose reduction. Overall, the study showed that oral tetracycline is a cost-effective measure that decreases afatinib-induced skin toxicity [Table 5].

Minocycline

In a prospective, Pan-Canadian, three-arm phase III trial, 150 patients (50 on each arm) with NSCLC receiving erlotininb were randomized to prophylactic minocycline (100 mg BID for 4 weeks, starting on the same day of erlotinib), or minocycline once Grade 2b skin rash appears or no treatment at all (Melosky *et al.*, 2015).[7] Participants were seen every 4 weeks for the first 3 months for the assessment of skin rash and later every 2 monthly until the end of the study. Patients were requested to maintain a diary to record the rash. There was no statistical difference in the incidence of rash between the three arms ($P = 0.8769$); however, there was a marked difference in the incidence of Grade 3 rash between prophylactic minocycline and control arm (12% vs. 28%, $P = 0.0455$) as well as between reactive arm and control arm (8% vs. 28%, $P = 0.0092$). Patients in prophylactic minocycline arm received treatment for longer duration with a median of 3.6 months, whereas in arms 2 and 3, it was 1.8 months. No significant differences for QoL were seen between the three treatment arms. Although QoL was lower initially in prophylactic arm, it improved throughout the study.[7]

In a retrospective study from Japan by Shinohara *et al.*,[22] 96 patients with pancreatic cancer receiving erlotinib and gemcitabine were assessed for incidence or severity of erlotininb-associated skin rash. Patients were treated with minocycline (200 mg a day) starting on the same day (prophylactic group) or once patients develop Grade 2 or 3 skin rash (deferred group). In both groups, emollients were applied to the susceptible regions, and skin treatment with strong- and medium-class topical steroids was initiated after the emergence of any skin toxicities. The incidence of acneiform rash of any grade was significantly lower in the prophylactic than in the deferred treatment group (47.7% vs. 80.8%, respectively; $P = 0.001$). The incidence of xerosis of any grade was also significantly lower in the prophylactic group than in the deferred treatment group (2.3% vs. 19.2%, respectively; $P = 0.01$). However, no significant difference was observed in the incidence of paronychia of any grade between the two treatment groups. There was no significant difference in response rate, disease control rate, or progression-free survival between the prophylactic and the deferred minocycline groups. Thus, prophylactic minocycline treatment did not appear to have a significant impact on the antitumor effects of erlotinib plus gemcitabine [Table 5].

Doxycycline

In a large randomized trial by Deplanque *et al.*,[19] the role of prophylactic doxycycline versus placebo was evaluated in 147 NSCLC patients being treated with erlotinib. Patients were randomly assigned to erlotinib with or without doxycycline (100 mg/day) and were monitored for folliculitis, skin-specific QoL index, and other AEs using the CTCAE version 3.0. Serial photographs were taken for blind review. The primary objective of the study was to assess the efficacy of doxycycline in reducing the incidence of erlotinib-induced folliculitis during the first 4 months of treatment. The secondary objective was to assess the impact of doxycycline on rash severity.

Intention-to-treat analysis showed no significant difference of folliculitis incidence between two arms (71% vs. 82%, $P = 0.117$), but when patients who did not take their doxycycline were excluded, a marked reduction in folliculitis was witnessed (68% vs. 82%, $P = 0.055$). Doxycycline showed significant reduction in the severity of erlotinib-induced folliculitis ($P \leq 0.001$) and the severity of other treatment-induced cutaneous AEs [Table 5].[19]

Azithromycin

In a retrospective study reported by Nikolaou *et al.*,[21] the authors assessed the efficacy and safety of azithromycin in patients who developed PPE. Twenty cancer patients (ten lung cancer, five colorectal, three pancreatic, and

Table 5: Agents used for epidermal growth factor receptor-tyrosine kinase inhibitor-associated skin toxicity

Agent	Indication	Efficacy
Tetracycline	EGFR-TKI- and EGFR-mAb-associated skin rash	Reduces the severity of rash
Minocycline	EGFR-TKI-associated skin rash	Reduces the severity of rash
Doxycycline	EGFR-TKI-associated skin rash	Reduces the incidence and severity of skin toxicity
Azithromycin	EGFR-TKI-associated skin rash	Reduces the incidence and severity of skin toxicity

