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ORIGINAL REPORT

Pan Canadian Rash Trial: A Randomized Phase III Trial Evaluating the Impact of a Prophylactic Skin Treatment Regimen on Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor–Induced Skin Toxicities in Patients With Metastatic Lung Cancer

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ABSTRACT

Purpose

Erlotinib is an epidermal growth factor receptor inhibitor approved for patients with advanced non–small-cell lung cancer (NSCLC) whose epidermal growth factor receptor expression status is positive or unknown. Although it is efficacious, erlotinib can cause skin toxicity. This prospective, randomized phase III trial examined the effect of prophylactic treatment of erlotinib-induced skin rash.

Patients and Methods

Patients receiving erlotinib in the second- or third-line setting for advanced NSCLC were randomly assigned to prophylactic minocycline (100 mg twice per day for 4 weeks), reactive treatment (after rash developed, per grade of rash), or no treatment unless severe (grade 3). Rash incidence and severity, time to maximal rash, time to resolution, and overall survival (OS) were compared among treatment groups.

Results

In all, 150 patients were randomly assigned, 50 to each of three treatment arms. The incidence of skin toxicity was 84% regardless of treatment arm. Prophylactic treatment with minocycline significantly lengthened the time to the most severe grade of rash. Grade 3 rash was significantly higher in the no-treatment arm. OS was not significantly different among treatment arms, but patients receiving prophylactic or reactive treatments had a longer OS (7.6 and 8 months, respectively) than those who received no rash treatment (6 months). Rash was not self-limiting.

Conclusion

The incidence of all grades of rash did not differ statistically among the three arms, so the trial was negative. The incidence of grade 3 skin toxicities was reduced in patients who were treated with prophylactic minocycline or reactive treatment. Efficacy was not compromised. Prophylactic minocycline and reactive treatment are both acceptable options for the necessary treatment of erlotinib-induced rash in the second- or third-line setting of metastatic NSCLC.

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INTRODUCTION

Epidermal growth factor receptor (EGFR) is overexpressed in patients with advanced lung cancer.[1] It is now understood that mutations in the *EGFR* gene act as oncogenic drivers in a subgroup of nonsquamous non–small-cell lung cancer (NSCLC). EGFR tyrosine kinase inhibitors (TKIs) such as erlotinib are effective in inhibiting the growth of lung cancer in patients who harbor these mutations.

The physiologic roles of EGFR include stimulation of epidermal growth, inhibition of differentiation, and acceleration of wound healing. EGFR is expressed in the basal layer of the epidermis.[2] Inhibition of this normal physiologic pathway can result in an inflammatory response. Retrospective analyses have demonstrated that there is an inverse relationship between rash severity and TKI efficacy.[3,4] Many physicians are reluctant to prevent the skin toxicity, in case the efficacy of EGFR TKIs is compromised.

Although erlotinib and other TKIs are efficacious, they do come with a variety of cutaneous skin toxicities.[5] Erlotinib-induced rash is acne-like in appearance and can be described as a papulopustular

eruption characterized by inter- and intrafollicular papulopustules and pruritus (itching).[6] Although rarely life threatening, the skin rash can have an impact on quality of life (QOL) through both physical discomfort and psychological distress and on compliance and the likely efficacy of erlotinib. Effective management of EGFR-TKI–induced skin toxicities is critical to ensure dose-intensity and to maintain patient QOL. Tetracycline and minocycline have been shown to decrease the severity of papulopustular rash.[7,8]

The National Cancer Institute of Canada Clinical Trials Group BR.21 (NCIC-CTG BR.21; OSI-774 [Tarceva] in Treating Patients With Stage III or Stage IV Non-Small Cell Lung Cancer) trial showed an overall survival (OS) advantage of erlotinib over placebo (6.7 *v* 4.7 months; hazard ratio, 0.70; $P < .001$).[9] Erlotinib was approved by Health Canada for treating patients with locally advanced or metastatic NSCLC after the failure of at least one prior chemotherapy regimen. The NCIC-CTG BR.21 trial was designed before the impact of *EGFR* mutations was known and included a largely non–*EGFR*-mutated population.

The Pan Canadian Rash Trial is a randomized phase III study that was initiated to determine the best treatment for EGFR inhibitor–induced rash in patients who were treated with erlotinib in the second-line or greater setting.

PATIENTS AND METHODS

Patient Selection

Eligible patients (CONSORT diagram; Fig 1) had a histologic or cytologic documented diagnosis of metastatic NSCLC, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 3. The study was initiated on November 7, 2008, and concluded with the last patient in December 2012. Research ethics boards at each participating institution approved the study.

Study Objectives

The co-primary objectives in this study were to determine and compare the overall incidence of any grade of erlotinib-induced rash among the three treatment arms and to determine whether rash caused by erlotinib is self-limiting. The sample size of 150 patients was chosen to satisfy both co-primary end points. Secondary objectives included the time to reduce the severity of the erlotinib-induced rash by one grade, the maximum severity of erlotinib-induced rash, the time to first presentation of rash, the relationship between the incidence and maximum severity of rash, tumor response to erlotinib for those patients with measurable disease as determined by RECIST 1.1, and OS for all study patients. QOL with Dermatology Life Quality Index (DLQI) scores and incidence and severity of adverse events (AEs) were captured.

