

Risk of Skin Rash Associated with Erlotinib in Cancer Patients: A Meta-Analysis

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The epidermal growth factor receptor (EGFR) is an important mediator of cell growth, differentiation, and survival.¹⁻³ EGFR dysregulation results in oncogenic processes, including uncontrolled cell growth and proliferation, angiogenesis, and metastasis.⁴⁻⁸ Overexpression of EGFR has been associated with advanced disease, poor prognosis, and resistance to anticancer treatment in many solid tumors.⁹⁻¹¹

Erlotinib (Tarceva), a competitive inhibitor of adenosine triphosphate (ATP) binding to the intracellular tyrosine kinase domain of EGFR, blocks EGF-induced receptor autophosphorylation, resulting in decreased cancer cell growth and angiogenesis.¹² Erlotinib has been approved by the Food and Drug Administration for the treatment of patients with advanced non-small cell lung cancer (NSCLC) after failure of one or two standard chemotherapy treatments as a single agent^{13,14} and patients with pancreatic cancer when combined with gemcitabine (Gemzar).¹⁵ The antitumor activity of erlotinib has been reported in other tu-

Abstract Skin rash is a major side effect of erlotinib, an inhibitor of the epidermal growth factor receptor widely used in cancer treatment and clinical trials. This study aims to evaluate the risk of skin toxicity with erlotinib through a systematic review and meta-analysis of randomized controlled clinical trials (RCTs). Eligible studies included prospective RCTs in which erlotinib was compared with controls at the starting dose of 150 mg daily. Incidence, relative risk (RR), and 95% confidence intervals (CIs) were calculated using a random-effects or fixed-effects model based on the heterogeneity of included studies. A total of 2,911 patients with a variety of solid tumors from 9 RCTs were included for analysis. The overall incidence of all-grade skin rash associated with erlotinib was 70.4% (95% CI: 67.2%–73.4%), with 9.4% (95% CI: 8.0%–11.0%) being high grade (grade 3 or above). There was a significantly increased risk of all-grade rash with erlotinib in comparison with controls (RR, 3.43; 95% CI: 2.13–5.52; $P < 0.001$). The incidence of all-grade rash was significantly lower in patients treated with the combination of erlotinib and chemotherapy than with erlotinib alone (risk ratio, 0.84; 95% CI, 0.77–0.93; $P = 0.001$). In addition, RR of all-grade rash was 4.72 (95% CI: 3.56–6.20) for erlotinib alone and 2.34 (95% CI: 1.64–3.34) for the erlotinib combination. In conclusion, erlotinib is associated with substantial skin toxicity that may be modified by chemotherapy.

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mors, including squamous cell carcinoma of the head and neck (SCCHN), ovarian cancer, renal cell cancer (RCC), colorectal cancer (CRC), and others.¹⁵⁻²¹

One of the major side effects observed in erlotinib trials is skin toxicity, including rash, dry skin, hair growth disorders, pruritus, and nail changes.^{22,23} The most common skin toxicity is described as an acne-like or acneiform rash, although the term papulopustular eruption is a more accurate description. The rash is commonly mild to moderate but may be severe, and the severity of the skin rash has been proposed to be one of the biomarkers for the efficacy of erlotinib treatment in cancer patients.²⁴ The recognition and subsequent management of skin toxicity are critical issues because severe skin toxicity leads to morbidity and compromises the efficacy of treatment due to dose reduction or even discon-

tinuation of erlotinib.

The reported incidences of erlotinib-associated skin rash vary widely across clinical trials, ranging from 46.3%–75.6%,^{13,25} and factors underlying the variation are unclear. To determine the overall incidence and risk of developing skin rash in patients receiving erlotinib and to explore potential risk factors, we have conducted a systemic review and meta-analysis of randomized controlled clinical trials (RCTs).

Methods

DATA SOURCE

A search of citations was conducted using the database PubMed. Key words were erlotinib and cancer. The search was limited to RCTs and the time period between 1990 and October 2008. The search also used text terms, including skin rash, EGFR, and inhibitors, to identify relevant information. In addition, we searched abstracts containing the term “erlotinib” that were presented at the American Society of Clinical Oncology (ASCO) conferences held between 2004 and October 2008 to identify relevant clinical trials. An independent search using the citation database Web of Science (developed by the Institute for Scientific Information) also was performed to ensure that no relevant studies were missed.

