Do Patients Die from Rashes from Epidermal Growth Factor Receptor Inhibitors? A Systematic Review to Help Counsel Patients About Holding Therapy

AMINAH JATOI,a PHUONG L. NGUYENb

aDepartment of Oncology and bDepartment of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, Minnesota, USA

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ABSTRACT

Rash from epidermal growth factor receptor inhibitors is common and negatively impacts the quality of life of cancer patients. Published guidelines recommend holding cancer therapy if the rash is severe. Does this recommendation hinge solely on improving patients’ quality of life, or does it also hinge on the prevention of a potentially fatal, cutaneous adverse event? In other words, do patients die from rashes from epidermal growth factor receptor inhibitors? To our knowledge, the latter question has never been asked and answered in an evidence-based fashion. Therefore, we conducted a systematic review of the published, prospectively conducted clinical trial literature on epidermal growth factor receptor inhibitors. The primary aim was to determine whether rash-related death has ever been reported in such trials. Among 117 such trials, which included 8,998 cancer patients, the rate of rash development was >50%, as expected. However, there were no reported deaths from a rash. Although we cannot conclude that a rash-related death from this class of agents can never occur, this systematic review provides evidence-based guidance on how best to counsel cancer patients who develop a rash from an epidermal growth factor receptor inhibitor. It suggests that quality of life issues should remain at the forefront as cancer patients and health care providers make decisions about holding cancer therapy.

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INTRODUCTION

Epidermal growth factor receptor inhibitors have become one of the most frequently prescribed anticancer agents; therefore, increasing attention has focused on these agents’ most common side effect: a rash that occurs in 50%–90% of patients, arises primarily on the face, and appears similar but not identical to acne [1].

This rash negatively impacts the quality of life of cancer patients, and published guidelines for rash management as well as drug package inserts recommend holding therapy in the event of a severe rash [2–4]. However, such guidelines raise several questions. Is holding life-prolonging therapy really necessary, particularly when a growing literature has demonstrated that rash is an indicator of drug efficacy [5, 6]? If a cancer patient is not bothered by the rash, maintains a good quality of life despite its presence, and would like to continue cancer therapy, is it appropriate to counsel this patient that it is acceptable to do so, or do potentially life-threatening concerns preclude this option? In short, do patients die from rashes caused by epidermal growth factor receptor inhibitors?
This latter question is particularly germane, as previous case reports have shown that patients receiving epidermal growth factor receptor inhibitors can die from drug-related pulmonary and hepatic toxicity. Moreover, although to our knowledge previous case reports have described that the characteristic, acneiform rash results in death, Lin and others have reported a single case of fatal toxic epidermal necrolysis from cetuximab [7]. Others have described severe but nonlethal cutaneous reactions when this class of agents is prescribed with radiation [8, 9]. As health care providers counsel patients to stop these agents because of rash development, it becomes imperative to discern whether the rationale for this recommendation should hinge exclusively on improving patients’ quality of life or whether it should also hinge on the prevention of a potentially fatal, cutaneous adverse event.

The present study was undertaken to gather additional information that might enable health care providers to better counsel patients on the rationale for holding therapy when a severe rash occurs. A systematic review of the published clinical trial literature on epidermal growth factor receptor inhibitors was undertaken to determine whether rash-related death occurs with these agents, and, if so, how often.

METHODS

Overview

This study examined the prospective clinical trials that had tested a group of epidermal growth factor receptor inhibitors that had been approved by the U.S. Food and Drug Administration at the time of this report. Clinical trials that tested cetuximab, erlotinib, or panitumumab either as single agents, with other cancer agents, or with radiation were the focus of this study and were acquired and reviewed in a systematic fashion. The primary aim was to report the incidence of rash-related deaths from a comprehensive series of published prospective clinical trials.

All published trials that met this study’s eligibility criteria were systematically sought and reviewed. The decision to focus exclusively on the rate of rash-related death rests in the following facts: (a) a notable literature has already examined the negative quality of life aspects of rash in adults, and thus it appeared reasonable to focus on other detrimental rash-related effects [10]; (b) the survival benefits of these agents in certain metastatic cancer settings have already been well established, thereby underscoring the importance of evaluating rash-related death as a potentially competing endpoint [11, 12]; and (c) these rashes often remit spontaneously even with continued therapy, an observation that challenges the need to hold therapy for reasons other than those related to patients’ quality of life [13].

Search Strategy

Eligible articles consisted of those that comprised the primary report of a prospective clinical trial that tested one of the epidermal growth factor receptor inhibitors listed above. PubMed (http://www.ncbi.nlm.nih.gov/sites/entrez/) was used to search for articles because it is one of the largest public repositories of all published medical journals and interfaces with MEDLINE [14]. A deliberate decision was made to focus only on fully published articles, because previous studies have shown that abstracts presented at scientific meetings often do not provide complete and accurate information on adverse events [15, 16]. The search terms “cetuximab,” “erlotinib,” and “panitumumab” as well as their commercial and premarketing names were used to generate a list of publications. Time limits were not used in the search strategy.

