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Symptom Management and Supportive Care

Does Sunscreen Prevent Epidermal Growth Factor Receptor (EGFR) Inhibitor–Induced Rash? Results of a Placebo-Controlled Trial from the North Central Cancer Treatment Group (N05C4)

AMINAH JATOI,[a] ABBY THROWER,[b] JEFF A. SLOAN,[a] PATRICK J. FLYNN,[c] NICOLE LEA WENTWORTH-HARTUNG,[c] SHAKER R. DAKHIL,[d] BASSAM I. MATTAR,[d] DANIEL A. NIKCEVICH,[e] PAUL NOVOTNY,[a] ALEKSANDAR SEKULIC,[f] CHARLES L. LOPRINZI[a]

[a]Mayo Clinic Foundation, Rochester, Minnesota, USA; [b]Cedar Rapids Oncology Project CCOP, Cedar Rapids, Iowa, USA; [c]Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, Minnesota, USA; [d]Wichita Community Clinical Oncology Program, Wichita, Kansas, USA; [e]Duluth CCOP, Duluth, Minnesota, USA; [f]Mayo Clinic, Scottsdale, Arizona, USA

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ABSTRACT

Purpose. **Rash occurs in >50% of patients prescribed epidermal growth factor receptor (EGFR) inhibitors. This study was undertaken to determine whether sunscreen prevents or mitigates these rashes.**

Methods. **This placebo-controlled, double-blinded trial enrolled rash-free patients starting an EGFR inhibitor. Patients were randomly assigned to sunscreen with a sun protection factor of 60 applied twice a day for 28 days versus placebo. They were then monitored for rash and quality of life (Skindex-16) during the 4-week intervention and for an additional 4 weeks.**

Results. **Fifty-four patients received sunscreen, and 56 received placebo; the arms were balanced at baseline. During the 4-week intervention, physician-reported rash occurred in 38 (78%) and 39 (80%) sunscreen-treated and placebo-exposed patients, respectively ($p = 1.00$); no significant differences in rash rates emerged over the additional 4 weeks. There were no significant differences in rash severity, and patient-reported outcomes of rash yielded similar conclusions. Adjustment for sun intensity by geographical zone, season, and use of photosensitivity medications did not yield a significant difference in rash across study arms ($p = .20$). Quality of life scores declined but remained comparable between arms.**

Conclusions. **Sunscreen, as prescribed in this trial, did not prevent or attenuate EGFR inhibitor–induced rash.**
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Correspondence: Aminah Jatoi, M.D., Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905, USA. Telephone: 507-284-3902; Fax: 507-284-1803; e-mail: jatoi.aminah@mayo.edu Received March 19, 2010; accepted for publication June 18, 2010; first published online in ***The Oncologist*** *Express* on August 26, 2010. 1083-7159/2010/$30.00/0 doi: 10.1634/theoncologist.2010-0082

INTRODUCTION

A rash that closely resembles acne occurs in >50% of patients prescribed epidermal growth factor receptor (EGFR) inhibitors. Although the factors that prevent or palliate this rash have not been well characterized, recent clinical data suggest that sun exposure may exacerbate rash development. Luu and others reported on a patient who had developed an EGFR inhibitor–induced rash on unprotected skin. However, the face and neck, which had been treated with sunscreen, were spared [1]. Moreover, patient educational resources instruct patients to avoid the sun while on an EGFR inhibitor and imply that sunscreen might prevent this rash or attenuate its severity [2]. Such reports and recommendations suggested that sunscreen merits further study for rash prevention or palliation.

The rationale for studying sunscreen was further bolstered by preclinical data demonstrating that the EGFR marshals skin repair mechanisms, even after minor injury. Jost and others showed that specific activation of the EGFR leads to prolonged cell proliferation and survival of keratinocytes after UV light exposure [3, 4]. In the setting of EGFR inhibition, a growing body of literature describes the effects of UV light on keratinocyte apoptosis, which in turn leads to obstruction of skin follicles from dead cells with subsequent inflammatory changes that appear to result in the EGFR inhibitor–induced rash [5]. The foregoing preclinical observations appear to advance the hypothesis that, in the setting of EGFR inhibition, sunscreen prevents or attenuates EGFR inhibitor–induced rash by means of preventing minor, sun-induced skin injury.