We reviewed each publication, and only the complete or most recent report of a clinical trial was included when duplicated publications of the trial were identified. The updated manufacturer’s package insert of erlotinib was reviewed for adverse events and related information.²⁶ When data were not clear, efforts also were made to contact the investigators and the manufacturer of erlotinib.

STUDY SELECTION

The goal of this study was to determine the contribution of the EGFR inhibitor erlotinib to the risk of rash observed in cancer patients. Thus, only RCTs with a comparison between erlotinib and a control without EGFR inhibitors were included for analysis. Erlotinib has been approved for use in patients with NSCLC or pancreatic cancer. For comparison among clinical trials, we assessed the risk of rash with erlotinib starting at 150 mg daily. Phase I trials and single-arm phase II trials were excluded from analysis due to a lack of controls. Phase II and III RCTs in which erlotinib was used as a single agent or combined with other agents were included. Specifically, clinical trials that met the following criteria were chosen for analysis: (1) prospective phase II and III RCTs of patients with cancer; (2) patients randomly assigned to be treated with erlotinib at the starting dose of 150 mg daily or a control; and (3) available data regarding the events or incidences of skin rash and sample sizes.

CLINICAL ENDPOINTS

The clinical endpoints were selected from the safety profile of each trial. The included studies reported the incidence of skin rash of grade 1 to 5 (all grade) or grade 3 and above (high

grade). They were recorded according to version 2 or 3 of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI). Both versions are the same regarding the grading of skin rash. Grade 1 is macular or papular eruption or erythema without associated symptoms; grade 2 is macular or papular eruption or erythema with pruritus or other associated symptoms, localized desquamation or other lesions covering < 50% of the body surface area (BSA); grade 3 is severe generalized erythroderma or macular, papular, or vesicular eruption, desquamation covering > 50% BSA; grade 4 is generalized exfoliative, ulcerative, or bullous dermatitis; and grade 5 is death. Version 3.0 has additional grading for acne or acneiform rashes. However, the data for acne or acneiform rash were limited among included studies. Thus, we have focused on skin rashes for analysis.

STATISTICAL ANALYSIS

All statistical analyses were performed using version 2 of the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ). The numbers of patients with skin rash, both for all grade and high grade, were summarized from the extracted safety data in patients receiving erlotinib. For each study, the proportion of patients with skin rash was calculated and the 95% exact confidence interval (CI) was derived. The relative risk (RR) of skin rash among patients assigned to erlotinib was calculated and compared only with that of patients assigned to a control treatment in the same trial.

For meta-analysis, both the fixed-effects model (weighted with inverse variance) and the random-effects model were considered. For each analysis, the Cochran’s Q statistic was first calculated to assess the heterogeneity of the included trials. When P values for Cochran’s Q statistic were less than 0.1, the assumption of homogeneity was deemed invalid, and the random-effects model was used only after substantial efforts were made to explore the possible reasons for the heterogeneity. Otherwise, data were assessed using both the fixed-effects model and the random-effects model. A two-tailed P value of less than 0.05 was judged to be statistically significant.

Results

SEARCH RESULTS

Our search yielded a total of 385 articles on erlotinib from the PubMed database (see Figure 1 for the selection process of these studies). After reviewing each article, we identified six original RCTs that met our inclusion criteria.^{13,15,20,27–30} One RCT was excluded because erlotinib was started at 100 mg as well as 150 mg daily.¹⁵ From the abstracts published during ASCO conferences (2004 to October 2008), we identified 100 abstracts that were related to erlotinib. After reviewing each abstract, three additional trials met our inclusion criteria.^{31–33} Two RCTs were not included for analysis because control arms contained either erlotinib or cetuximab (Erbix), another inhibitor for EGFR.^{34,35} Overall, we have included nine RCTs for analysis.

