Adapalene Gel 0.1% Versus Placebo as Prophylaxis for Anti-Epidermal Growth Factor Receptor-Induced Acne-Like Rash: A Randomized Left-Right Comparative Evaluation (APPEARANCE)

NAKO CHAYAHARA,a TORU MUKOHARA,a,d MOTOKO TACHIHARA,b YOSHIKI FUJISHIMA,a,c ATSUSHI FUKUNAGA,g KEN WASHIO,g MASATSUGU YAMAMOTO,b KYOSUKE NAKATA,b KAZUYUKI KOBAYASHI,b KEI TAKENAKA,a MASANORI TOYODA,a NAOMI KIYOTA,a,d KAZUTOH TOSIMATSU,c HISAYO DOI,e NAOMI MIZUTA,f NAHO MARUGAMI,f ATSUSHI KAWAGUCHI,h CHIKAKO NISHIGORI,g YOSHIHIRO NISHIMURA,b HIRONOBU MINAMIa,d

Divisions of a Medical Oncology and Hematology, b Respiratory Medicine, and c Gastroenterology, Department of Internal Medicine, Kobe University Graduate School of Medicine, Kobe, Japan; d Cancer Center, e Department of Nursing, and f Department of Hospital Pharmacy, Kobe University Hospital, Kobe, Japan; g Division of Dermatology, Department of Internal related, Kobe University Graduate School of Medicine, Kobe, Japan; h Education and Research Center for Community Medicine, Faculty of Medicine, Saga University, Saga, Japan

TRIAL INFORMATION

- UMIN Trial Identifier: UMIN000016692
- Sponsor: Hyogo Prefecture Health Promotion
- Principal Investigator: Toru Mukohara
- IRB Approved: Yes

LESSONS LEARNED

- The results of the APPEARANCE trial indicate that adapalene does not prevent acne-like rash over placebo when added to topical moisturizer and oral minocycline but instead may have a detrimental effect. Therefore, adapalene is not recommended as prophylaxis against acne-like rash induced by anti-epidermal growth factor receptor therapies.
- Given that acne-like rash was completely controlled with placebo in approximately half of patients, predictive measures to identify patients needing intensive prophylaxis are required.

ABSTRACT

Background. Anti-epidermal growth factor receptor (EGFR) therapies are frequently associated with acne-like rash. To evaluate the prophylactic efficacy of adapalene, a topical retinoid used as first-line therapy for acne vulgaris, we conducted a randomized, placebo-controlled, evaluator-blinded, left-right comparative trial.

Methods. Patients with non-small cell lung, colorectal, or head and neck cancer scheduled to receive anti-EGFR therapies were randomly assigned to once-daily adapalene application on one side of the face, with placebo on the other side. All patients had topical moisturizer coapplied to both sides of the face, and received oral minocycline. The primary endpoint was the difference in total facial lesion count of acne-like rash at 4 weeks. Secondary endpoints included complete control rate (CCR) of acne-like rash (≤5 facial lesions) and global skin assessment (Investigator’s Global Assessment [IGA] scale, grade 0–4) at 4 weeks. Two blinded dermatologists independently evaluated the endpoints from photographs.

Results. A total of 36 patients were enrolled, of whom 26 were evaluable. Adapalene treatment was associated with a greater lesion count than placebo at 4 weeks, although the difference was not statistically significant (mean, 12.6 vs. 9.8, p = .12). All four patients with a difference >10 in lesion count between face sides had a greater count on the adapalene-treated side. No significant differences were observed in CCR of acne-like rash (54% vs. 50%) or IGA scale (mean grade, 1.9 vs. 1.7) between the adapalene and placebo sides.

Conclusion. Adapalene is not recommended as prophylaxis against acne-like rash induced by anti-EGFR therapies. The Oncologist 2019;24:885–e413

DISCUSSION

Acne-like rash is the most problematic skin toxicity induced by anti-EGFR therapies. Although the Multinational Association for Supportive Care in Cancer (MASCC) guideline...
gives a grade A recommendation only for oral minocycline or doxycycline as prophylaxis for acne-like rash induced by anti-EGFR therapies, the development of more effective prophylactic measures is required. Because previous reports have suggested that adapalene is effective for the treatment of acne-like rash induced by anti-EGFR therapies, we conducted a placebo-controlled, evaluator-blinded, left-right comparative trial to clarify the prophylactic effect of adapalene against the particular type of acne-like rash.