Finally, few interventions have shown notable efficacy in preventing or palliating EGFR inhibitor–induced rash. A few previously published studies suggest that oral tetracycline or minocycline may perhaps carry palliative effects, but such effects are modest at best [6, 7]. Thus, the North Central Cancer Treatment Group (NCCTG) conducted this placebo-controlled trial to test whether sunscreen prevents rash in patients starting cancer therapy with an EGFR inhibitor.

METHODS

Overview

The institutional review boards within the NCCTG approved the study protocol. All patients provided written consent prior to enrollment.

Patient Eligibility

The following criteria were required: (a) patient age ≥18 years, (b) a cancer diagnosis, (c) an EGFR inhibitor started or about to be started by the patient within 3 days of randomization, and (d) patient appearing capable of applying sunscreen as instructed and of completing questionnaires independently or with help.

Patients were not allowed to enroll in the event of the following: (a) a previous allergic reaction to sunscreen or one of its derivatives, (b) rash at randomization, (c) a history of a skin problem that might "flare" during cancer treatment, (d) inability or unwillingness to avoid heavy sun exposure for the first 8 weeks of study participation, or (e) planned use of a tanning bed in the 8 weeks after randomization.

Treatment

Prior to randomization, patients were stratified based on the following: (a) first-line cancer therapy versus other therapy, (b) type of EGFR inhibitor prescribed/anticipated: small molecule (such as erlotinib) versus monoclonal antibody (such as cetuximab), and (c) use of a concurrent medication that increases sun hypersensitivity (a list of such medications was included with the protocol): yes versus no.

Thereafter, patients were randomly assigned to receive sunscreen with a sun protection factor (SPF) of 60 to be applied to the face, trunk, and extremities twice a day for a total of 4 weeks versus an identical-appearing placebo. Sunscreen was provided by Pharmaceutical Specialties Incorporated (Rochester, MN) and included 7.5% titanium dioxide and 7.5% zinc oxide. In preclinical testing, this formulation had been shown to block >90% of both UVA and UVB light. The placebo formulation was identical to the sunscreen but lacked titanium dioxide and zinc oxide. The interventions were to start within 3 days after randomization. In view of the well-established safety profile of sunscreen, the protocol specified that patients were to stop only in the unlikely event that the treating oncologist thought that the sunscreen/placebo was causing "undue side effects."

The protocol required that patients be instructed to stay indoors or in a covered area between 10 a.m. and 3 p.m. in order to avoid peak sun exposure. They were also instructed to not use any other topical sunscreens for a total of 8 weeks after enrollment. The protocol also stated that all other supportive care measures be allowed throughout the study.

Assessments

All patients underwent a history, physical exam, and assessment of performance status score within 14 days of randomization to a study arm. After randomization, patients were monitored for rash, quality of life, and adverse events. Patients reported baseline and weekly assessments that included: (a) a brief rash incidence questionnaire, 2) the Skindex-16 questionnaire [8], and 3) a previously used