Study Design and Treatment Schedule

This multicenter, open-label, randomized, three-arm phase III trial in Canada studied patients who received erlotinib as treatment for stage IV NSCLC after progression on first- or second-line chemotherapy. Patient treatment was initiated at the recommended dose of 150 mg of erlotinib per day. Eligible patients were randomly assigned to one of three treatment groups within 48 hours before starting erlotinib (Fig 2). Any dose reductions, delays, or lowered starting doses were documented.

Grading and Assessment of Rash

Patients were assessed every 4 weeks for 3 months, after which they were observed every 2 months while on study. Patients recorded the rash in patient diaries and were instructed to see their doctor if the rash became intolerable.

Because the rash induced by EGFR inhibitors can often be severe in a small area, the rash was assessed by using an adapted grading system developed by Perez-Soler et al[10] (Appendix Table A1, online only). Based on the National Cancer Institute Common Toxicity Criteria grading scale (version 3), this adapted grading system accounts for many aspects of erlotinib-induced skin manifestations including facial and scalp acneiform eruptions, truncal rash, dry skin, pruritus, and nail changes. In addition to grades of 1 to 3 corresponding to mild, moderate, and severe rash, the adapted grading system introduced grades 2a and 2b, which differ based on whether the rash interferes with patient activities of daily living. Tumor response was evaluated by using RECIST 1.0 criteria at 2-month intervals. After the erlotinib treatment period, patients were observed every 12 weeks for survival. A DLQI questionnaire was administered at baseline, at rash diagnosis, at each subsequent clinic visit, and on progression. Concomitant medications and AEs reported during the study were recorded.

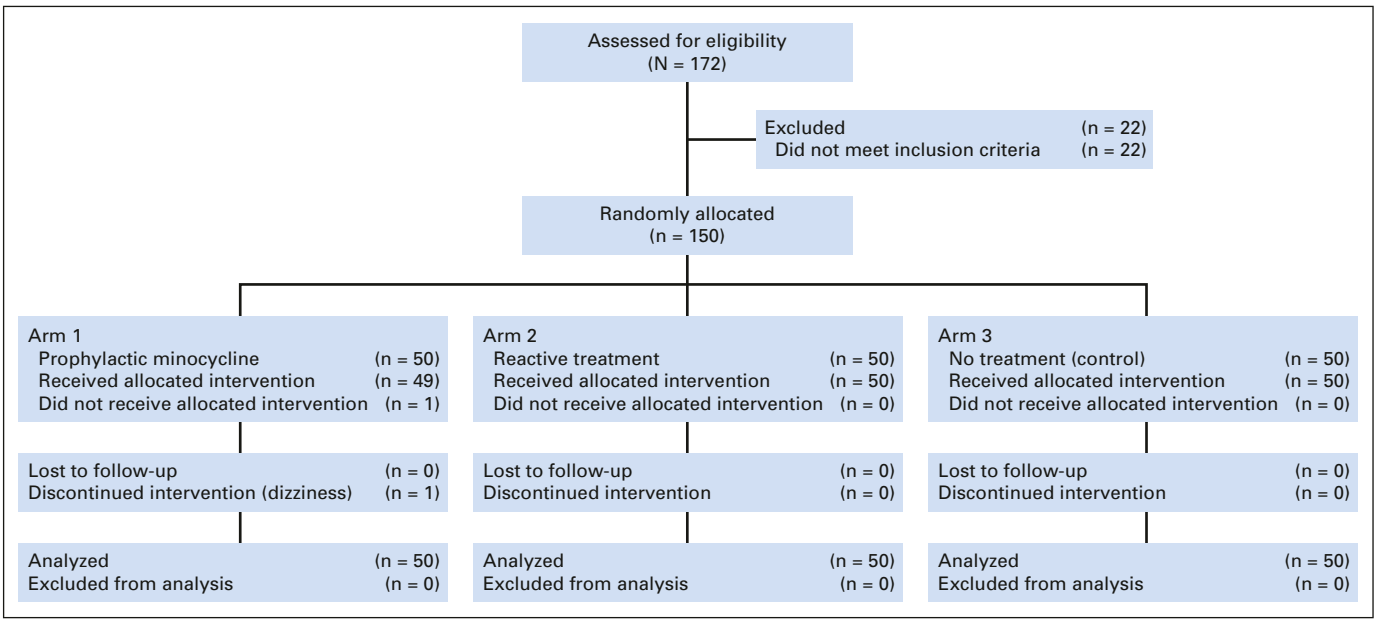

Fig 1. CONSORT diagram.