We enrolled patients with advanced cancers, who were ≥20 years of age, with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and adequate organ function, and who scheduled to receive treatment with an anti-EGFR drug (cetuximab, panitumumab, gefitinib, erlotinib, or afatinib) (Table 1).

Although there were no statistically significant differences in any of the efficacy endpoints between adapalene-treated and placebo-treated sides, there was a tendency for adapalene-treated sides to have worse outcome than placebo-treated sides (Figs. 1–4, Table 2). On the IGA scale, 15 of 26 patients scored equally between the placebo and adapalene sides, and 8 of the remaining 11 patients had a higher score on the adapalene side compared with the placebo side (Tables 3 and 4). Similarly, on the MASSC scale, whereas 16 of 26 patients had the same score for both sides, 8 of the remaining 10 patients had a greater score on the adapalene-treated side compared with the placebo-treated side (Tables 5 and 6).

The most commonly observed skin adverse events other than acne-like rash were dry skin, pruritus, pain, and erythema, and the overall incidence of each adverse event was similar between adapalene- and placebo-treated sides.

To the best of our knowledge, this is the first prospective and randomized study to evaluate the prophylactic effect of adapalene against acne-like rash induced by anti-EGFR therapies. In contrast to our hypothesis, our findings indicate that adapalene should not be recommended for the prevention of acne-like rash induced by anti-EGFR therapies, although its use for the treatment of the particular type of rash may still be considered.

| Trial Information |  |
|---|---|
| **Diseases** | Head and neck cancers, non-small cell lung cancer, and colorectal cancer |
| **Stage of Disease/Treatment** | Metastatic / Advanced |
| **Prior Therapy** | No designated number of regimens |
| **Type of Study – 1** | Phase II |
| **Type of Study – 2** | Randomized |
| **Primary Endpoint** | Left-right difference (the placebo side minus the adapalene side) in total rash count after 4 weeks of therapy |
| **Secondary Endpoints** | IGA scale after 4 weeks |
|  | Incidence of grade ≥2 acne-like rash based on the MASCC scale after 4 weeks |
|  | Interval to the occurrence of acne-like rash based on patient diaries |
|  | Complete control rate of acne-like rash defined as number of facial lesions ≤5 |
Incidence and severity of adverse events according to Common Terminology Criteria for Adverse Events version 4.0
Adherence based on patient diaries

Additional Details of Endpoints or Study Design
The total facial lesion count at 4 weeks following prophylactic treatment with 100 mg oral minocycline for acne-like rash was previously reported to be an average of 61. For the evaluation of half-faces in the present study, the lesion count for a half-face following oral treatment with minocycline was estimated to be 30, with reduction of the rash count to 15 per half-face with concomitant adapalene treatment judged clinically significant. A sample size of 26 has 80% power to detect the mean of paired differences of 15 with an estimated SD of differences of 25 and a significance level of 0.05 using a Wilcoxon signed-rank test. Therefore, the target sample size was set at 30, accounting for several patient discontinuations. The difference between placebo and adapalene sides in rate of complete control of acne-like rash and incidence of grade 2 or higher acne-like rash based on the MASCC scale and dermatologist global assessment using the IGA scale was evaluated using McNemar’s tests and a Wilcoxon signed-rank test, respectively. A p value less than .05 was considered to be statistically significant.

Investigator’s Analysis
Inactive because results did not meet primary endpoint

Drug Information

| Drug 1 |  |
|---|---|
| Generic/Working Name | Adapalene gel 0.1% |
| Trade Name | Differin Gel 0.1% |
| Company Name | Galderma |
| Drug Type | Topical retinoid |
| Route | Topical application |

Schedule of Administration
Patients were randomly assigned to once-daily adapalene application on one side of the face and placebo on the other side before bedtime. All patients also applied topical moisturizer to both sides of the face twice a day and received oral minocycline 100 mg once a day. Topical and oral treatments were started on the same day as initiation of anti-EGFR therapy.

