Epidermal Growth Factor Receptor (EGFR) Inhibitor-Induced Rash: A Consecutive Patient Series that Illustrates the Need for Rigorous Palliative Trials

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Abstract

Purpose: Rash is the most common side effect of epidermal growth factor receptor (EGFR) inhibitors and negatively impacts quality of life. This single-institution study sought to explore how rash is currently managed outside a clinical trial setting and to further characterize general clinical aspects of this rash.

Methods/Results: Among 4101 consecutive patients with cancer of the lung, colorectum, pancreas, and head and neck, 138 had received an EGFR inhibitor. Within this group, 96 (69%) developed a rash. Forty-nine of these patients were prescribed rash therapy, and a total of 26 different palliative regimens were used. Surprisingly, most patients, with the exception of 2, appear to have manifested evidence of rash improvement—even when unproven or disproved therapies had been prescribed. Fourteen patients stopped their EGFR inhibitor because of rash, and 11 were then able to restart. No demographic variables were able to predict rash development.

Conclusion: The observation that multiple, largely unproven, anecdotal therapies are being prescribed to palliate EGFR inhibitor-induced rashes underscores the need for more rigorous, prospective palliative trials.

Introduction

RASH IS THE MOST COMMON SIDE EFFECT of epidermal growth factor receptor (EGFR) inhibitors, occurring in 50%–90% of patients and primarily arising on the face and trunk. Interestingly, therapeutic clinical trials suggest that those patients who develop such a rash are likely to manifest better cancer outcomes.^{1,2} Despite this favorable prognostic effect, these rashes are distressing to patients, triggering cutaneous discomfort and negatively impacting quality of life.^{3,4}

A lack of evidence-based guidelines only adds to the clinical quandary of how best to manage patients who develop these rashes. Recently, Melosky and others⁵ published rash management recommendations, which describe how, “A proactive, multidisciplinary approach to management can help to improve skin rash and optimize clinical outcomes by preventing EGFR dose reduction or discontinuation.” In fact, however, only a handful of studies have methodically studied palliative interventions^{6–9}; most have not yielded conclusively effective strategies; and many have not relied on a rigorous placebo-controlled study design.

This lack of evidence-based guidance raises questions about general rash characteristics, particularly outside a clin-

ical trial setting; how these rashes are currently being managed; and how they should be best dealt with in the future.

Methods

Overview

This study was approved by the Mayo Clinic Institutional Review Board. The Mayo Clinic Tumor Registry provided information to enable the study team to retrieve the medical records of all Mayo Clinic Rochester, Minnesota, patients who had received treatment with an EGFR inhibitor in the recent past but prior to 2009.

One member of the study team (B.M.S.) examined the medical records of several thousand patients based on cancer type and based on the date the Food and Drug Administration (FDA) had approved a specific EGFR inhibitor for patients with a specific malignancy. For example, all non-small-cell lung cancer patients had their medical records reviewed from 2004 (the year of FDA approval of erlotinib) to determine if they had received an EGFR inhibitor. The same approach was used for patients with cancer of the colorectum, pancreas, and head and neck. The final result was a comprehensive, single-institution catalogue of all consecutive patients who had

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recently received a commercially available EGFR inhibitor. This catalogue served to meet the study goals described herein.

Ascertainment of data

The medical records of all these patients were then examined for age at the time of initiation of the EGFR inhibitor, gender, cancer type, date of cancer diagnosis, ethnicity, type of EGFR inhibitor prescribed, concurrent chemotherapy or radiation, and date of death or last follow-up by one investigator (B.M.S.). If dates were unable to be obtained with precision from the medical record, a mid-month date was used as an estimate. Furthermore, information was gleaned as to whether or not a rash occurred during EGFR inhibitor therapy; whether rash treatment or prophylaxis had been used and, if so, what; whether the EGFR inhibitor therapy was interrupted because of rash; and whether patients were rechallenged with an EGFR inhibitor after holding therapy, and, if so, rash-related outcomes.