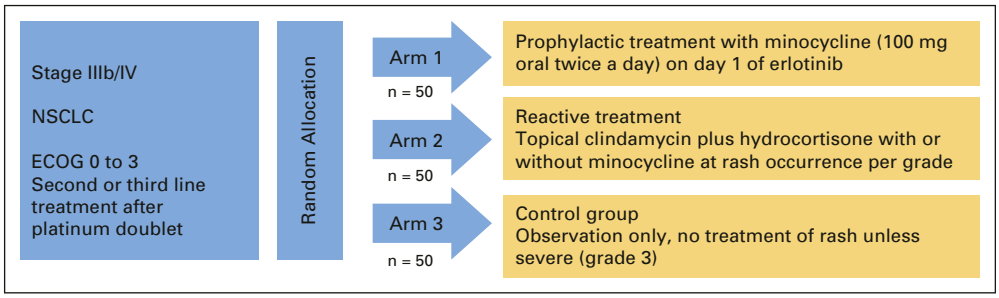

Fig 2. Study design for the multicenter, open-label, randomized, three-arm phase III trial for patients receiving erlotinib as treatment for stage IIIB or IV non–small-cell lung cancer (NSCLC) for whom first- or second-line chemotherapy had failed. Patients were randomly assigned to arm 1, prophylactic minocycline; arm 2, reactive treatment on rash occurrence; or arm 3, no treatment unless severe rash (grade 3). ECOG, Eastern Cooperative Oncology Group performance status.

Rash Treatment

Treatment arm 1: prophylactic treatment with minocycline. Patients received prophylactic treatment with minocycline 100 mg orally twice per day for 4 weeks on the initiation of erlotinib therapy. If rash occurred during or after the completion of the 4-week prophylaxis period, rash treatment was initiated according to the treatment arm 2 schedule. In this case, minocycline could be used again later.

Treatment arm 2: reactive treatment. Patients received treatment at the initiation of rash, depending on the rash grade as described in Appendix Table A1. Treatment for grade 1 rash treatment was optional with topical clindamycin 2%, with hydrocortisone 1% in a lotion base applied twice per day. Grade 2a rash was treated with topical clindamycin 2%, with hydrocortisone 1% in a lotion base applied twice per day until resolution or improvement of rash by one grade. Grade 2b rash was treated with topical clindamycin 2%, with hydrocortisone 1% in a lotion base applied twice per day and oral minocycline 100 mg twice per day for a minimum of 4 weeks and continued until resolution or improvement of the rash by one grade. For grade 3 rash, erlotinib was delayed for 1 week and restarted at a lower dose; the rash was then treated using the same method as for grade 2b rash. Erlotinib dose re-escalation was optional, at the discretion of the investigator, with improvement of rash by one grade. Scalp lesions were treated with a topical solution containing clindamycin 2% with triamcinolone acetonide 0.1% until resolution.

Treatment arm 3: control group. Patients were treated only if grade 3 severity rash developed or if symptoms were intolerable to the patient. For grade 3 rash, treatment was in accordance with that for grade 3 rash in treatment arm 2 (Appendix Table A1).

Statistical Analysis

For the sample size calculations, the end point of occurrence of rash was used. It was assumed that 50% of the patients who did not receive prophylactic treatment would develop any grade of severity of rash during the treatment with erlotinib. In addition, it was assumed that if patients did receive prophylactic treatment, approximately 25% of them would present with any type of rash during the study. By using a two-sided χ^2 test corrected for continuity and assuming the treatment allocation of 1:2 (prophylactic group *v* nonprophylactic groups; group 1 *v* groups 2 and 3 combined) with a significance level of 5% and power of 80%, 50 patients were required for each treatment arm. The sample size was 150 patients.

For the second co-primary end point, a time variable was defined to identify the duration from onset of rash until resolution. Resolution was defined as resolution to severity grade 1 for patients with rash of maximum severity grade more than 1 and resolution to grade 0 for patients with maximum rash severity of 1. For patients in whom resolution was not observed, the time considered was the maximum time from onset of rash until the end of the study. Statistical analysis of secondary end points is described in the Appendix (online only). Analyses were initially conducted by the Inventive Health Clinical Biostatistics and Programming group using SAS, Release 9.2 (SAS Institute, Cary, NC).

RESULTS

In all, 150 patients were enrolled onto this study and were randomly assigned to one of three treatment arms. As of the analysis data cutoff date (December 31, 2012), all patients had discontinued treatment.

Patient characteristics and smoking status are recorded in Appendix Table A2 (online only). There were no clinically meaningful demographic or baseline differences noted among the treatment groups; 75% were white and 83% were current or former smokers.

The number of prior chemotherapy regimens was similar among the treatment arms, although patients were not stratified (data not shown). Eighty-eight patients (58.7%) had one previous line of chemotherapy, 45 (30%) had two previous lines, and 14 (9.3%) had three or more previous lines. Most patients (61.3%; n = 92) had an ECOG performance status (PS) of 1 at the beginning of the study, 40 (26.7%) had ECOG PS 2, eight (5.3%) had ECOG PS 3, and 10 (6.7%) had ECOG PS 0. The distribution of patients in each arm is provided in Appendix Table A2.

Progressive disease (92 of 150 [61.3%]) was the most common reason for patients discontinuing study, followed by death (26 of 150 [17.3%]), AEs or unacceptable toxicity (eight of 150 [5.3%]), and withdrawal of consent and/or other reasons (24 of 150 [16%]). At the end of the study, six patients (4%) were still alive.

Incidence of Rash

The overall incidence of rash (all grades) was similar in all treatment groups, at 82% to 84% (Table 1). No statistically significant difference was observed in overall incidence of rash between treatment arm 1 and arms 2 and 3 combined ($P = .8769$). The incidence of grade 3 rash was significantly different between arms 1 (prophylactic) and 3 (control; 12% and 28%, respectively; $P = .0455$) and between arms 2 (reactive) and 3 (control; 8% and 28%, respectively; $P = .0092$).