Patient Characteristics

| Number of Patients, Male | 21 |
| Number of Patients, Female | 15 |
| Age | Median (range): 65 (47–82) |
| Performance Status: ECOG | 0 — 12 |
| | 1 — 21 |
| | 2 — 3 |
| | 3 — 0 |
| | Unknown — 0 |

Other

Anti-EGFR drug: cetuximab, 12; panitumumab, 7; afatinib, 11; erlotinib, 4; gefitinib, 2. Concurrent therapy: cytotoxic agent, 18; bevacizumab, 2; monotherapy, 16

Cancer Types or Histologic Subtypes

Non-small cell lung cancer, 17; colorectal cancer, 14; head and neck cancer, 5

Primary Assessment Method

| Title | Primary analysis |
| Number of Patients Screened | 36 |
| Number of Patients Enrolled | 36 |
| Number of Patients Evaluable for Toxicity | 35 |
Number of Patients Evaluated for Efficacy: 26

Evaluation Method: Left-right difference (the placebo side minus the adapalene side) in total rash count after 4 weeks of therapy

Outcome Notes: Mean lesion count, adapalene-treated versus placebo-treated sides, 12.6 versus 9.8, p = .12

Adverse Events: Adapalene Side

| Name                    | NC/NA | 1  | 2  | 3  | 4  | 5  | All grades |
|-------------------------|-------|----|----|----|----|----|-----------|
| Rash acneiform          | 51%   | 43%| 6% | 0% | 0% | 0% | 49%       |
| Dry skin                | 43%   | 54%| 3% | 0% | 0% | 0% | 57%       |
| Pruritus                | 77%   | 23%| 0% | 0% | 0% | 0% | 23%       |
| Pain of skin            | 77%   | 20%| 3% | 0% | 0% | 0% | 23%       |
| Erythema multiforme     | 80%   | 17%| 3% | 0% | 0% | 0% | 20%       |

Although the overall incidence of each adverse event was similar between adapalene- and placebo-treated sides, some grade 2 events were observed only on adapalene-treated sides.

Abbreviation: NC/NA, no change from baseline/no adverse event.

Adverse Events: Placebo Side

| Name                    | NC/NA | 1  | 2  | 3  | 4  | 5  | All grades |
|-------------------------|-------|----|----|----|----|----|-----------|
| Rash acneiform          | 48%   | 49%| 3% | 0% | 0% | 0% | 52%       |
| Dry skin                | 46%   | 54%| 0% | 0% | 0% | 0% | 54%       |
| Pruritus                | 86%   | 14%| 0% | 0% | 0% | 0% | 14%       |
| Pain of skin            | 80%   | 20%| 0% | 0% | 0% | 0% | 20%       |
| Erythema multiforme     | 86%   | 14%| 0% | 0% | 0% | 0% | 14%       |

Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion: Study completed

Investigator’s Assessment: Inactive because results did not meet primary endpoint

Anti-epidermal growth factor receptor (EGFR) therapies, either anti-EGFR monoclonal antibodies (MABs) or EGFR tyrosine kinase inhibitors (TKIs), are commonly used to treat patients with colorectal, non-small cell lung, pancreatic, and head and neck cancers. The acne-like rash that develops mainly on the face and trunk is a particularly problematic toxicity of anti-EGFR therapies because it occasionally leads to diminished quality of life in patients and treatment interruption [1, 2]. Additionally, the severity of the acne-like rash has been reported to correlate with the therapeutic effects of anti-EGFR drugs in some types of cancer [3, 4]. It is therefore critical to optimize the prophylactic management of the acne-like rash induced by these treatments.

Several randomized trials have shown that tetracyclines such as doxycycline and minocycline are useful as prophylaxis against skin toxicity caused by anti-EGFR therapies [5, 6]. For example, prophylaxis with a topical steroid and oral doxycycline was shown to reduce the incidence of grade ≥2 skin toxicities induced by panitumumab, compared with the same treatment given in a reactive manner in the Skin Toxicity Evaluation Protocol with Panitumumab (STEPP) trial [6]. Based on these findings, the Multinational Association for Supportive Care in Cancer (MASCC) guideline gives a grade A recommendation for the use of oral minocycline 100 mg daily or doxycycline 100 mg twice daily as prophylaxis for acne-like rash induced by anti-EGFR therapies [7]. However, the recommendation for prophylaxis with topical hydrocortisone 1% cream remains at grade C [7]. Because regular use of topical corticosteroids can cause various forms of skin toxicity such as skin atrophy and telangiectasia, development of other prophylactic therapies is required.

