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Epidermal Growth Factor Receptor Inhibitor Skin Rash Prophylaxis in a Community Oncology Setting

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Abstract

Epidermal growth factor receptor inhibitors (EGFRIs) can potentially cause a debilitating rash despite use of reactive-based treatment. Prophylactic rash management is a controversial rash-mitigating approach. The impact of a prophylactic rash treatment protocol for EGFRIs at a community hospital was evaluated. This was a retrospective, institutional review board–approved examination of patient data for those patients who received EGFRIs from August 1, 2012, through May 31, 2015. Patients were grouped according to treatment with EGFRIs prior to standardized prophylactic rash management protocol (August 1, 2012, through July 31, 2014) and treatment after protocol implementation (September 1, 2014, through May 31, 2015). The outcomes measured included incidence of rash within the 6-week treatment period and occurrence of EGFRI dose reductions and/or delays. Of the 44 patients eligible for the analysis, 29 were evaluated in the reactive treatment group and 15 in the rash prophylaxis group. The incidence of rash over the 6-week EGFRI treatment period was 76% and 47% for the reactive treatment and rash prophylaxis groups, respectively (p = .09). There was a lower incidence of EGFRI dose delays and modifications in the rash prophylaxis group compared to the reactive treatment group: 26.7% and 6.7% compared to 41.4% and 20.7%, respectively. There was an overall decrease in rash incidence seen in patients who received prophylactic intervention; however, due to the failure to meet statistical significance and power, it is not possible to determine if rash prophylaxis decreases EGFRI rash incidence.

Epidermal growth factor receptor inhibitors (EGFRIs) are effective agents for the treatment of a variety of cancers (e.g., breast, lung, head and neck, and colorectal) due to the overexpression of EGFR in these malignancies. Although normally EGF is responsible for the maintenance of skin health, a receptor mutation is associated with tumor cell proliferation, invasion, angiogenesis, and treatment resistance (Patel, 2008). When EGFRIs target either the ex-

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tracellular domain of the EGFR (monoclonal antibodies) or the intracellular domain (tyrosine kinase inhibitors), cell signaling is suppressed and tumor cell apoptosis is preserved (Melosky et al., 2009; Patel, 2008). Epidermal growth factor receptor inhibitors are a potent alternative to traditional chemotherapy; however, notable dermatologic toxicities are common.

Papulopustular rashes develop in up to 90% of patients treated with EGFRIs, with an average onset of 1 to 3 weeks from their initial EGFRI dose (Patel, 2008). This rash affects areas of the skin with the highest densities of seborrheic glands, such as the face, neck, chest, and back. The appearance of this rash, although associated with treatment response, can be debilitating to the patient, limiting the patient's treatment and quality of life (Liu et al., 2013). Reactionary treatments have historically been the mainstay for managing EGFRI-induced rash, with the use of agents such as topical corticosteroids along with oral antibiotics in an effort to prevent dose delay or discontinuation (Melosky et al., 2009).

PROPHYLACTIC RASH THERAPY

Based on recent studies, prophylactic management of EGFRI-associated rash has become an option for decreasing rash severity. By improving patient tolerability of this common adverse effect, this may aid in preventing treatment modification and discontinuation. One major study that looked at this strategy was the Skin Toxicity Evaluation Protocol With Panitumumab (STEPP) trial. This trial compared reactive-based treatment with prophylactic use of oral doxycycline, topical corticosteroids, and skin moisturizers in patients undergoing treatment with panitumumab (Vectibix)-containing regimens over a 6-week treatment period. This trial showed a statistically significant decrease by 33% in the incidence of grade 2 or greater skin toxicities during the treatment period (Lacouture et al., 2010).

Another notable trial was conducted by Scope and colleagues, which looked at the prophylactic use of minocycline in patients receiving cetuximab (Erbitux) for the treatment of metastatic colorectal cancer. This study demonstrated a significantly lower number of facial lesions at weeks 1 to 4 for those initiated on prophylactic minocycline in comparison to the placebo group (Scope et al., 2007). Neither of these studies showed a decrease in progression-free survival with the use of the stated prophylactic regimens (Lacouture et al, 2010; Scope et al., 2007). As demonstrated by these trials, prophylactic use of oral synthetic tetracyclines (doxycycline and minocycline) and topical steroids decreased rash incidence and severity in EGFRI-treated patients without decreasing their response to the EGFRI agents (Lacouture et al., 2010; Melosky et al., 2009; Scope et al., 2007).