Time to Maximum Rash Experienced

Mean time to maximum rash experienced (all grades) was significantly longer in arm 1 at 17.4 days versus arms 2 (13.3 days) and 3 (12.0 days; $P = .0147$; Table 1). This was an exploratory analysis and was not specified in the statistical analysis plan.

Resolution of Rash

For patients with a maximum severity of rash of grade 1, 2a, or 2b, median duration from onset of rash until resolution was 133.0 days in

Table 1. Maximal Rash Grade and Mean Days to Maximal Rash Onset Experienced, by Treatment Arm

Treatment Arm	Overall Incidence of All Grades of Rash, No. (%)*	Mean Days to Maximum Rash Onset†	Maximal Rash Grade, No. (%)			No. of Patients
			0/1	2	3‡	
Arm 1, prophylactic treatment	42 (84)	17.4	25 (50)	19 (38)	6 (12)	50
Arm 2, treatment at rash initiation	42 (84)	13.3	28 (56)	18 (36)	4 (8)	50
Arm 3, treatment at grade 3 rash initiation only	41 (82)	12.0	28 (56)	8 (16)	14 (28)	50
Total	125		81	45	24	150

*P = .8769 for arm 1 *v* arms 2 and 3 combined (χ^2 test).
†P = .0147 for arm 1 *v* arms 2 and 3 combined (Wilcoxon rank sum test).
‡P = .0455 for arm 1 *v* arm 3 and P = .0092 for arm 2 *v* arm 3 (χ^2 test).

arm 1, 92.0 days in arm 2, and 98.0 days in arm 3. For patients with maximum severity of grade 3 rash, median duration from onset of rash until resolution was 201.0 days in arm 1, 76.0 days in arm 2, and 54.0 days in arm 3 (Table 2). No patients in any of the arms that experienced rash had complete resolution to grade 0 (data not shown).

Duration of Treatment

Duration of treatment was calculated from the time treatment was started to the date treatment was stopped, regardless of the reason why treatment was stopped (Table 3 and Fig 3A). Median duration of treatment was 3.6 months (95% CI, 2.1 to 4.6 months) for arm 1, 1.8 months (95% CI, 1.3 to 2.7 months) for arm 2, and 1.8 months (95% CI, 1.7 to 2.4 months) for arm 3 (P = .0624).

OS

OS by treatment arm for all 150 patients was analyzed (Table 3 and Fig 3B). Although median survival in arm 3 was the shortest (6 months *v* 7.6 for arm 1 and 8 months for arm 2), there was no significant difference in survival among the three treatment arms (P = .3834; Fig 3).

DISCUSSION

In NSCLC, a mutation in the EGFR pathway is now recognized as an oncogenic driver. Inhibition of this pathway is an effective treatment strategy, and TKIs have become standard of care in first-line treatment for *EGFR*-mutated metastatic NSCLC. The NCIC-CTG BR.21 trial[9] demonstrated that patients without a known *EGFR* mutation also benefited. After this pivotal trial, erlotinib was approved in the second- or third-line settings in many countries regardless of the patient's EGFR mutation status. This Pan Canadian rash trial was conducted before the widespread mutational analysis of EGFR, and it studied erlotinib in patients with NSCLC who had been pretreated with a platinum doublet. The majority of patients in this investigator-sponsored study (83%) were current or previous smokers, most likely reflecting a population of nonmutated patients.

Rash, a major AE resulting from EGFR inhibition, can have a negative impact on QOL, patient compliance, and therapeutic efficacy. The optimal treatment strategy for the rash induced by EGFR inhibition is not well defined. Meta-analyses of numerous trials have demonstrated this relationship between rash, response to EGFR inhibitors, and both OS and progression-free survival in the NSCLC setting.[3,4] Thus, rash secondary to EGFR inhibition has been correlated with positive efficacy parameters. For this reason, prophylactic treatment or prevention of rash has been controversial.

A total of 150 patients with metastatic NSCLC to be treated with erlotinib were randomly assigned to one of three arms: arm 1, prophylactic minocycline 100 mg twice per day for 1 month; arm 2, reactive treatment as per rash grade; and arm 3, no treatment until rash was severe. The two co-primary end points were the overall incidence of rash in each arm and the time to resolution of rash.

Because the primary end point of changing the incidence of rash was not different among treatment arms, this trial was negative. The

Table 2. Median Number of Days From Onset of Rash Until Resolution

Treatment Arm	Patients With Maximum Severity of Rash			
	Grade 1, 2a, or 2b		Grade 3	
	Median Days (IQR)	No.	Median Days (IQR)	No.
Arm 1, prophylactic treatment	133.0 (80.5-308.5)	36	201.0 (77.0-449.0)	6
P (arm 1 *v* arm 2)	.1503		.1658	
Arm 2, treatment at rash initiation	92.0 (51.0-301.0)	38	76.0 (56.5-90.5)	4
P (arm 2 *v* arm 3)	.4681		> .9999	
Arm 3, treatment at grade 3 rash only	98.0 (47.0-143.0)	27	54.0 (50.0-158.0)	14
P (arm 1 *v* arm 3)	.0196		.285	

NOTE. Resolution was defined as resolution to severity grade 1 for patients with rash of maximum severity grade > 1 and resolution to grade 0 for patients with maximum rash severity of grade 1. For patients in whom resolution was not observed, the time considered was the maximum time from onset of rash until the end of the study. *P* values were calculated by using the Wilcoxon rank sum test for comparisons between two treatment groups.
Abbreviation: IQR, interquartile range.