The retrospective nature of this study posed some limitations. First, because extent or severity of the rash and exact time of rash onset would likely not be able to be obtained with accuracy from the medical record, no attempts were made to acquire these data. Second, because previous, prospectively conducted studies have demonstrated that rash does indeed confer a favorable prognosis and because the current study includes patients with multiple cancer types with different cancer stages, no attempt was made to reestablish the prognostic effect of rash. Third, although these rashes negatively impact quality of life, the current study was not able to assess this end point with accuracy in the absence of prospective or patient-reported data. Despite such limitations, this retrospective approach was valuable in that it provided an unbiased view of what patients had utilized for rash palliation.

Statistical analyses

Data are primarily presented descriptively, but, for statistical analyses, JMP, version 8.0 was used (SAS Institute Incorporated, Cary, NC). Univariate and multivariate logistic regression models were used to examine associations between rash development and the specific demographics of patient age, gender, and type of EGFR inhibitor. The type and number of regression variables were formulated *a priori* based on prior reports of rash risk, the distribution of each candidate variable within the patient group, and constraints related to the size of the patient group.^{10,11} A deliberate decision was made to include a contained number of variables and to forego the examination of certain other variables such as concomitant chemotherapy in order not to exceed this limit and report potentially spurious findings. Odds ratios and *p*-values were derived. A *p* value of <0.05 was deemed statistically significant.

Results

Patient characteristics

Among 4101 patients with the cancer types described earlier, 138 had received an EGFR inhibitor, and 96 (69%) had developed a rash. Baseline demographics are shown in Table 1. Median survival for patients with rash had not been reached at the time of data analyses; and, for those without a rash, it was 7.6 months.

TABLE 1. BASELINE DEMOGRAPHICS^{a,b}

	No rash (n = 42)	Rash (n = 96)
Age, mean in years (standard deviation)	59 (13)	57 (13)
Gender		
Male	21 (50)	62 (65)
Female	21 (50)	34 (35)
Cancer type		
Non-small-cell lung	9 (21)	14 (15)
Colorectal	16 (38)	47 (49)
Pancreas	7 (17)	9 (9)
Head and neck	10 (24)	26 (27)
Concomitant therapy		
Radiation	6 (14)	25 (26)
Chemotherapy	27 (64)	79 (82)
Ethnicity		
Black	0	1 (1)
White	38 (90)	88 (92)
Other	4 (10)	7 (7)
Epidermal growth factor receptor inhibitor		
Erlotinib	16 (38)	24 (25)
Cetuximab	24 (57)	70 (73)
Panitumumab	1 (2)	2 (2)

^aNumbers in parentheses denote percentages unless otherwise specified.

^bPercentages may not sum to 100 because of category type or missing data.

Rash characteristics and outcomes

Rash occurred on the face only in 22 patients (24%), body only in 3 (3%), and face and body in 67 (73%). Two patients were prescribed prophylactic antibiotics but nonetheless developed a rash. Fourteen patients stopped their EGFR inhibitor because of rash, and 11 were then able to restart.

Fifty patients were prescribed rash treatment (Table 2). It is unclear from the medical record why rash treatment was administered to some patients and not others, but presumably patients who received it had been more bothered by their rash. In every instance except two, when a patient did receive rash therapy, the medical record described partial or complete resolution of rash after the initiation of such therapy. In one patient, who received a combination of oral trimethoprim-sulfamethoxazole/oral fexofenadine/oral hydroxyzine/topical hydrocortisone/topical triamcinolone/topical fluocinolone/topical benzoyl peroxide, there was complete rash resolution in the absence of holding the EGFR inhibitor.

In addition, 18 patients were rechallenged with an EGFR inhibitor after rash development. Nine of these patients restarted with a more than 5% dose reduction. Although other intervening morbidity made it difficult to consistently assess subsequent rash outcomes, in 8 patients, the rash was apparently less severe upon drug reexposure.