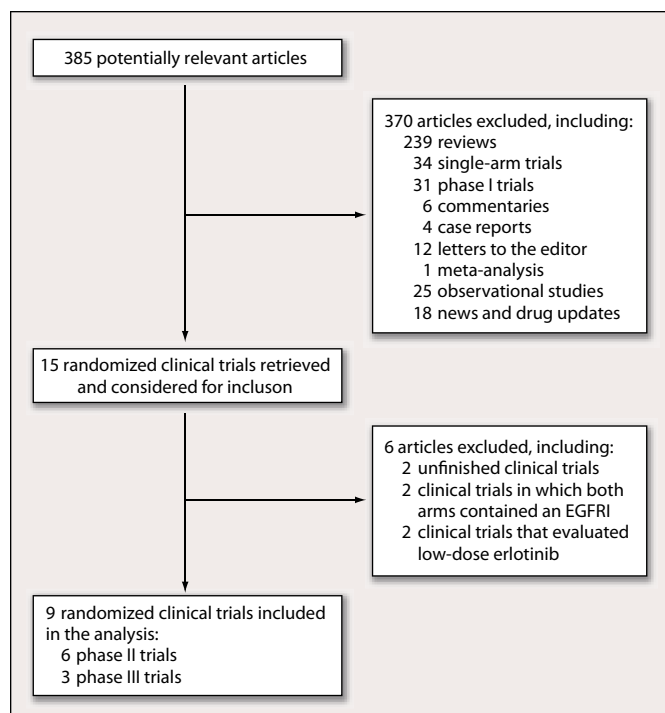


Figure 1 Selection Process for Randomized Controlled Trials Included in the Meta-Analysis

EGFR = epidermal growth factor receptor inhibitor

PATIENTS

A total of nine RCTs were included in the study, with a total of 2,911 patients having available data on rashes for analysis (Table 1). Three trials were phase III, with the rest of the trials being phase II. Two trials had the three-arm design,^{28,33} and the

rest of the trials had two arms. Four RCTs had a double-blind design. Four trials used erlotinib as a single agent in one arm, with controls including placebo (one trial), chemotherapy (two trials), and erlotinib plus chemotherapy or chemotherapy (one trial). Six trials used erlotinib in combination with other agents in one arm, with controls including placebo plus chemotherapy (three trials), chemotherapy (two trials), and single-agent erlotinib or chemotherapy (one trial). The chemotherapeutic agents used in these trials included gemcitabine, capecitabine (Xeloda), paclitaxel, docetaxel (Taxotere), pemetrexed (Alimta), temozolomide (Temodar), cisplatin or carboplatin, and bevacizumab (Avastin). The follow-up time was specified only in three trials.^{20,29,33} Rash was not mentioned as a preexisting condition in any of these trials. Underlying malignancies in these studies included NSCLC (six trials), CRC (one trial), RCC (one trial), and glioblastoma multiforme (one trial). Patients were randomly assigned to treatment with erlotinib or the control arm.

INCIDENCE OF SKIN RASH

Data for all-grade skin rash were available from 5 clinical trials, in which 846 patients with various advanced solid tumors were given erlotinib as a single agent or in combination with chemotherapeutic agents. The incidence of all-grade skin rash ranged from 62.0%–76.6% among these trials. Using a random-effects model, meta-analysis showed that the overall incidence of all-grade rash was 70.4% (95% CI: 67.2%–73.4%).

We further determined separately incidences of rash in patients treated with erlotinib alone and in combination (Table 2). For single-agent erlotinib, the summary incidence of all-grade rash was 75.2% (95% CI: 71.3%–78.7%) in a total of 522 patients from 2 trials.^{13,30} For the erlotinib combination, the summary incidence of all-grade rash was 63.5% (95% CI: 58.1%–68.6%) in a total of 324 patients from 3 trials.^{28,29,31}

Table 1

Characteristics of Randomized Controlled Clinical Trials Included in the Meta-Analysis