Table 3. Duration of Treatment and Overall Survival by Treatment Arm

Treatment Arm	Median (95% CI) Duration of Treatment (months)	Median (95% CI) Survival (months)
Arm 1, prophylactic treatment with minocycline	3.6 (2.1 to 4.6)	7.6 (4.7 to 12.4)
Arm 2, treatment at initiation of rash	1.8 (1.3 to 2.7)	8.0 (3.5 to 11.8)
Arm 3, treatment at initiation of grade 3 rash only	1.8 (1.7 to 2.4)	6.0 (5.5 to 7.3)
*P**	.0624	.3834

*Log-rank test was used to compare time to treatment failure and overall survival among the treatment arms.

incidence of rash observed in this prospective randomized trial was 84% (Table 1).

To determine whether erlotinib-induced rash is self-limiting, the duration from onset of rash until resolution was compared among treatment groups. The statistical method included all patients in whom resolution was not observed and measured the maximum time from onset of rash until the end of the study. Although the time to resolution of rash was statistically significant between arms 1 and 3, these data included patients whose rash never resolved. Thus, we are unable to make a conclusion from these results. It is more clinically meaningful to observe arm 3 in which no treatment was administered for rash. None of the patients in arm 3 who experienced any grade of rash had a rash that resolved to grade 0. Although some patients had their rash reduced, none had a rash that was completely resolved. Indeed, none of the patients in any of the arms who experienced any grade of rash had their rash spontaneously resolve while they were being treated with erlotinib. Therefore, the rash is not self-limiting and must be addressed and treated appropriately.

Our trial revealed important clinical findings. There was a significant difference in the incidence of grade 3 rash between arm 1 (prophylactic) and arm 3 (control; 12% and 28%, respectively; $P = .0455$) and between arm 2 (reactive) and arm 3 (control; 8% and 28%, respectively; $P = .0092$). Mean time to maximum rash experienced was significantly longer in arm 1 (17.4 days) versus arms 2 (13.3 days) and 3 (12.0 days; $P = .0147$), although this analysis was exploratory. The reduction in incidence and increased time to severe rash are important clinical findings and support the strategies of preventing and treating rash in patients treated with erlotinib.

Patients treated prophylactically with minocycline received erlotinib for a longer period of time, which may reflect improved patient tolerance and compliance. Median duration of treatment was 3.6 months (95% CI, 2.1 to 4.6 months) for arm 1, 1.8 months (95% CI, 1.3 to 2.7 months) for arm 2, and 1.8 months (95% CI, 1.7 to 2.4 months) for arm 3 ($P = .0624$). Although dose reductions were highest in arm 1, these numbers were too small to be significant and may reflect patient factors that were not stratified, including PS (Appendix Table A3, online only).

OS was not significantly different by treatment arm. Patients in arm 3 demonstrated the shortest survival of 6 months compared with arms 1 (7.6 months) and 2 (8 months; $P = .3834$); however, this was not statistically significant, which may reflect poor compliance in patients with untreated rash. More importantly, prophylactic treatment with minocycline did not reduce erlotinib efficacy.

Contrary to our hypothesis, treatment of EGFR inhibitor–induced rash did not significantly affect QOL (Appendix Table A4, online only). Although QOL was measured extensively in this prospective trial, there were no significant differences among treatment arms. Patients in arm 1 had the lowest QOL at the beginning, but it improved throughout the study. Patients in arm 2 had the highest QOL for the duration of the study, and patients in arm 3 had a decreasing QOL near the end of the study. This is likely a result of