The objective of this analysis was to investigate if prophylactic management of EGFRI-induced skin rash was a more effective approach in decreasing the incidence and severity of skin toxicities when compared to current reactionary-based practices during a 6-week skin treatment (Gerber et al., 2012; Lacouture et al., 2010; Melosky et al., 2009).

METHODS

Study Population

Patients were included in the retrospective analysis if they were aged 18 or older and received intravenous EGFRIs during the specified study period. Patients were excluded from the analysis if their data were inaccessible or incomplete for review, or if they failed to receive at least one full treatment dose of an eligible EGFRI.

Study Design

Approval was obtained from the hospital's institutional review board prior to the initiation of the research project. Data were gathered via retrospective review of the electronic medical record (EMR) during the time period from August 2012 to May 2015. A report was created utilizing the existing functionality of the EMR and the key words "cetuximab" and "panitumumab" to identify which patients had received either of the two EGFRIs during the specified time frame. Only intravenous EGFRIs were included due to limitations in data mining for oral EGFRIs. Patients were then assessed for inclusion eligibility in the retrospective analysis through the predefined inclusion and exclusion criteria. Relevant information was identified through an assessment of the patient's electronic chart, including medication administration record, oncology treatment plan, and notes

present in the EMR. Data gathered included demographic data (age, sex, race), cancer type, Eastern Cooperative Oncology Group (ECOG) performance status, information pertaining to cancer treatment, rash development and location, rash prophylactic and treatment medications, and other adverse effects that developed. Dose modification was defined as any alteration or reduction in the dose of the EGFRI agent due to the development and/or severity of adverse effects attributed to the patient's treatment. Dose delay was defined as any postponement of a planned treatment cycle due to the development and/or severity of adverse effects attributed to the patient's treatment.

The included patients were divided based on two different date ranges during which they received EGFRI therapy: In time frame 1 (August 1, 2012, through July 31, 2014), patients were treated prior to a standardized prophylactic rash protocol, and in time frame 2 (September 1, 2014, through May 31, 2015), patients were treated after prophylactic protocol standardization. Patients were subsequently sorted into either the reactive treatment group or rash prophylaxis group, based on the utilization of prophylactic doxycycline or minocycline prior to the initiation of EGFRI therapy.

The prophylactic rash treatment protocol was updated based on data from the STEPP trial completed by Lacouture and colleagues and a second trial conducted by Scope and colleagues where patients received a prophylactic skin treatment regimen including either doxycycline or minocycline, respectively (Lacouture et al., 2010; Scope et al., 2007). A standardized prophylactic regimen was employed for a minimum of 6 weeks following initiation of EGFRI therapy. The prophylactic regimen included the use of either twice daily doxycycline at 100 mg or once daily minocycline at 100 mg in conjunction with hydrocortisone 1% cream and skin moisturizer applied twice daily (to chest, arms, hands, neck, face, back, and feet). Applying a sunscreen of SPF 15 or greater to exposed skin areas before going outdoors was also encouraged. Physicians and nurses were educated on the updates to the rash protocol and the literature behind the change. Prior to the initiation of intravenous EGFRI therapy (cetuximab or panitumumab), patients were verbally counseled by one of the investigators, outlining the prophylactic rash treatment strategy and ensuring prescriptions for prophylactic medications were provided. An educational document discussing the EGFRI therapy, rash prophylaxis instructions, and common questions were provided to all participating patients after the initiation of the standardized prophylactic rash protocol. The receipt of this document was recorded in each patient's chart as part of their treatment education.

Statistical Analysis

The primary objective of the retrospective analysis was to investigate whether utilization of a standardized prophylactic EGFRI rash protocol decreased the incidence of EGFRI-induced skin rash over the course of a 6-week treatment period. Secondary objectives were to investigate if the standardized rash prophylaxis protocol prevented EGFRI dose reduction or delay and slowed the onset of rash.