STUDY	PHASE	STUDY DESIGN	NO. OF PATIENTS ENROLLED	NO. OF PATIENTS FOR ANALYSIS	MEDIAN DURATION OF FOLLOW-UP, MO (RANGE)	UNDERLYING MALIGNANCY
Bukowski et al (2007) ²⁰	II	Erlotinib + bevacizumab vs placebo + bevacizumab (double-blind)	104	104	9.8 (N/A)	Renal cell cancer
Gatzemeier et al (2007) ²⁷	III	Erlotinib + cisplatin + gemcitabine vs placebo + cisplatin + gemcitabine (double-blind)	1,172	1,159	N/A	Non-small cell lung cancer
Herbst et al (2005) ²⁹	III	Erlotinib + carboplatin + paclitaxel vs placebo + carboplatin + paclitaxel	1,079	417	4.6/5.3 (N/A)	Non-small cell lung cancer
Herbst et al (2007) ²⁸	II	Erlotinib + bevacizumab vs chemotherapy + bevacizumab vs chemotherapy alone	120	78	N/A	Non-small cell lung cancer
Lee et al (2008) ³¹	II	Erlotinib + chemotherapy vs placebo + chemotherapy (double-blind)	154	154	N/A	Non-small cell lung cancer
Lilenbaum et al (2008) ³⁰	II	Erlotinib vs chemotherapy	103	103	N/A	Non-small cell lung cancer
Shepherd et al (2005) ¹³	III	Erlotinib vs placebo (double-blind)	731	727	N/A	Non-small cell lung cancer
Van Den Bent et al (2005) ³²	II	Erlotinib vs temozolomide or carmustine	110	110	N/A	Glioblastoma multiforme
Vincent et al (2007) ³³	II	Erlotinib + capecitabine vs capecitabine alone	59	59	3.8 (0.2–12)	Colorectal cancer

N/A = data not available

Table 2

Relative Risk of Skin Rash with Erlotinib

CATEGORY	NUMBER OF STUDIES	NUMBER OF EVENTS/SAMPLE SIZE		INCIDENCE (95% CI)	RELATIVE RISK (95% CI)
		ERLOTINIB	CONTROL		
All grades					
Overall	5	599/846	135/620	70.4% (67.2–73.4)	3.43 (2.13–5.52)
Single agent	2	393/522	44/294	75.2% (71.3–78.7)	4.72 (3.56–6.20)
Combination	3	206/324	91/326	63.5% (58.1–68.6)	2.34 (1.64–3.34)
High grade					
Overall	8	137/1,490	6/1,251	9.4% (8.0–11.0)	11.27 (5.74–22.14)
Single agent	4	53/589	0/371	9.1% (7.0–11.7)	14.27 (3.36–60.54)
Combination	5	83/901	6/901	9.2% (6.4–13.1)	10.09 (4.80–21.24)

CI = confidence interval

High-grade skin toxicity leads to treatment interruption, dose reduction, and serious morbidity. We analyzed the data from those trials in which the incidence of high-grade rash was reported (Table 2). A total of 1,490 patients from 8 trials were available for analysis. The incidences ranged between 2.6% and 15.7%. Meta-analysis showed that the overall incidence of high-grade skin rash was 9.4% (95% CI: 8.0%–11.0%).

We also determined separately the incidence of high-grade rash in patients treated with erlotinib alone or in combination (Table 2). Patients treated with erlotinib alone had an incidence of high-grade rash ranging from 8.0%–15.4%; the summary incidence was 9.1% (95% CI: 7.0%–11.7%). Patients treated with erlotinib in combination had an incidence of high-grade rash ranging from 2.6%–15.7%; and the summary incidence was 9.2% (95% CI: 6.4%–13.1%).

THE RR OF SKIN RASH

To define the specific contribution of erlotinib to the development of skin toxicity and to exclude the influence of confounding factors, we have determined the RR of rash from erlotinib treatment. A pooled analysis of RRs associated with erlotinib was calculated on five RCTs for all-grade skin rash and eight RCTs for high-grade skin rash. The controls includ-

ed placebo with or without chemotherapy.

Meta-analysis showed that the overall RR was 3.43 (95% CI: 2.13–5.52; $P < 0.0001$) with erlotinib versus controls for all-grade rash according to a random-effects model (Figure 2). The overall RR was 11.27 (95% CI: 5.74–22.14; $P < 0.001$) for high-grade rash according to a fixed-effects model (Table 2). Thus, erlotinib was associated with a significantly increased risk of all-grade and high-grade rashes when compared with controls.

We also determined RRs separately in patients treated with erlotinib as a single agent or in combination with chemotherapy (Table 2). Single-agent erlotinib had summary RRs of 4.72 (95% CI: 3.56–6.2) and 14.27 (95% CI: 3.36–60.54) for all-grade and high-grade rashes, respectively; the erlotinib combination had summary RRs of 2.34 (95% CI: 1.64–3.34) and 10.09 (95% CI: 4.80–21.24) for all-grade and high-grade rashes, respectively (Figure 3). Thus, erlotinib as a single agent or in combination is associated with a significantly increased risk of rash.

