Comparison of Skin Toxic Effects Associated With Gefitinib, Erlotinib, or Afatinib Treatment for Non–Small Cell Lung Cancer

Epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) have been widely used to treat non–small cell lung cancer. Four major skin toxic effects with different incidences have been reported from clinical studies, including acneiform eruption (60%-94%), pruritus (16%-60%), xerosis (4%-38%), and paronychia (6%-12%).1,2 However, a direct comparison of the incidences and severities of the 4 types of skin toxic effects for 3 different EGFR-TKIs in the same patient cohort has been lacking to date.

Methods | This retrospective study was approved by the research ethics committee of National Taiwan University Hospital. We recruited patients within a named patient program for compassionate use before registration who had ever received afatinib treatment for non–small cell lung cancer between November 1, 2007, and April 30, 2013. Most of the patients had received gefitinib or erlotinib hydrochloride treatment before commencing afatinib therapy, although some patients had been prescribed afatinib as their first EGFR-TKI. The dates of our study analysis were November 1, 2013, to December 30, 2014. The inclusion criteria for the present analysis were (1) EGFR-TKI exposure for at least 30 consecutive days, (2) a minimum 30-day washout interval between each drug exposure if 2 or more EGFR-TKIs were used, and (3) clinical follow-up for at least 6 months. Any skin toxic effects occurring during each of the EGFR-TKI exposure periods that fulfilled the inclusion criteria were reviewed retrospectively. A χ² test was used to compare the incidences of skin toxic effects for the different EGFR-TKIs. An unpaired 2-tailed t test was used to compare the number of dermatologic visits during the first 180 days of each drug exposure. P ≤ .05 was considered statistically significant.

Results | Among 146 patients fulfilling the inclusion criteria, 61 patients, 117 patients, and 93 patients had ever received gefitinib, erlotinib, and afatinib, respectively (Figure, A and B). In general, the incidence of acneiform eruption was the lowest but differed significantly among the 3 EGFR-TKIs (9.8% [6 of 61] for gefitinib, 12.8% [15 of 117] for erlotinib, and 39.8% [37 of 93] for afatinib; P < .001) (Figure, C). Similar findings remained significant among 21 patients receiving sequential gefitinib-erlotinib-afatinib treatment courses (Figure, A and D) and among patients whose first EGFR-TKI treatment course fulfilled the inclusion criteria (Figure, A and E). Among patients with treatment courses extending at least 180 consecutive days (Figure, A), we found that afatinib therapy resulted in an earlier onset of paronychia (Table) and more dermatologic visits for any skin toxic effects within the first 180 days. However, this finding was attenuated in patients who developed skin toxic effects (Figure, F).

Discussion | All of our patients who developed skin toxic effects were diagnosed and managed by specialized dermatologists (K.-L.C., Y.-T.C., C.-W.Y., and C.-Y.C.) within integrated oncology clinics based on the recommendations of experts.1 Therefore, their diagnoses are more accurate than those in clinical trials. The earlier onset and higher incidence of paronychia in patients treated with afatinib, which remained significant when considering individual variation or accumulation effect, may be explained by 2 reasons. First, afatinib, which is an irreversible EGFR-TKI exhibiting strong affinity to wild-type EGFR,3 may result in greater skin inflammation. Second, synergistic effects could occur with dual inhibition of EGFR and ERBB2 (formerly HER2 or HER2/neu) by afatinib,4 with 27.5% of patients receiving adjuvant trastuzumab (an ERBB2 monoclonal antibody) manifesting nail toxicity.5 The increased dermatologic visits during the first 6 months of treatment with afatinib seemed to be related to higher incidences of skin toxic effects. The frequencies of dermatologic visits decreased after the first 6 months, demonstrating that skin toxic effects can be managed effectively similarly, regardless of the causative agent. Therefore, aggressive dermatologic care for patients receiving EGFR-TKIs should be mandatory.