A power analysis was conducted with the power set to 80%, and a sample size of 63 patients was determined to achieve the power to detect a 30% difference between groups. Fisher's exact test was utilized for comparison of all nonparametric data (including primary and secondary endpoints) and student t-test for parametric data. A p value of $< .05$ was considered statistically significant.

RESULTS

During the specified time frame, 45 patients were evaluated in this analysis. One patient was excluded from the analysis due to incomplete infusion of initial intravenous EGFRI dose after a complaint of chest pain and difficulty breathing midway through the first EGFRI cycle. Among the remaining 44 patients eligible for the analysis, 29 patients were included in the reactive treatment group and 15 patients in the rash prophylaxis group. It should be noted that two patients received prophylactic rash treatment in time frame 1 and two patients failed to receive prophylactic management in time frame 2, requiring reclassification or redistribution.

To characterize the two studied groups, baseline patient demographics and cancer treatments for each group are displayed in Table 1. The primary outcome, incidence of rash in each group over the 6-week treatment period, can be found in

Table 1. Patient Demographic Data

	Reactive treatment (n = 29)	Rash prophylaxis (n = 15)	*p* value
Age (years ± SEM)	63.1 ± 2.12	64.1 ± 3.58	.79
Male (%)	15 (52)	9 (60)	.75
Race (%)			
Caucasian	27 (93)	15 (100)	.54
African American	2 (7)	0 (0)	
Cancer diagnosis (%)			
Head/neck	25 (86)	10 (67)	.24
Colorectal	4 (14)	5 (33)	
ECOG score (%)			
0	7 (24)	1 (7)	.05
1	10 (35)	11 (73)	
2	3 (10)	2 (13)	
Not reported	9 (31)	1 (7)	
EGFRI received			
Cetuximab	13 (44.8)	9 (60)	.77
Panitumumab	14 (48.3)	5 (33.3)	
Both	2 (6.9)	1 (6.7)	
Adjunctive therapy used[a]	17 (58.6)	8 (53.3)	.76

Note. SEM = standard error of the mean; ECOG = Eastern Cooperative Oncology Group; EGRFRI = epidermal growth factor receptor inhibitor.
[a]Adjunctive therapy incudes radiotherapy and/or chemotherapy used in conjunction with the EGFRI agent.

Figure 1. Table 2 shows incidences of dose modification and dose delay of EGFRI treatment. Table 3 details the onset of rash development during the EGFRI treatment course.

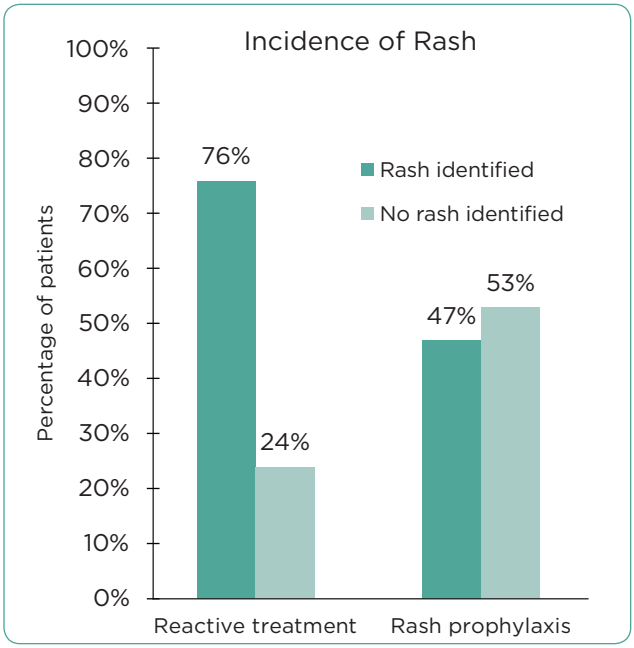

Figure 1. Incidence of rash between the studied groups over the course of 6 weeks (reactive treatment: n = 29; rash prophylaxis: n = 15; *p* = .09).