THE EFFECT OF CHEMOTHERAPY ON THE RISK OF SKIN RASH ASSOCIATED WITH ERLOTINIB

The risk of rash with erlotinib may be modified by chemotherapeutic agents because of the potential drug-drug interac-

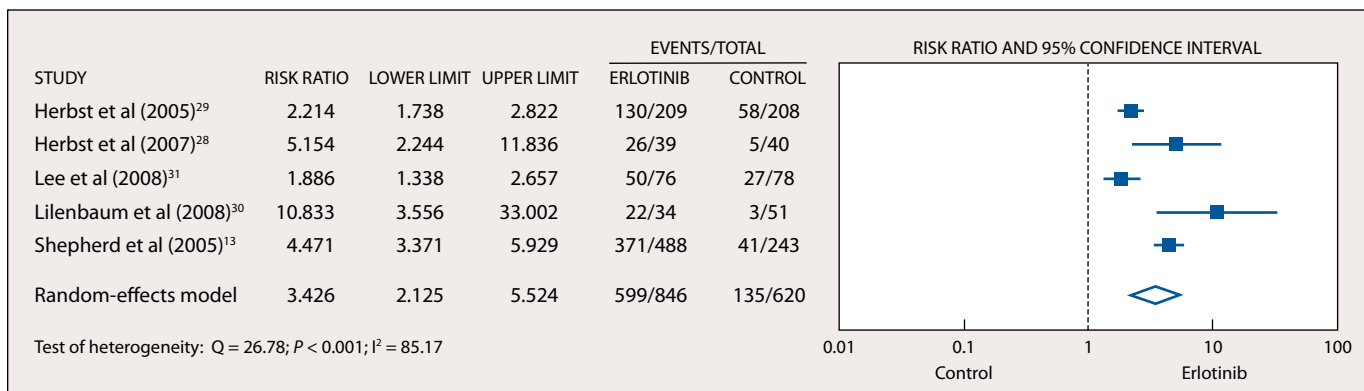


Figure 2 Relative Risk of Rash with Erlotinib

Risk ratios of rash (all grades) with erlotinib were calculated using a random-effects model. The risk ratio for each study is displayed numerically on the left and graphically on the right. Total events and sample sizes are also displayed for each study. Filled-in squares = incidence; lines = 95% confidence interval; diamond plot = overall result of the included trials. The P -value for all comparisons (erlotinib vs control) was < 0.001 .