Data Extraction

The title and/or abstract of all articles were then reviewed by a member of the study team to confirm that each represented a prospectively conducted clinical trial that included an epidermal growth factor receptor inhibitor. If an article met the study’s aforementioned inclusion criteria, the full publication was reviewed in depth and the following information was extracted: (a) further confirmation that the article did in fact represent a prospective clinical trial with an epidermal growth factor receptor inhibitor; (b) the type of epidermal growth factor receptor inhibitor tested; (c) the number of patients treated with the epidermal growth factor receptor inhibitor; (d) the rate of rash development within the individual study cohort; (e) whether other cancer therapy had been administered concomitantly, and, if so, what type; and (f) whether a rash-related death was reported, and, if so, how often. Initially, an attempt was made to also determine the percentage of patients in whom the epidermal growth factor receptor inhibitor had had to be held because of rash development, but this information was impossible to glean consistently from the publications.

RESULTS

In total, 2,317 articles were identified. Most were review articles, secondary analyses, or laboratory-based studies and therefore did not meet this study’s eligibility criteria. Seven articles appeared to meet these criteria but were not able to be retrieved. In total, 117 articles, which included 8,998 unique patients, met the eligibility criteria, were able to be retrieved and reviewed, and are the focus of this report.

These clinical trials tested cetuximab in 50 trials (43%), erlotinib in 62 (53%) trials, and panitumumab in five (4%) trials. Concomitant chemotherapy was administered in 58 (50%) trials, concomitant radiation was administered in 13 (11%) trials, and a concomitant nonconventional antineo-
plastic agent was administered in 13 (11%) trials, with some trials having included overlapping modalities.

It was not the purpose of this study to report on the percentage of patients who developed a rash, but it should be noted that, in general, rates of rash development were consistent with previous observations [1, 13]. Trials varied as to whether they reported grade ≥2 rashes versus grade ≥3 rashes versus all rashes, but, in general, rash occurred in >50% of the patients in each study, with only 16% of studies reporting a lower rate and 10% not reporting any specific rate.

Although rash toxicity occurred in the majority of patients, there were no reported rash-related deaths. In other words, this study observed that, among these 8,998 unique cancer patients who were prescribed an epidermal growth factor receptor inhibitor, there was not a single reported death that was attributed to a rash from this class of agents.

**DISCUSSION**

This study found no rash-related deaths reported in the published prospective clinical trial literature that tested epidermal growth factor receptor inhibitors. To our knowledge, this conclusion has never before been formulated and reported in such a systematic fashion, and this finding will be of value to health care providers as they counsel cancer patients and their families about holding drug therapy because of rash development. In their article entitled, “An Interdisciplinary Consensus on Managing Skin Reactions Associated with Human Epidermal Growth Factor Receptor Inhibitors,” Eaby and others comment, “…these toxicities rarely are life-threatening…” [17]. The present study allows health care providers to counsel patients now with more accurate and comprehensive information: among 8,998 cancer patients treated with epidermal growth factor receptor inhibitors, no rash-related deaths were reported. Thus, at this time, quality of life factors should remain at the forefront as decisions are made about holding therapy in the event of a severe but typical rash induced by an epidermal growth factor receptor inhibitor.

We are unable to conclude that epidermal growth factor receptor inhibitors are incapable of causing rash-related deaths. The case report from Lin and others suggests that they can [7]. The present study can only conclude that, based on prospective clinical trial reports, the risk of death from a typical rash caused by these agents appears nonexistent. However, two points relevant to this conclusion merit further discussion. First, it should be noted that, in some instances, postmarketing surveillance has revealed serious adverse events that had not been previously reported. Such was the case with erythropoietin and its effects on tumor growth and thrombophlebitis, and such was also the case with bisphosphonates and osteonecrosis of the jaw [18, 19]. Thus, time will tell if lethal, rash-related sequelae might also occur from epidermal growth factor receptor inhibitors. Second, the option of holding the epidermal growth factor receptor inhibitor in the event of a severe rash appears to have been extensively propagated [20], and it is possible that this practice was used in many of the clinical trials reviewed in this study, although, as noted earlier, this information was unable to be gleaned consistently from the clinical trials we reviewed. Despite our findings, it remains possible that continued therapy in the setting of a severe rash might prove to be unsafe.

Finally, two other points merit mention. First, although the typical rash from an epidermal growth factor receptor inhibitor does not appear to result in death, there may be other serious rash-related morbidity. For example, at least two previous publications have described serious rash-related infections [21, 22]. Thus, it is not the intention of this report to suggest that, in the absence of a lethal event, treatment with an epidermal growth factor receptor inhibitor is completely benign. Second, it should be noted that there are therapies that do appear to help with rash palliation, but such therapies do not detract from the need to understand whether such drug-induced rashes can be fatal [23, 24].

In summary, the present study provides important evidence-based guidance on how to better counsel cancer patients who develop a rash from an epidermal growth factor receptor inhibitor, and it allows patients and health care providers further insight into how best to strike a balance between the risks and benefits of therapy with epidermal growth factor receptor inhibitors. Quality of life issues should remain at the forefront as cancer patients and health care providers make decisions about holding cancer therapy.

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**AUTHOR CONTRIBUTIONS:**

Conception/design: Aminah Jatoi, Phuong L. Nguyen
Provision of study materials: Aminah Jatoi, Phuong L. Nguyen
Manuscript writing: Aminah Jatoi, Phuong L. Nguyen
Final approval of manuscript: Aminah Jatoi, Phuong L. Nguyen

**REFERENCES**