Adapalene, a naphthoic acid derivative that is used to treat acne vulgaris, has high affinity toward retinoic acid receptors β and γ and may normalize keratinocyte proliferation and differentiation and reduce inflammation [8]. Some case reports and case series have shown that adapalene is effective for the treatment of acne-like rash induced by anti-EGFR therapies [9–11]. In a Japanese phase II trial, the incidence of grade ≥2 skin toxicities during 6 weeks of prophylactic
therapy with topical adapalene and oral minocycline in patients receiving panitumumab was 29.2%, and it was similar to that in the STEPP trial [12]. To date, however, the prophylactic effect of adapalene has not been adequately evaluated, and we therefore conducted the present study. Adapalene unexpectedly did not demonstrate a prophylactic effect on acne-like rash induced by anti-EGFR therapies when coadministered with topical moisturizer and oral minocycline, but instead appeared to have a detrimental effect compared with placebo.

The study design comparing the sides of a patient’s face can eliminate background differences and enable the sample size to be minimized. We used the base of the 0.1% adapalene gel (Differin Gel, Galderma, La Defense, France) as the placebo. Because tiny particles of adapalene can be visualized in the gel, this study was not strictly double-blinded but instead was evaluator-blinded. The dermatologists evaluated the skin condition based on photographic images without seeing the patients and thus minimized the risk of bias.

A somewhat detrimental effect of topical retinoic acid receptor-specific retinoid as prophylaxis for acne-like rash was not entirely unexpected. In a previous study, tazarotene 0.05% cream, another retinoid, was applied to one half of the face only, starting from initiation of cetuximab treatment [5]. Although there were fewer skin eruptions, on average, in the tazarotene group, global assessment by a dermatologist at week 4 was equivalent for both sides in 87% of patients but worse for tazarotene-treated sides in 10% of patients. However, in 14 out of 43 patients (32.6%), tazarotene application was interrupted because of local irritation. We therefore suggest that the unsuccessful outcome of tazarotene prophylaxis might have been attributable to skin-irritating toxicity. We used adapalene in the present study because it is less irritating than tazarotene [13], and evidence of its effect on EGFR inhibitor-induced acne-like rash is accumulating [10–12]. Based on our results, however, adapalene might still have had an irritating effect and render the skin more susceptible to acne-like rash compared with placebo. Our findings, however, do not negate the effect of adapalene for the treatment of acne-like rash induced by anti-EGFR therapies. When used for the treatment of acne-like rash, adapalene is applied as a dot onto each lesion rather than in a planar fashion, as used for prophylactic purposes, and therefore might not irritate normal skin around the lesion.

We estimated that there would be 30 facial lesions on the placebo side based on a study with mainly white subjects, but there were fewer lesions in our study, with a mean of 9.8. Additionally, the complete control rate on the placebo side was 50%, and 42% and 46% of patients had grade 0 or 1 IGA scale and grade 1A or 1B MASCC scale on the placebo side, respectively. This may indicate that East Asians are less susceptible to anti-EGFR therapies, and that a topical moisturizer and oral minocycline may be sufficient treatment for approximately half of the patients. However, the remaining patients may still require prophylactic measures to prevent the development of an acne-like rash.

Our study had several limitations. First, although we evaluated patients who received different EGFR-TKIs and EGFR-MABs together, pathology and the response to adapalene may differ between acne-like rashes depending on the causative agent. In our study, three of four patients with a facial lesion count of >10 on the adapalene-treated side compared with the placebo-treated side received an EGFR-TKI (afatinib for one patient and erlotinib for two patients). Second, because there is no standardized method for lesion counting, the generalizability of our results is limited. However, there was a high consistency in the lesion count by the two evaluators in the present study (Cronbach’s coefficient alpha >0.9).

In conclusion, our findings indicate that adapalene should not be recommended for the prevention of acne-like rash induced by anti-EGFR therapies. Predictive measures to identify patients needing intensive prophylaxis over topical moisturizer and oral minocycline are required. There is also a requirement for more effective and less toxic prophylactic agents than topical corticosteroids.

**ACKNOWLEDGMENTS**

We thank Kayoko Nakano for her work as a clinical research coordinator and Yukari Yamaguchi and Mamoru Okuno for preparing the study drugs. We also thank Clare Cox, Ph.D., and Jodi Smith, Ph.D., from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript. T.M. is currently affiliated with the Department of Breast and Medical Oncology, National Cancer Hospital East, Kashiwa, Japan.