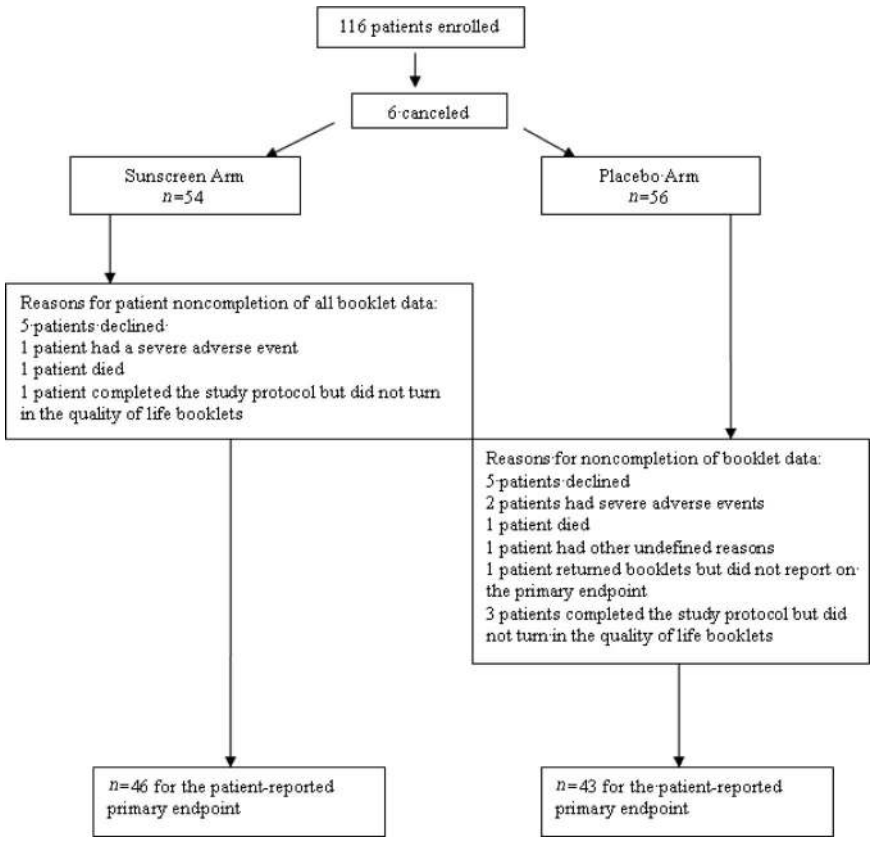

Figure 1. The consort diagram showed a balance in dropouts between study arms.

questionnaire on patient compliance with the EGFR inhibitor therapy [7]. The Skindex-16 was chosen because it provides a comprehensive patient-reported skin assessment by means of 16 questions on itching, burning or stinging, skin pain, skin irritation, and patient-related concerns on a variety of other skin problems.

The treating oncologist evaluated patients at the end of 4 weeks and 8 weeks. At these time points, a history and physical examination, an assessment of performance status, and a recording of adverse events (Common Terminology Criteria for Adverse Events, version 3.0) occurred.

Statistical Analyses

The primary objective was to compare the incidence of rash between sunscreen-treated and placebo-exposed patients. A sample size of 50 patients per group provided an 85% probability of detecting a difference in rash cumulative incidence of 30% between the two study arms and of thereby rejecting the null hypothesis of equal proportions with a p-value of .05 as a two-sided test. Observing an effect size of this magnitude was considered a reasonable trade-off that would offset the inconvenience of applying a topical therapy twice a day. Physician- and patient-reported rash cumulative incidence rates were analyzed and reported separately. The primary endpoint of physician-reported cumulative rash rate used an intention-to-treat analysis in which patients with no reported outcome were assumed to have developed a rash. Patient-reported rash rates relied exclusively on what patients reported. A Fisher's exact test was used to compare rates between study arms.

In addition to the primary endpoint described above, a logistic regression model was constructed to further assess the potential impact of sunlight on rash development. This model included factors that might potentially modulate sun exposure or rash development, including study arm, gender, use of photosensitivity medications, geographical region of sun intensity [9], season at enrollment, type of EGFR inhibitor, use of corticosteroids, and use of antibiotics. The main purpose of this model was to explore whether any benefits of sunscreen might have been obscured by any of these factors.

Other secondary endpoints were assessed. The study team compared the cumulative incidence of rash severity between study arms. Analyses were performed with data gathered at both the 4-week and 8-week time points. The latter was assessed in case there were any rebound effects that might have occurred after stopping the sunscreen. Comparisons of changes in quality of life scores from base-