Of the patients in the reactive treatment group with EGFRI-induced skin rash, 82% of patients reported an appearance of rash on their face, 73% on their chest, 59% on their back, 46% in a nonlisted location, and 36% on their scalp. For those in the rash prophylaxis group with EGFRI-induced skin rash, 71% reported an appearance of rash on their face, 57% in a nonlisted location, 43% on their chest, 43% on their back, and 29% on their scalp (percentages are greater than 100% due to appearance of rash on multiple body sites for both groups).

The *p* values comparing rash location between the two groups were not statistically significant. All patients in the rash prophylaxis group were initiated on twice daily doxycycline prior to the initiation of EGFRI therapy. Topical steroid selection was based on physician preference and varied in patients: 53% prescribed hydrocortisone 1% cream, 27% prescribed alclometasone dipropionate 0.05% cream, and 20% did not document any topical corticosteroid. Although papulopustular rash is the most predominant adverse effect with EGFRI use, other notable adverse effects were investigated and reported in Table 4.

Table 2. Therapy Modifications to Allow for Continued Treatment With Epidermal Growth Factor Receptor Inhibitors

	Reactive treatment n = 29, n (%)	Rash prophylaxis n = 15, n (%)	*p* value
Dose delay	12 (41.4)	4 (26.7)	.51
Dose modification	6 (20.7)	1 (6.7)	.39

DISCUSSION

This analysis suggested a trend toward a decrease in EGFRI rash in patients initiated on the prophylactic rash protocol on day 1 of EGFRI treatment. A reduction in rash by 29% in this analysis is reflective of the primary outcome from the STEPP trial that demonstrated a similar reduction; however, it is not statistically significant based on this study due to small sample size and that it was underpowered to detect a difference (Lacouture et al., 2010). An 11% reduction of patients with facial lesions was noted in this analysis; however, this was nonsignificant. Comparatively, a 22% reduction in facial lesions was reported by Scope and colleagues (2007).

All patients in the rash prophylaxis group were initiated on doxycycline in concordance with the outlined protocol. Compliance was verified through a review of documentation in the patient's chart, with specific regard for the first day of EGFRI treatment. The initiation of doxycycline as compared to minocycline, although not clearly stated by the participating physicians, could be due to the reduced cost and familiarity. The use of a topical steroid was encouraged, and hydrocortisone was predominantly prescribed in the rash prophylaxis group; however, no direct correlation to benefit was observed due to the overall lack of consistency in prescription and/or documentation of topical corticosteroids. Preference for hydrocortisone could similarly be due to the relatively low cost, ease of access, and familiarity with the product. Despite appropriate prescription of prophylactic medications and instruction on use, patient compliance was difficult to determine and was not directly assessed. During the STEPP trial, compliance was reinforced through the usage of instructional videos and daily diaries to encourage and assess pre-emptive treatment compliance (Lacouture et al., 2010). Due to the retrospective nature of this analysis, there was an inability to integrate compliance-measuring documentation such as those used in the STEPP trial. With the intensive nature of the prophylactic regimen, including multiple applications of topical steroids and sunscreen within a day, perfect compliance to the prophylactic regimen can be understandably difficult to maintain.

There was an overall decrease in the incidence of EGFRI dose delays and/or modifications in the group receiving prophylactic rash treatment that led to the ability to maintain dose intensity in this group. The reduction in dose delays in this analysis modestly exceeds that which was reported in the STEPP trial (15% vs. 9%; Lacouture et al., 2010). There was a decreased incidence of rash reported between cycles 1 to 6 of EGFRI treatment in the rash prophylaxis group as compared to the control

Table 3. Epidermal Growth Factor Receptor Inhibitor Cycle Noted With the Development of Skin Rash

Cycle rash developed	Reactive treatment n = 29, n (%)	Rash prophylaxis n = 15, n (%)	*p* value
1	19 (65.5)	6 (40)	.12
2	1 (3.4)	0 (0)	1
3	1 (3.4)	0 (0)	1
4	1 (3.4)	0 (0)	1
5	0 (0)	1 (6.7)	1
6	0 (0)	0 (0)	1
No rash within 6 weeks	7 (24)	8 (53.3)	.09

Table 4. Comparison of Reported Adverse Effects Between Studied Groups Over the Course of 6 Weeks