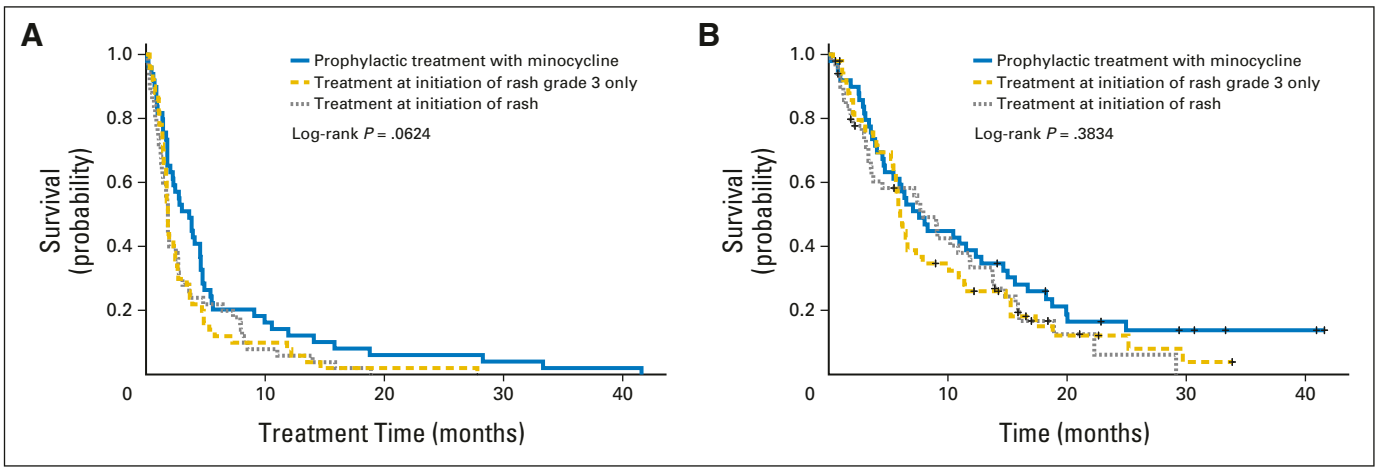

Fig 3. Duration of treatment and overall survival by treatment arm. Kaplan-Meier plots show (A) differences in duration of treatment as determined for each of the three treatment arms ($P = .0624$) and (B) differences in overall survival as determined for each of the three treatment arms ($P = .3834$). Time was calculated from the consent date.

patients not stratified for PS. Adverse events were not significantly different between arms (Appendix Table A5, online only).

The rash associated with EGFR inhibitors is a class effect, but there are differences in rash severity depending on the agent used. The STEPP (Skin Toxicity Evaluation Protocol with Panitumumab) trial conducted by Lacouture et al[11] was an open-label, randomized phase II trial evaluating the impact of a prophylactic treatment regimen in patients with metastatic colorectal cancer who received the anti-EGFR monoclonal antibody panitumumab. Similar to our trial, the STEPP trial also showed a reduction of severe rash and delayed time to experience severe rash. A meta-analysis by Ocvirk et al[12] examined four studies that used prophylactic treatment for EGFR-induced skin rash and concluded that although antibiotics did not reduce the incidence of EGFR inhibitor–induced rash, they could reduce the relative risk of severe rash by 42% to 77%,[12] similar to what we observed.

This randomized, prospective investigator-initiated phase III trial was conducted across Canada and observed rash treatment and efficacy in advanced NSCLC. This trial was started before EGFR mutation testing was routinely conducted. Because patient survival is often directly correlated with successful therapeutic drug delivery, successful management of EGFR-related cutaneous AEs is important to ensure an adequate QOL and treatment compliance for these patients and may avoid discontinuation or dose reduction of the drug. This study showed that prophylactic or reactive treatment of rash when using erlotinib in the second- or third-line setting in advanced NSCLC did not decrease the occurrence of rash but decreased the severity of rash without compromising efficacy. Both treatment approaches are acceptable options for the necessary treatment of erlotinib-induced rash.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Provision of study materials or patients: Helen Anderson, Ronald L. Burkes, Natasha B. Leighl
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Manuscript writing: All authors
Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Methods

Statistical analysis of secondary end points. The time to reduce the severity of rash caused by erlotinib was defined as the time when the first incidence of rash was reported until any episode of rash from the maximum severity observed during the study decreased by one grade. If any decrease in severity of rash was not observed, the time used for analyses was the maximum time of study duration. The comparison between the treatment groups with respect to time to occurrence of event (decrease of one grade in severity of rash) was analyzed with a log-rank test.

The maximum severity of rash per patient was summarized by treatment group. The summary included only patients who indicated any occurrence of rash. The summary statistics were presented with counts and percentages. The comparison between any two treatment groups was performed with Pearson χ^2 test or Fisher's exact test if the expected number of observations in any cell was less than 5.

Time to first presentation of rash was considered as the time from the random assignment to the first reported incidence of rash. This time variable was derived only for patients who were indicated as having rash. The comparison between any two treatment groups was performed by using a Wilcoxon rank sum test.

Summary statistics were presented with counts and percentages for the following relationships: overall incidence of rash and response, overall incidence of rash and survival, maximum severity of rash and response, and maximum severity and survival. The comparison between any two treatment groups was performed with Pearson χ^2 test or Fisher's exact test if expected number of observations in any cell was less than 5.

The Dermatology Quality of Life Index was analyzed as the total score with six domains: Symptoms and Feelings, Daily Activities, Leisure, Work and School, Personal Relationships, and Treatment. Summary statistics for the total score and domains were presented by treatment group with mean, standard deviation, median, 25th and 75th percentile, and range.

The comparisons between treatment groups for total Dermatology Quality of Life Index score and its domains were performed with actual data at baseline, actual data at onset of rash, actual data at maximum intensity of rash, actual data at end of treatment of rash, percent change and absolute change at end of treatment related to onset of rash, and percent change and absolute change at end of treatment related to the time point of maximum severity of rash.

The evaluation of drug safety was based on a review of adverse events (AEs). All safety presentations were based on patients who were treated with at least one dose of study medication. Frequency distributions and individual subject listings of all AEs were generated. All AEs were coded and grouped into preferred terms by system organ class by using the Medical Dictionary for Regulatory Activities version 11.0. All safety data collected by using the Case Report Form were listed by treatment group and patient number.