**DISCLOSURES**

Toru Mukohara: Chugai Pharmaceutical (RF); Naomi Mizuta: Eli Lilly Japan KK (E [spouse]); Yoshihiro Nishimura: AstraZeneca (H); Hiroubo Obumi: Novartis, Asahi-Kasei Pharma, Astellas, AstraZeneca, Bayer, Behringer, Bristol-Myers Squibb, Celgene, Chugai, DaiichiSankyo, DaiNipponSumitomo, Eisai, Janssen, Kowa, Kyowa-Kirin, Eli Lilly & Co., Merck Serono, Merck Sharp & Dohme, Nihon Shinyaku, Nippon Chemiphar, Eisai, Ono Yakuhin, Ohtsuka, Pfizer, Sanofi, Shire Japan, Taiho, Taisho-Toyama, Takeda, Teijin Pharma, Yakult, Genomic Health, CSL Behring, Nihon Kayaku (RF, including personal fees and clinical trial support). The other authors indicated no financial relationships.

© AlphaMed Press 2019

**REFERENCES**

1. Joshi SS, Ortiz S, Witherspoon JN et al. Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life. Cancer 2010;116:3916–3923.

2. Wagner UJ, Lacouture ME. Dermatologic toxicities associated with EGFR inhibitors: The clinical psychologist’s perspective. Impact on health-related quality of life and implications for clinical management of psychological sequelae. Oncology (Williston Park) 2007;21:34–36.

3. Salts LB, Mopopol NJ, Loeher PJ Sr et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 2004;22:1201–1208.

4. Perez-Soler R, Chachoua A, Hammond LA et al. Determinants of tumor response and survival with erlotinib in patients with non–small-cell lung cancer. J Clin Oncol 2004;22:3238–3247.

5. Scope A, Agero AL, Dusza SW et al. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-
associated acne-like eruption. J Clin Oncol 2007; 25:5390–5396.

6. Lacouture ME, Mitchell EP, Piperdi B et al. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-Emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:1351–1357.

7. Lacouture ME, Anadkat MJ, Bensadoun RJ et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer 2011;19:1079–1095.

8. Czernielewski J, Michel S, Bouclier M et al. Adapalene biochemistry and the evolution of a new topical retinoid for treatment of acne. J Eur Acad Dermatol Venereol 2001;15(suppl 3):5–12.

9. DeWitt CA, Siroy AE, Stone SP. Acneiform eruptions associated with epidermal growth factor receptor-targeted chemotherapy. J Am Acad Dermatol 2007;56:500–505.

10. Taguchi K, Fukunaga A, Okuno T et al. Successful treatment with adapalene of cetuximab-induced acneiform eruptions. J Dermatol 2012;39:792–794.

11. Tachihara M, Tokunaga S, Tamura D et al. Successful treatment with adapalene for EGFR-TKI-induced acneiform eruptions. Jpn J Lung Cancer 2014;54:978–982.

12. Yanai T, Hashimoto H, Yamazaki N et al. Prophylactic topical adapalene and oral minocycline for panitumumab-induced skin toxicity. Ann Oncol 2012;23:i514–i515.

13. Pariser D, Colon LE, Johnson LA et al. Adapalene 0.1% gel compared to tazarotene 0.1% cream in the treatment of acne vulgaris. J Drugs Dermatol 2008;7(suppl 6):s18–23.
Table 1. Patient demographic and baseline disease characteristics

| Demographics and Characteristics | Patients, n (%) | Evaluable patients, n (%) |
|----------------------------------|----------------|--------------------------|
| Age, median (range), years       |                |                          |
| 65 (47–82)                      | 63 (47–82)     |                          |
| Gender, male                     |                |                          |
| 21 (58.3)                       | 17 (65.4)      |                          |
| ECOG performance status          |                |                          |
| 0                                | 12 (33.3)      | 10 (38.5)                |
| 1                                | 21 (58.3)      | 5 (19.2)                 |
| 2                                | 3 (8.3)        | 1 (3.8)                  |
| Tumor type                       |                |                          |
| Non-small cell lung              | 17 (47.2)      | 13 (50.0)                |
| Colorectal                       | 14 (38.9)      | 9 (34.6)                 |
| Head and neck                    | 5 (13.9)       | 4 (15.4)                 |
| EGFR inhibitor                   |                |                          |
| Cetuximab                        | 12 (33.3)      | 7 (26.9)                 |
| Panitumumab                      | 7 (19.4)       | 6 (23.1)                 |
| Afatinib                         | 11 (30.6)      | 8 (30.8)                 |
| Erlotinib                        | 4 (11.1)       | 3 (11.5)                 |
| Gefitinib                        | 2 (5.6)        | 2 (76.9)                 |
| Concurrent therapy               |                |                          |
| Cytotoxic agent                  | 18 (50.0)      | 12 (46.2)                |
| Bevacizumab                      | 2 (5.6)        | 2 (76.9)                 |
| Monotherapy                      | 16 (44.4)      | 12 (46.2)                |