Adverse effect (any grade)	Reactive treatment n = 29, n (%)[a]	Rash prophylaxis n = 15, n (%)[a]	p value
Diarrhea	13 (44.8)	3 (20)	.19
Hair loss or thinning	1 (3.4)	0 (0)	1
Paronychia/fissures	5 (17.2)	0 (0)	.15
Pruritus	7 (24.1)	2 (13.3)	.7
Mucositis	8 (27.6)	5 (33.3)	.74
Edema	6 (20.7)	1 (6.7)	.39

Note. [a]Percentages not equal to 100% due to the lack of or presence of multiple adverse effects.

group, possibly allowing for more cycles of EGFRI therapy before the development of rash impacted treatment duration.

The adverse effects reported between the two groups differed. Reduction in notable EGFRI adverse effects such as pruritus, paronychia, diarrhea, and edema may be due to the use of a prophylactic rash regimen, with similar reductions reported in both the STEPP trial and the trial conducted by Scope and colleagues. Some of the other notable adverse effects could be due to varying sample sizes and concomitant chemotherapy/radiotherapy with known dose-limiting adverse effects, such as diarrhea (irinotecan) and mucositis (fluorouracil, radiation).

There are several limitations to this analysis, including the small patient population and the failure to enroll enough patients to achieve power. A statistically significant difference was not recognized in the incidence of rash between the two studied groups or any of the other analyzed data. Since the analysis was underpowered, a statistically significant difference could be present but unable to be detected. Another limitation is the retrospective nature of this analysis and the use of only one reviewer, despite the lack of subjective data. In addition, due to the retrospective nature of the analysis, the investigator is limited by the data documented in the EMR. Another limitation is the failure of the physician to consistently implement the full EGFRI rash protocol. This led to reclassification of patients into the reactive treatment group. Adherence to the rash protocol was encouraged, but was ultimately left up to the physician's judgment to fully implement the protocol, as well as the patient's effort to comply with the prescribed instructions. This can create variability in the data and could affect the development of rash in patients treated under the rash protocol. Patient compliance was encouraged through verbal and written education; however, it was not directly assessed during the analysis.

Despite the limitations of this analysis, there was a reduction in the incidence of rash appearance, EGFRI dose modification, and EGFRI cycle delays. Regardless of the cost incurred by the patient for use of the prophylactic rash medications, there could be an overall cost benefit if excess clinic appointments are avoided; however, studies are needed in this area for corroboration. With the data from this analysis and recommendations from current guidelines, such as those from the Multinational Association of Supportive Care in Cancer (MASCC) Skin Toxicity study group shown in Table 5, the prophylactic regimen will continue to be implemented in patients newly started on EGFRI therapy (Lacouture et al., 2011). Due to a lack of clear consistency and correlation with topical steroids and rash reduction in the rash prophylaxis group in this analysis and the general lack of data regarding topical agents in literature, the use of a topical steroid will be dependent on physician preference (Lacouture et al., 2011).

CONCLUSION

In conclusion, due to the failure to achieve statistical significance, this study is indeterminate as to whether a prophylactic rash treatment strategy is effective in reducing the incidence of EGFRI-associated rash in a 6-week treatment period. However, a general reduction in rash appearance and EGFRI dose modification and delay was asso-

Table 5. Summary of Pharmacologic Rash Prevention Recommendations From MASCC Guidelines

Mode of delivery	Recommended	Not recommended
Topical	• Hydrocortisone 1% cream with moisturizer and sunscreen twice daily[a]	• Pimecrolimus 1% cream • Tazarotene 0.05% cream • Sunscreen as a single agent
Systemic	• Minocycline at 100 mg daily[a] • Doxycycline at 100 mg twice daily[a]	• Tetracycline at 500 mg twice daily

Note. MASCC = Multinational Association of Supportive Care in Cancer.
[a]Preventive regimens recommended for weeks 1–6 and 8 of epidermal growth factor receptor inhibitor initiation.

ciated with the rash prophylaxis group, supporting the already existing data that this treatment strategy could be an effective option to prolong the viability of EGFRI treatment. Further studies with a more robust patient population are needed in order to further validate this rash mitigation strategy as an effective option.

Disclosure

The authors have no conflicts of interest to disclose.

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