Categorical data were summarized by using counts and percentages. For continuous variables, summary statistics included number of patients, mean, standard deviation, median, minimum, maximum, and 25th and 75th percentiles. For categorical variables, summary statistics included frequencies and percentages. Missing observations were treated as missing at random and no imputation was performed. Overall survival and time to treatment failure were analyzed by using Kaplan-Meier methodology. All statistical tests were two-sided and were performed by using a 5% significance level, leading to a 95% (two-sided) CI.

Results

Dose reductions, stops, and dose density. The number of dose reductions and drug discontinuations was documented as a measure of patient tolerance and compliance (Appendix Table A3). In the study, a total of 34 of 148 patients had a dose reduction, and a total of 39 had a dose interruption. Of those who had at least one dose reduction, there were 14 patients (28%) in arm 1, six patients (12%) in arm 2, and 14 patients (28%) in arm 3 (χ^2 test $P = .0818$). Of those who had at least one dose delay, there were 17 patients (35%) in arm 1, eight (16%) in arm 2, and 14 (28%) in arm 3 (χ^2 $P = .1000$). The mean dose-intensity for erlotinib over the total treatment period was 131.8 mg per day for arm 1, 144.0 mg per day for arm 2, and 137.2 mg per day for arm 3. Performing the nonparametric Wilcoxon rank sum test yields a P value of .0312, indicating that arm 2 patients had the highest dose-intensity. Dose-intensity was the lowest in arm 1, reflecting that the duration of erlotinib was twice as long for arm 1 (3.6 months *v* 1.8 months in arms 2 and 3).

Quality of life. Quality-of-life analysis was performed at baseline, at the beginning of every cycle, and at study termination. A Wilcoxon signed rank test was used to test whether the treatment arms differed in total quality-of-life score between (1) cycle 1 and baseline and (2) study termination and baseline. Results indicated no significant difference between treatment arms: (1) $P = .4601$; (2) $P = .3904$ (Appendix Table A4).

Safety. A total of 18 patients (12%) experienced 29 treatment-emergent adverse events (TEAEs; Appendix Table A5). In this large investigator-sponsored study, it was agreed that only serious AEs secondary to the minocycline treatment would be recorded. TEAEs were not recorded for erlotinib because it is considered standard of care.

Of 149 patients, only one patient (2.0%) from treatment arm 1 discontinued the study drug as a result of a TEAE (dizziness). One patient (2%) from treatment arm 1 experienced an SAE (pancreatitis); however, this did not lead to discontinuation of treatment.

Table A1. Rash Grading and Treatment

Grade	Toxicity	Treatment
1	Mild macular or papular eruption or erythema with no associated symptoms	Treatment optional per grade 2.
2a	Moderate macular or papulopustular eruption or erythema with pruritus or other symptoms that are tolerable	Topical clindamycin 2% with hydrocortisone 1% in lotion base applied twice per day until resolution of rash by one grade.
2b	Moderate macular or papulopustular eruption or erythema with pruritus or other symptoms that interfere with daily life	Topical clindamycin 2% with hydrocortisone 1% in lotion base applied twice per day and oral minocycline 100 mg twice per day for a minimum of 4 weeks and continued until resolution of rash by one severity grade. Scalp lesions treated with a topical solution containing clindamycin 2% with triamcinolone acetonide 0.1%.
3	Severe, generalized erythroderma or macular, papular, or vesicular eruption	Stop erlotinib therapy for 1 week and restart at 100 mg once per day. Treatment of rash with topical clindamycin 2% with hydrocortisone 1% in lotion base applied twice per day and oral minocycline 100 mg twice per day for a minimum of 4 weeks and continued until resolution of the rash to grade 1 or 2A. Scalp lesions were treated with a topical solution containing clindamycin 2% with triamcinolone acetonide 0.1% until resolution. Erlotinib dose re-escalation was optional based on the discretion of the investigator and on whether rash improved by one grade.

NOTE. Rash was graded by using a revised grading system based on National Cancer Institute Common Toxicity Criteria version 3.[10]

Table A2. Patient Characteristics and Smoking Status

Characteristic	Arm 1, Prophylactic Minocycline (n = 50) No. (%)	Arm 2, Reactive (n = 50) No. (%)	Arm 3, Observation (n = 50) No. (%)
Median age for all groups, years		64.9	
Smoking status			
Percent who have never smoked (all groups)		17	
Percent who are current/former smokers (all groups)		83	
Sex			
Male	33 (66)	23 (46)	23 (46)
Female	17 (34)	27 (54)	27 (54)
Race/ethnicity			
White	36 (72)	41 (82)	35 (70)
Asian	13 (26)	8 (16)	14 (28)
Other	1 (2)	1 (2)	1 (2)
Histology*			
Adenocarcinoma	39 (78)	42 (82)	38 (76)
Squamous	11 (22)	8 (16)	12 (24)
Stage			
IIIB	3 (6)	1 (2)	4 (8)
IV	47 (94)	49 (98)	46 (92)
No. of previous regimens			
0	1 (2)	0 (0)	2 (4)
1	30 (60)	32 (64)	26 (52)
2	15 (30	14 (28)	16 (32)
3-7	4 (8)	4 (8)	6 (12)
ECOG performance status at baseline			
0	2 (4)	4 (8)	4 (8)
1	27 (54)	30 (60)	35 (70)
2	18 (36)	14 (28)	8 (16)
3	3 (6)	2 (4)	3 (6)
Reasons for discontinuing treatment			
Progressive disease	32 (64)	27 (54)	33 (66)
Death	6 (12)	14 (28)	6 (12)
Adverse event/toxicity	4 (8)	2 (4)	2 (4)
Withdrawal of consent/other reasons	8 (16)	7 (14)	9 (1)

Abbreviation: ECOG, Eastern Cooperative Oncology Group.
*History of non–small-cell lung cancer at screening.