EGFR: Epidermal growth factor receptor, TKI: Tyrosine kinase inhibitors, mAb: Monoclonal antibody

two head and neck) who were treated with different EGFR-directed therapies (ten erlotinib, five cetuximab, and five panitumumab) received azithromycin 500 mg a day for 3 days for 2 consecutive weeks once they developed Grade 2 PPE. Additional topical agents such as pimecrolimus cream, metronidazole gel 0.75%, corticosteroids, and clindamycin gel were used by 19 patients. The CTCAE, version 3.0, was used to grade the rash. A total of 11 patients (55%) showed complete resolution of the rash within the first 2–3 weeks of treatment, while seven patients (35%) showed partial response and one patient developed new PPE lesions on treatment and therefore was offered oral tetracycline. No clinical concerns were raised as patients treated with azithromycin showed the expected responses to their tumors, according to their stage and previous treatments. Azithromycin was not found to be photosensitizing [Table 5].

Discussion

All reviewed trials/retrospective studies have looked into an important issue of EGFR-TKI-associated skin toxicity which not only results in treatment interruption but also affects QoL.

All the agents show efficacy mainly in reducing the severity of skin toxicity associated with different TKIs. Tetracycline was used at two different doses (500 or 250 mg twice a day) in three different studies with variable results in each trial. Combined analysis of both NCCTG studies[18,20] concluded with no added advantage of prophylactic use of tetracycline. These conflicting results are possibly secondary to small population size, patients with different diagnoses, use of different agents (most had cetuximab as compared to TKIs), or these were chance findings; remain a speculation. Nearly half of patients in both studies also did not complete full treatment duration secondary to various reasons which might explain negative outcome. On the other hand, possible explanation for the positive results with low-dose tetracycline study[23] could be the use of afatinib, as it is associated with more skin toxicity than other EGFR-TKI, larger sample size with no dropouts, and use of low-dose tetracycline in single patient population.

Furthermore, minocycline was proved to reduce the severity of erlotinib-related skin rash in Pan-Canadian trial[7] as well as in a retrospective study[22] without affecting the QoL. Weekly pulses of azithromycin in other small cohort with different diseases and treatments showed remarkable efficacy.[21] Doxycycline also showed promising results in terms of reduced intensity and severity of erlotinib-associated skin toxicity in a prospectively conducted phase III trial in patients with NSCLC being treated with erlotinib.[19] Though this trial is still not published completely, results should be taken with caution, but does show beneficial effect.

Main unanswered questions remain the duration of treatment as well as the choice of agent. Different studies have used varying duration of treatment as well as antibiotics; ranging from 4 to 8 weeks in both NCCTG studies,[18,20] 6 weeks or longer of minocycline in patients receiving erlotininb,[7,22] 4 weeks of low-dose tetracycline in patients taking afatinib,[23] longer duration of doxycycline for patients taking erlotininb,[19] and new concept of pulse azithromycin for 2 weeks in divergent patient population. Hence, the available data cannot confirm the "best" antibiotic to be used, the optimum dose, or treatment period. Nevertheless, data do indicate that the use of prophylactic antibiotics does help in reducing the rash severity if not the incidence.

There is a different side effect profile with each antibiotic. Overall, tetracyclines cause low levels of gastrointestinal toxicity, but they vary with the type of molecule used.[14] In patients with renal dysfunction, doxycycline shows more favorable safety profile, whereas minocycline, being a less photosensitizing agent, is preferably used in geographical areas with high UV index.[5]

Since the half-life of EGFR-TKIs is long, management of adverse skin reactions should continue until those reactions have sufficiently diminished or resolved, even if treatment is discontinued or reduced.[10] Continuous dose of tetracycline (250 mg twice daily for 4 weeks) could be recommended for preventive therapy. Due to the anti-inflammatory effect of tetracycline, it might be useful when administered for a prolonged course.[25] Studies by Melosky *et al*.[7] and Deplanque *et al*.[19] showed beneficial effects of minocycline and doxycycline, respectively, in reducing erlotinib-associated rash severity.

Conclusion

EGFR-TKI-associated skin toxicity remains a major concern not only for patients but also for treating health-care providers. There are phase III data based on EGFR-TKI-associated skin AEs but with conflicting outcomes. Despite limitations, the data do indicate some benefits with antibiotic use, at least in patients who are taking erlotinib or afatinib with all the three types of antibiotics. The use of pulse dose of azithromycin is intriguing which needs further supporting data. Future studies targeting homogeneous population with large sample size and using same intervention may be able to show a meaningful or significant outcome in favor of or against antibiotic use for EGFR-TKI-associated skin toxicity.

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Conflicts of interest

There are no conflicts of interest.

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