Table 1. Baseline characteristics

	Sunscreen arm ($n = 54$)	Placebo arm ($n = 56$)	p-value
Median age, yrs (range)	63 (36–90)	62 (37–88)	.74
Gender			
Female	29 (54)	29 (52)	.84
Male	25 (46)	27 (48)	
Performance status score			
0	28 (52)	30 (53)	.77
1	22 (41)	24 (43)	
2	3 (6)	1 (2)	
3	1 (1)	1 (2)	
First-line chemotherapy			
Yes	18 (33)	18 (32)	.89
No	36 (67)	38 (68)	
Epidermal growth factor receptor inhibitor			
Erlotinib (or other small molecule)	21 (39)	22 (39)	.97
Cetuximab (or other antibody)	33 (61)	34 (61)	
Corticosteroid therapy			
Yes	10 (18)	8 (14)	.55
No	44 (82)	48 (86)	
Cancer type			
Lung	22 (41)	17 (30)	.37
Gastrointestinal	22 (41)	23 (41)	
Other	10 (18)	16 (29)	
Potentially curable malignancy			
Yes	8 (15)	11 (20)	.50
No	46 (85)	45 (80)	
Geographic sun intensity zone			
Northeastern/Great Lakes region	30 (56)	32 (57)	.87
Southern and Northern Prairie region	24 (44)	24 (43)	
Season of enrollment			
Spring	32 (59)	32 (57)	.37
Fall	0	2 (4)	
Winter	22 (41)	22 (39)	

Numbers in parentheses denote percentages unless otherwise specified.

line between study arms were also undertaken, and the incidence of adverse events was also compared between arms with a Fisher's exact test.

Results

Patient Demographics

Between October 2006 and June 2007, 116 patients were accrued. Fifty-eight were assigned to each study arm, but patient cancellations prior to starting any study agent resulted in 54 and 56 evaluable patients in the sunscreen and placebo arms, respectively (Fig. 1). Patients in the two study arms were comparable at baseline (Table 1).

Time on Study and Compliance

The median time on study was comparable between study arms. For patients assigned to the sunscreen arm, it was 28 days (range, 3–44 days) and for patients in the placebo arm it was 29 days (range, 6–60 days) ($p = .16$). Fifty-five percent of patients assigned to the sunscreen arm completed all components of the study, and 73% of those in the placebo arm did the same. Reasons for premature withdrawal in-

Table 2. Rash incidence and severity

	Cumulative rash incidence (%)					
	Physician-reported			Patient-reported[a]		
Time point (rash extent)	Sunscreen arm ($n = 54$)	Placebo arm ($n = 56$)	p-value	Sunscreen arm ($n = 46$)	Placebo arm ($n = 43$)	p-value
4 wks (any)	38 (78)	39 (80)	0.36	38 (83)	39 (91)	.36
4 wks (grade 2 or >50% surface area)	18 (33)	29 (52)	0.06	13 (28)	10 (23)	.63
8 wks[b] (any)	42 (78)	42 (75)	0.82	39 (85)	40 (93)	.32
8 wks (grade 2 or >50% surface area)	21 (39)	29 (52)	0.19	17 (37)	17 (40)	.83

[a]21 patients did not submit a quality of life booklet.
[b]As noted, patients continued on therapy for 4 weeks with a subsequent 4-week period of observation.

cluded adverse events/refused further therapy in 37% and 23% of patients assigned to sunscreen and placebo, respectively. Death was the reason in <2% of patients in each arm, and a nonspecified reason was noted in 6% and 2% of patients, respectively.

Compliance with the EGFR inhibitor was assessed because stopping cancer treatment would lead to rash prevention or resolution. Ten patients, four receiving sunscreen and six receiving placebo, stopped taking the EGFR inhibitor within the first month. One sunscreen-treated patient stopped taking cancer therapy because of rash development, as did four placebo-exposed patients.

Rash Development

The primary endpoint of rash cumulative incidence was comparable between study arms (Table 2).

As noted earlier, the logistic regression model included study arm, gender, use of photosensitivity medications (yes versus no), sun intensity by geographical zone [9], season at enrollment, type of EGFR inhibitor (erlotinib versus cetuximab versus panitumumab), use of corticosteroids (yes versus no), and use of antibiotics (yes versus no). Despite such adjustments, there was no statistically significant difference in rash development based on study arm.