Table A3. Erlotinib Dose Reductions, Interruptions, and Dose-Intensity per Treatment Arm

Treatment Arm	Treatment Arm 1 (n = 49) No. (%)	Treatment Arm 2 (n = 50) No. (%)	Treatment Arm 3 (n = 50) No. (%)	Combined Treatment Arms (N = 149) No. (%)	*P**
Patients with at least one erlotinib dose reduction	14 (29)	6 (12)	14 (28)	34 (22.8)	.0818
Patients with at least one erlotinib dose interruption during treatment period	17 (35)	6 (12)	14 (28)	37 (22.8)	.1000
Mean dose-intensity, mg per day	131.8	144.0	137.2	—	

*χ^2 test.

Table A4. Total QOL Scores at Baseline, Cycle 1, and Study Termination

Treatment Arm	Mean of Total QOL Scores (No. of Patients)		
	Baseline	Cycle 1	Study Termination
Arm 1, prophylactic treatment with minocycline	0.44 (50)	2.32 (37)	2.92 (26)
Arm 2, treatment at rash initiation	0.62 (50)	3.43 (37)	4.15 (26)
Arm 3, treatment at grade 3 rash initiation only	0.6 (50)	3.38 (40)	1.86 (29)

NOTE. Wilcoxon signed rank test was used to test whether the treatment arms differed in total quality-of-life (QOL) score between (1) cycle 1 and baseline and (2) study termination and baseline. Results indicated no significant difference: (1) $P = .04601$ and (2) $P = .3904$.

Table A5. Incidence of All Adverse Events Related to Minocycline by Severity (NCI-CTC grade)

	Treatment Arm 1 (n = 49)* No. (%)/Events			Treatment Arm 2 (n = 50)* No. (%)/Events			Treatment Arm 3 (n = 50)* No. (%)/Events			Combined Treatment Arms (N = 149)* No. (%)/Events		
Adverse Event	1	2	3	1	2	3	1	2	3	1	2	3
Diarrhea	1 (2)/1	1 (2)/1	0	0	0	0	0	0	0	1 (0.7)/1	1 (0.7)/1	0
Dyspepsia	1 (2)/1	0	0	0	0	0	0	0	0	1 (0.7)/1	0	0
Gastroesophageal reflux disease	1 (2)/1	0	0	0	0	0	0	0	0	1 (0.7)/1	0	0
Nausea	5 (10.2)/5	0	0	0	0	0	1 (2)/1	0	0	6 (4.0)/6	0	0
Pancreatitis	0	1 (2)/1	0	0	0	0	0	0	0	0	1 (0.7)/1	0
Fatigue	1 (2)/1	1 (2)/1	0	0	0	0	0	0	0	1 (0.7)/1	1 (0.7)/1	0
Hyperbilirubinemia	0	0	0	0	0	0	1 (2)/1	0	0	1 (0.7)/1	0	0
Anorexia	0	1 (2)/1	0	0	0	0	0	0	0	0	0	0
Decreased appetite	1 (2)/1	0	0	0	0	0	0	0	0	1 (0.7)/1	0	0
Dizziness	2 (4.1)/2†	0	0	0	0	0	2 (4.0)/2	0	0	4 (2.7)/4	0	0
Dysgeusia	0	1 (2)/1	0	0	0	0	0	1 (2)/1	0	0	2 (1.3)/2	0
Headache	0	0	0	0	0	0	1 (2)/1	0	0	1 (0.7)/1	0	0
Parosmia	0	0	0	0	0	0	0	1 (2)/1	0	0	1 (0.7)/1	0
Chromaturia	1 (2)/1	0	0	0	0	0	0	0	0	1 (0.7)/1	0	0
Dry skin	0	0	0	1 (2)/1	0	0	0	0	0	1 (0.7)/1	0	0
Skin pain	0	0	0	0	0	0	1 (2)/1	0	0	1 (0.7)/1	0	0
Blister	0	0	1 (2)/1	0	0	0	0	0	0	0	0	1 (0.7)/1
Rash	0	0	1 (2)/1	0	0	0	0	0	0	0	0	1 (0.7)/1

Abbreviation: NCI-CTC, National Cancer Institute Common Toxicity Criteria.

NOTE. Medical Dictionary for Regulatory Activities (MedDRA) version 11.0 was used to code all events. Although some patients experienced multiple adverse events, there were no serious adverse events leading to death and there were no grade 4 or 5 events.

*Arm 1: 12 patients (24.5%), 21 treatment-emergent adverse events (TEAEs); arm 2: one patient (2%), one TEAE; arm 3: five patients (10%), seven TEAEs; combined arms: 18 patients (12%), 29 TEAEs.

†Only one patient in arm 1 (2%) discontinued the study drug because of a TEAE (dizziness).