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Table 2. Rates of complete control of acne-like rash

| Time point | n   | Placebo, n (%) | Placebo side, n (%) | Adapalene side, n (%) | p value
|------------|-----|----------------|---------------------|-----------------------|-------|
| Week 2     | 25  | 15 (60)        | 14 (56)             | 14 (56)               | .56   |
| Week 4     | 26  | 13 (50)        | 14 (54)             | 14 (54)               | .32   |

aDetermined as (the number of faces with an acne-like rash count of 5 or less) / (total number of faces in the efficacy analysis population).

bBased on a McNemar’s test.
Table 3. Dermatologists’ global assessment using the IGA scale

| IGA scale | Placebo side n (%) | Adapalene side n (%) | p valuea |
|-----------|--------------------|----------------------|----------|
| Grade 0   | 4 (15)             | 4 (15)               |          |
| Grade 1   | 7 (27)             | 8 (27)               |          |
| Grade 2   | 6 (23)             | 2 (8)                |          |
| Grade 3   | 9 (35)             | 10 (38)              |          |
| Grade 4   | 0                  | 2 (8)                |          |
| Mean grade| 1.7                | 1.9                  | .43      |

*aBased on a Wilcoxon signed-rank test.
Abbreviation: IGA, Investigator’s Global Assessment.

Table 4. Investigator’s Global Assessment Scale for acne vulgaris

| Grade | Description                                                                 |
|-------|-----------------------------------------------------------------------------|
| 0     | Clear skin with no inflammatory or noninflammatory lesions                  |
| 1     | Almost clear; rare noninflammatory lesions with no more than one small inflammatory lesion |
| 2     | Mild severity; greater than grade 1; some noninflammatory lesions with no more than a few inflammatory lesions (papules/pustules only, no nodular lesions) |
| 3     | Moderate severity; greater than grade 2; up to many noninflammatory lesions and may have some inflammatory lesions, but no more than one small nodular lesion |
| 4     | Severe; greater than grade 3; up to many noninflammatory and inflammatory lesions, but no more than a few nodular lesions |

Table 5. Incidence of grade 2 or higher acne-like rash based on the Multinational Association for Supportive Care in Cancer scale

| Patients with grade 2 or higher | Placebo side n (%) | Adapalene side n (%) | p valuea |
|---------------------------------|--------------------|----------------------|----------|
| Grade 1A                         | 4                  | 4                    | .56      |
| Grade 1B                         | 8                  | 9                    |          |
| Grade 2A                         | 3                  | 1                    |          |
| Grade 2B                         | 8                  | 4                    |          |
| Grade 3A                         | 2                  | 2                    |          |
| Grade 3B                         | 1                  | 6                    |          |

*aBased on a McNemar’s test.

Table 6. Multinational Association for Supportive Care in Cancer scale for papulopustular eruption by epidermal growth factor receptor inhibitors

| Grade | Description                                                                 |
|-------|-----------------------------------------------------------------------------|
| Grade 1 | Grade 1A | Papules or pustules <5; OR 1 area of erythema or edema <1 cm in size         |
| Grade 1 | Grade 1B | Papules or pustules <5; OR 1 area of erythema or edema <1 cm in size AND pain or pruritus |
| Grade 2 | Grade 2A | Papules or pustules 6–20; OR 2–5 areas of erythema or edema <1 cm in size     |
| Grade 2 | Grade 2B | Papules or pustules 6–20; OR 2–5 areas of erythema or edema <1 cm in size AND pain, pruritus, or effect on emotions or functioning |
| Grade 3 | Grade 3A | Papules or pustules >20; OR more than 5 areas of erythema or edema <1 cm in size |
| Grade 3 | Grade 3B | Papules or pustules >20; OR more than 5 areas of erythema or edema <1 cm in size; AND pain, pruritus, or effect on emotions or functioning |