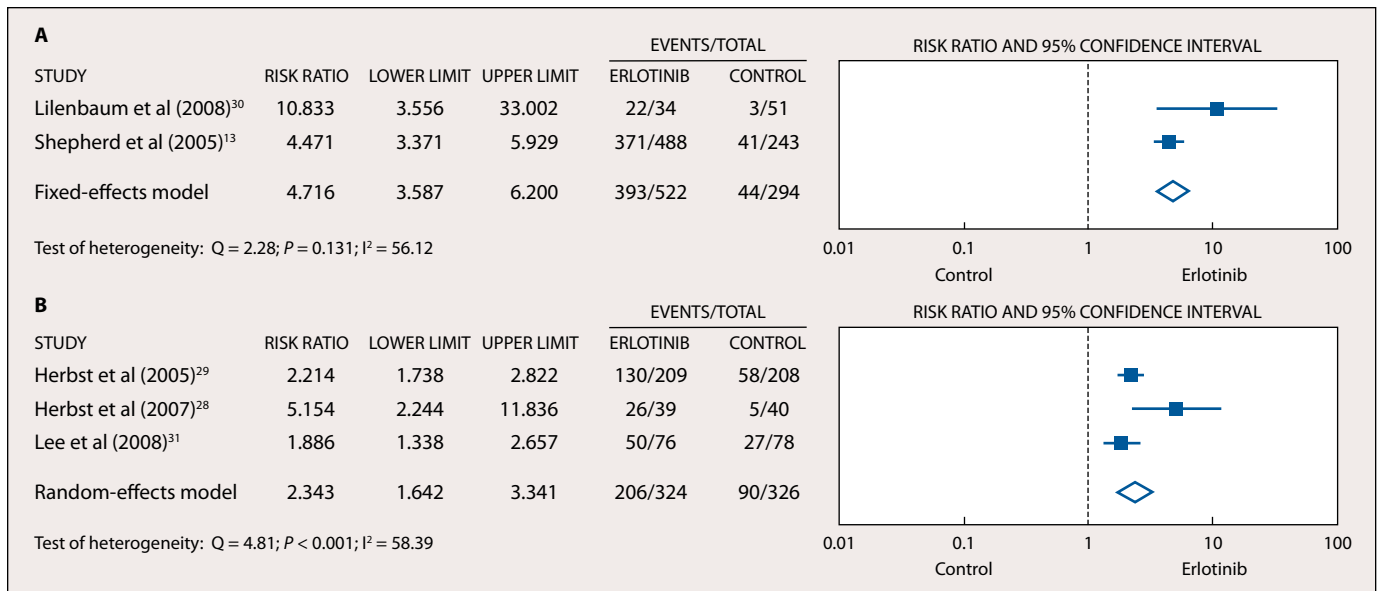


Figure 3 Relative Risk of Rash with Erlotinib as a Single Agent or in Combination with Chemotherapy

Risk ratios of rash (all grades) for single-agent erlotinib (A) or in combination with other agents (B) were calculated using a fixed-effects or random-effects model, respectively. The risk ratio for each study is displayed numerically on the left and graphically on the right. Total events and sample sizes are also displayed for each study. Filled-in squares = incidence; lines = 95% confidence interval; diamond plot = overall result of the included trials. The P -value for all comparisons (erlotinib vs control) was < 0.001 .

tions. To evaluate the impact of chemotherapy on the erlotinib-induced rash, we compared the risk in patients treated with erlotinib with and without concurrent chemotherapy. Interestingly, a significantly lower incidence of all-grade rash was observed in patients treated with erlotinib in combination with chemotherapy than in patients receiving erlotinib alone (RR = 0.84; 95% CI: 0.77–0.93; $P = 0.001$). For high-grade rash, no significant difference was found between erlotinib in combination and as a single agent (RR = 1.02; 95% CI: 0.74–1.42; $P = 0.89$).

Consistent with these incidence data, a distinctly lower RR of all-grade rash was observed in patients treated with the combination of erlotinib and chemotherapy (RR = 2.34; 95% CI: 1.64–3.34) than erlotinib alone (RR = 4.72; 95% CI: 3.56–6.20). For high-grade rash, the RR for the erlotinib combination (RR = 10.09; 95% CI: 4.80–21.24) appears lower than that for erlotinib alone (RR = 14.27; 95% CI: 3.36–60.54).

Discussion

Our study has shown that erlotinib is associated with a considerable risk of rash in cancer patients. The overall incidence of all-grade rash with erlotinib was 70.4% (95% CI: 67.2%–73.4%), and the RR was 3.43 (95% CI: 2.13–5.52) in comparison with controls. We also showed that erlotinib was associated with a substantial risk of developing high-grade skin rash (incidence, 9.4%; 95% CI: 8.0%–11.0%; RR, 11.27; 95% CI: 5.74–22.14). High-grade rashes affect activities of daily living and usually result in dose reduction or even discontinuation of therapy.³⁶ These rashes occur after approximately 1 week of treatment and reach a maximum intensity after 2–3 weeks.^{37–39} Therefore, appropriate early intervention is strongly

recommended. RCTs have shown benefit with the prophylactic use of oral tetracycline and its semisynthetic analogues doxycycline and minocycline.^{40–42}

Erlotinib may interfere with the physiologic role of EGF in the stimulation of epidermal growth, inhibition of cell differentiation, and facilitation of wound healing.^{22,23,43} The inhibition of EGFR activity results in impaired growth and migration of keratinocytes as well as increased production of chemokines, leading to the recruitment of inflammatory cells and cutaneous injury. In addition to erlotinib, other EGFR inhibitors are associated with skin toxicity.^{24,38}

We recently performed a meta-analysis to quantify the risk of rash with cetuximab (a chimeric antibody against EGFR) among a total of 2,037 cancer patients from 16 clinical trials (pending publication in *Oncology*). The overall incidence of all-grade rash with cetuximab was 88.2% (95% CI: 84.8%–91.0%) versus 70.4% (95% CI: 67.2%–73.4%) for erlotinib, and the RR was 6.8 (95% CI: 4.3–10.7) for cetuximab versus 3.43 (95% CI: 2.13–5.52) for erlotinib. We speculate that the difference in the risk of rash may be related to a complement-mediated cytotoxic effect associated with cetuximab,⁴⁴ which would be absent in erlotinib, a tyrosine kinase inhibitor of EGFR. However, the IgG2 isotype monoclonal antibody panitumumab (Vectibix), also leads to rash in up to 90% of patients; so other mechanisms involved in antibody-dependent receptor inhibition and degradation may also play a role.