Rash severity was assessed as a secondary endpoint, and no differences were observed between patients in the two study arms. The percentages of patients who reported a rash that covered <25%, 25%–50%, 51%–75%, and >75% of their body surface area during the first 4 weeks were 54%, 20%, 6%, and 2% among sunscreen-treated patients and 51%, 30%, 9%, and 0% among placebo-exposed patients, respectively ($p = .21$). Evaluating patient-reported rash severity at weeks 5–8 and physician-reported severity during the same time period did not yield any statistically or clinically significant observations.

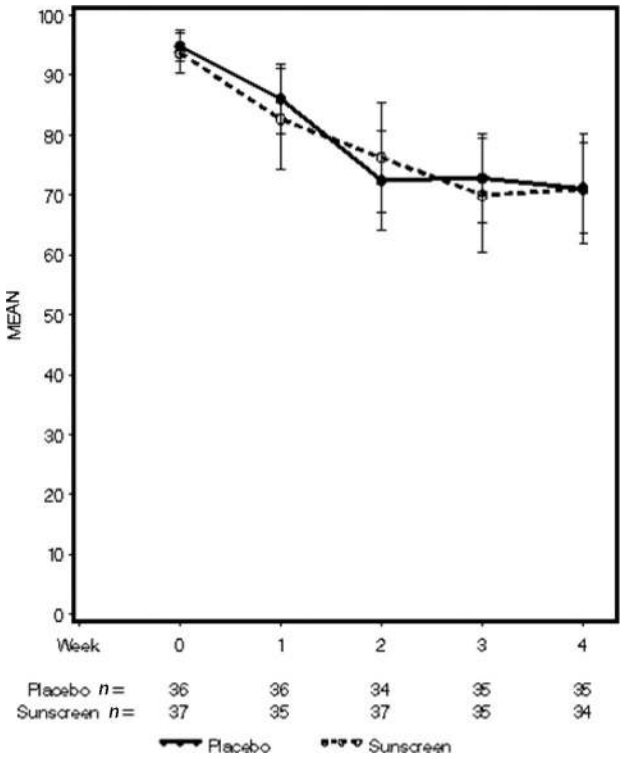

Figure 2. Weekly mean values from the Skindex-16, with bars denoting 95% confidence intervals, showed that quality of life dropped over time and remained comparable between arms.

Quality of Life

The patient-reported Skindex-16 questionnaire did not reveal major differences between the study arms. At baseline, mean scores were in the 90%+ range, providing evidence of high and favorable quality of life with respect to skin-related symptoms. However, mean scores dropped for all symptoms over the duration of the study, indicating a decline in quality of life (Fig. 2). For example, during the intervention, patients reported a >30% drop in quality of life

Table 3. Select adverse events after starting sunscreen/placebo

Adverse events[a]	Sunscreen arm ($n = 50$)[b]	Placebo arm ($n = 46$)[b]	p-value
Anorexia			
0	50 (100)	45 (98)	.48
3	0	1 (2)	
Fatigue			
0	46 (92)	42 (91)	.78
2	3 (6)	1 (2)	
3	1 (2)	3 (6)	
Nausea			
0	49 (98)	44 (96)	.36
2	1 (2)	0	
3	0	2 (4)	
Abdominal pain			
0	49 (98)	46 (100)	1.00
3	1 (2)	0	
Vomiting			
0	50 (100)	44 (96)	.38
3	0	2 (4)	

Numbers in parentheses denote percentages.
[a]As per the Common Terminology Criteria, version 3, and regardless of attribution.
[b]Lower numbers are related to patient dropout.

with respect to itching and burning/stinging over all time points, regardless of study arm (data not shown). They also reported a >30% change to indicate more worry about their skin condition and a >30% change to indicate embarrassment over their skin condition (data not shown). Overall, the Skindex-16 showed that the patients who participated in this study manifested a decline in quality of life that presumably was related to rash development.

Adverse Events

Finally as expected, the sunscreen was well tolerated with low and nearly identical rates of adverse events in the two study arms (Table 3).