Risk factors for rash

In examining candidate rash risk factors, we found that age, gender, and type of EGFR inhibitor prescribed (erlotinib versus cetuximab/panitumumab) yielded no statistically significant associations with rash development in either univariate or multivariate analyses (data not shown). As alluded to earlier, ethnicity was not included in the logistic model

TABLE 2. RASH INTERVENTIONS

<i>Palliative agent</i>	<i>Number of patients</i>
Oral minocycline	15
Oral doxycycline	7
Oral tetracycline	5
Oral azithromycin	1
Oral cephalexin	1
Oral dexamethasone	1
Oral doxycycline/oral cephalexin	1
Oral doxycycline/topical clindamycin	1
Oral doxycycline/topical clindamycin/topical metronidazole	1
Oral minocycline/oral tetracycline	1
Oral minocycline/topical clindamycin	1
Oral minocycline/topical clindamycin/topical tea tree oil	1
Oral minocycline/topical hydrocortisone	1
Oral minocycline/topical hydrocortisone/topical fluocinolone	1
Oral minocycline/topical oatmeal preparation	1
Oral minocycline/topical pimecrolimus	1
Oral minocycline/topical triamcinolone	1
Oral tetracycline/topical metronidazole/topical triamcinolone	1
Oral trimethoprim-sulfamethoxazole/oral fexofenadine/oral hydroxyzine/topical hydrocortisone/ topical triamcinolone/topical fluocinolone/topical benzoyl peroxide	1
Topical clindamycin	1
Topical coconut oil	1
Topical cosmetic agents/topical metronidazole/topical hydrocortisone/topical fluocinolone	1
Topical metronidazole/topical hydrocortisone/topical triamcinolone/topical mometasone	1
Topical sodium sulfacetamide	1
Topical triamcinolone	1
Topical triamcinolone/topical clindamycin/topical benzoyl peroxide/topical oatmeal preparation	1

because the patient group was disproportionately white, and concomitant therapy was not included because of sample size limitations.

Discussion

Rash is the most common side effect of EGFR inhibitors; and, arguably, it has become the most problematic. The current study observed that 69% of patients developed a rash. Although similar rates had been reported earlier, one important aspect of the current study is that it was conducted in a nonclinical trial setting, thereby making it a unique, broad-based clinical report and thereby underscoring the pervasively problematic nature of this adverse event.

Perhaps the most salient observation of this study is that over half of patients received some sort of palliative rash intervention, and, remarkably, in every single instance except two, the medical record described a subsequent improvement in rash. Interestingly, many of the agents prescribed, such as pimecrolimus and tetracycline, have demonstrated dubious efficacy in rash palliation in prospective clinical trials.^{6,7} Why did these wide-ranging, often anecdotal interventions appear to yield positive palliative outcomes? Previous reports suggest that these rashes can wax and wane in their severity, and previous studies also show that attempts to palliate symptoms typically yield a substantial placebo effect in as many as 40% of patients.¹² Thus, the positive outcomes described in these patients' medical records may have been the result of the natural history of these rashes or the strong desire on the part of patients, their families, and their health care providers to acquire some antidote that would provide rash relief. There is

a strong need to undertake rigorous clinical trials for rash palliation, particularly among patients who find the rash most troubling.

In contrast to previous studies,¹⁰ this report did not observe that gender, age, or type of EGFR inhibitor predicted rash development. It remains unclear why our findings are negative-neutral in this regard, but the fact that our outcome variable was rash of any grade—and not just severe rash, as assessed in previous studies—may have resulted in these nonconfirmatory findings. It should be noted that previous studies suggest rash severity is not directly associated with a negative impact on quality of life, and, in fact, patients with a mild rash can be enormously bothered by it.⁴ Thus, although we are unable to confirm any of the previously described associations between baseline demographics and rash development, our utilization of rash of any severity as the outcome variable may explain this lack of associations.

In conclusion, the current study confirms a high rash rate among patients treated with EGFR inhibitors within a general oncology clinic. It also underscores the real possibility that a series of anecdotal experiences, as captured here, might lead one to conclude that there had been palliative efficacy in instances where, in fact, objectively speaking, there had been none. We conclude that there is a strong need to test agents rigorously prior to prescribing them to patients for rash palliation.

Author Disclosure Statement

No competing financial interests exist.

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