The combination of antineoplastic agents is used widely to overcome resistance to single agents and to improve efficacy.^{45–48} Here, we have examined whether the combination of erlotinib with chemotherapy affects the risk of rashes. There was a significant difference between erlotinib alone and its combination

in the incidences of all-grade rash ($P = 0.001$); the RRs of all-grade rash for single-agent erlotinib and its combination were 4.72 (95% CI: 3.56–6.20) and 2.34 (95% CI: 1.64–3.34), respectively. These results revealed a distinct difference in the risk of rashes between single-agent erlotinib and its combination.

Potential reasons for this observation include an alteration in drug absorption or metabolism, pharmacologic interactions, or inflammatory response. Previous studies have found an association between drug steady-state plasma concentrations of EGFR inhibitors and the severity of skin toxicity.^{49–51} Maximum plasma concentration and area under the plasma concentration-versus-time curve of erlotinib tend to be lower when erlotinib is used alone than in combination with bevacizumab,⁴⁶ temozolomide,⁵² or capecitabine and docetaxel.⁵³ Thus, a negative pharmacokinetic interaction between erlotinib and other agents is possible. However, this explanation may not apply to all chemotherapeutic agents. Joining erlotinib with gemcitabine⁵⁴ or paclitaxel and carboplatin⁵⁵ did not cause a significant difference in erlotinib plasma level in comparison with erlotinib alone. Thus, chemotherapeutic agents may affect the development of rashes with erlotinib by reducing cytokines and inflammatory cells instead of pharmacokinetic interaction.

Rash has been proposed as a biomarker for the efficacy of EGFR inhibitors.²⁴ Our results showed that chemotherapy significantly reduced the risk of rash with erlotinib (Table 2). This finding is in contrast to the diverse efficacy data of erlotinib in combination with chemotherapeutic agents. The combination of erlotinib with gemcitabine was more effective than gemcitabine alone as the front-line treatment of pancreatic carcinoma.¹⁵ However, no added clinical benefit for erlotinib plus chemotherapy was found in the first-line treatment of NSCLC in comparison with controls.^{27,29} Thus, the occurrence of rash does not correlate well with the efficacy of erlotinib in this setting.

The present study has several limitations. The findings described here are affected by the limitations of the individual clinical trials that are included in the analysis. First, the assessment of rash may vary significantly among investigators and institutions involved in these studies. Second, trials in this study may have underestimated the incidence of severe skin rashes associated with erlotinib because of the imperfection of the NCI–CTCAE grading criteria, which may fail to reflect the clinical situation. Third, meta-analysis is subjected to the inherent methodologic deficiencies of the included trials. For example, the prevalence of baseline rash was not described in these trials. This fact may lead to an overestimation of the incidence of rash associated with erlotinib. To minimize the likelihood of bias, we only included RCTs that directly compared the incidence of skin rash in treatment and control groups. Finally, the results presented here were obtained from clinical trials conducted in major centers and institutes for patients with adequate organ function and therefore may not apply to a patient population with organ dysfunction treated in the community.

Conclusion

Our study has demonstrated that erlotinib is associated with a significant risk of skin toxicity in cancer patients. Early detection and effective management may reduce this risk, which may also be modified by concurrent chemotherapy. Further studies are needed to investigate risk factors and pathogenesis and to develop effective measures for the prevention and treatment of skin toxicity.

Conflicts of interest: Dr. Lacouture is a consultant for Bayer Pharmaceuticals and a speaker for Onyx Pharmaceuticals; Dr. Wu has received honoraria from Onyx Pharmaceuticals, Novartis, and Wyeth. Drs. Jia and Su have nothing to disclose.

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