Discussion

Anecdotes abound as to how best to prevent or palliate a rash induced by EGFR inhibitors. The use of sunscreen merited testing not only because of such favorable anecdotes but also because of a seemingly viable hypothesis that tied the EGFR to the healing of sun-induced skin damage. Despite such preliminary data, the present study observed that a sunscreen preparation with an SPF of 60 did not prevent EGFR inhibitor–induced skin rash and did not lessen its severity when prescribed in the context of the current trial. Moreover, constructing a model that attempted to predict rash development on the basis of sunscreen use and other factors related to sun exposure did not provide any other supportive evidence to suggest that sunlight modulates rash development, although admittedly this model did not capture patients' actual degree of sun exposure. Thus, based on these observations, this study suggests that other strategies besides those relevant to sun exposure should be explored to prevent or mitigate EGFR inhibitor–induced rashes.

These negative findings are particularly compelling in view of recent data generated from the Skin Toxicity Evaluation Protocol with Panitumumab trial [10]. That study tested the pre-emptive use of a multi-interventional approach that included sunscreen, a skin moisturizer, a topical steroid, and oral doxycycline. The use of pre-emptive rash therapy (therapy prior to rash development) that included sunscreen resulted in a 50% lower cumulative incidence of grade ≥2 panitumumab-induced rash. In essence, a pre-emptive therapy that included sunscreen resulted in a rash incidence of 29%, as compared with 62% in the arm in which patients received therapy only after rash development. These results are provocative, but in view of the negative findings reported here, one might question whether this multi-interventional approach could be truncated—with the deletion of sunscreen—without a compromise in palliation.

Finally, it should be noted that, despite the negative results reported here, the current study does provide some important observations about quality of life. A variety of symptoms, such as itching, burning/stinging, as well as worry and embarrassment, arose within this cohort and appeared to coincide with rash development. In general, quality of life, as assessed by the Skindex-16, declined in this cohort throughout the duration of this study. This notable decline in quality of life underscores the need to continue to search for interventions that may palliate this skin-related toxicity in patients who are prescribed EGFR inhibitors.

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Author Contributions

Conception/Design: Aminah Jatoi, Abby Thrower, Jeff A. Sloan, Patrick J. Flynn, Nicole Lea Wentworth-Hartung, Shaker R. Dakhil, Bassam I. Mattar, Daniel A. Nikcevich, Paul Novotny, Aleksandar Sekulic, Charles L. Loprinzi
Provision of study material or patients: Aminah Jatoi, Abby Thrower, Jeff A. Sloan, Patrick J. Flynn, Nicole Lea Wentworth-Hartung, Shaker R. Dakhil, Bassam I. Mattar, Daniel A. Nikcevich, Paul Novotny, Aleksandar Sekulic, Charles L. Loprinzi
Collection and/or assembly of data: Aminah Jatoi, Abby Thrower, Jeff A. Sloan, Patrick J. Flynn, Nicole Lea Wentworth-Hartung, Shaker R. Dakhil, Bassam I. Mattar, Daniel A. Nikcevich, Paul Novotny, Aleksandar Sekulic, Charles L. Loprinzi
Data analysis and interpretation: Aminah Jatoi, Abby Thrower, Jeff A. Sloan, Patrick J. Flynn, Nicole Lea Wentworth-Hartung, Shaker R. Dakhil, Bassam I. Mattar, Daniel A. Nikcevich, Paul Novotny, Aleksandar Sekulic, Charles L. Loprinzi
Manuscript writing: Aminah Jatoi, Abby Thrower, Jeff A. Sloan, Patrick J. Flynn, Nicole Lea Wentworth-Hartung, Shaker R. Dakhil, Bassam I. Mattar, Daniel A. Nikcevich, Paul Novotny, Aleksandar Sekulic, Charles L. Loprinzi
Final approval of manuscript: Aminah Jatoi, Abby Thrower, Jeff A. Sloan, Patrick J. Flynn, Nicole Lea Wentworth-Hartung, Shaker R. Dakhil, Bassam I. Mattar, Daniel A. Nikcevich, Paul Novotny, Aleksandar Sekulic, Charles L. Loprinzi

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