Kai-Lung Chen, MD
Chia-Chi Lin, MD, PhD
Yung-Tsu Cho, MD
Che-Wen Yang, MD
Yi-Shuan Sheen, MD
Hsiao-En Tsai, MD
Chia-Yu Chu, MD, PhD

Author Affiliations: Department of Dermatology, National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei (Chen, Cho, Yang, Sheen, Chu); Department of Oncology, National Taiwan University Hospital, Taipei (Lin); Department of Urology, National Taiwan University College of Medicine, Taipei (Lin); Department of Surgery, National Taiwan University Hospital Hsin-Chu Branch, Hsin-Chu City (Tsai).

Accepted for Publication: September 22, 2015.

Corresponding Author: Chia-Yu Chu, MD, PhD, Department of Dermatology, National Taiwan University Hospital, National Taiwan University College of Medicine, 7 Chung-Shan S Rd, Taipei, Taiwan 10002 (chiayu@ntu.edu.tw).


Author Contributions: Drs Chen and Chu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, and interpretation of data: All authors.

Drafting of the manuscript: Chen, Cho, Yang, Sheen, Tsai, Chu.

Critical revision of the manuscript for important intellectual content: Chen, Cho, Yang, Sheen, Chu.

Statistical analysis: Chen, Cho, Yang, Chu.

Obtained funding: Tsai, Chu.

Administrative, technical, or material support: Chen, Lin, Cho, Yang, Sheen, Chu.
Figure. Study Design and Comparison of Skin Toxic Effects Associated With Gefitinib, Erlotinib Hydrochloride, or Afatinib Treatment

A and B. Study design and patient enrollment. C-E. Comparison of the incidence of 4 major skin toxic effects. F. Comparison of the total dermatologic visits for any kind of skin toxicity within the first 180 days of drug exposure. A indicates afatinib; E, erlotinib; EA, erlotinib-afatinib; EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors; G, gefitinib; GA, gefitinib-afatinib; GE, gefitinib-erlotinib; GEA, gefitinib-erlotinib-afatinib.

Conflict of Interest Disclosures: Dr Chu reported receiving consulting fees, travel support, and payment for lectures from Boehringer Ingelheim and reported receiving honoraria from AstraZeneca and Roche. No other disclosures were reported.
Table. Comparison of the Incidence and Time to Onset of Skin Toxic Effects for EGFR-TKIs Within the First 180 Days of Drug Exposure

<table>
<thead>
<tr>
<th>Skin Toxicity</th>
<th>Gefitinib (n = 40)</th>
<th>Erlotinib Hydrochloride (n = 66)</th>
<th>Afatinib (n = 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence, %</td>
<td>Time to Onset, Median (Range), d</td>
<td>Incidence, %</td>
<td>Time to Onset, Median (Range), d</td>
</tr>
<tr>
<td>Acneiform eruption</td>
<td>42.5 (17 of 40)</td>
<td>37 (13-153)</td>
<td>54.5 (36 of 66)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>52.5 (21 of 40)</td>
<td>31 (7-145)</td>
<td>54.5 (36 of 66)</td>
</tr>
<tr>
<td>Xerosis</td>
<td>42.5 (17 of 40)</td>
<td>43 (13-194)</td>
<td>53.0 (35 of 66)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>7.5 (3 of 40)</td>
<td>101 (70-157)</td>
<td>7.6 (5 of 66)</td>
</tr>
</tbody>
</table>

Abbreviation: EGFR-TKIs, epidermal growth factor receptor tyrosine kinase inhibitors.

* Treatment courses that fulfilled the inclusion criteria and lasted longer than 180 days were selected. There were 3 patients with 3 different EGFR-TKI treatment courses exceeding 180 days, 31 patients with 2 different EGFR-TKI treatment courses exceeding 180 days, and 84 patients with 1 EGFR-TKI treatment course exceeding 180 days. In total, 119 patients with 155 treatment courses were analyzed.

### Observations

**Paradoxical Reaction During a Course of Terbinafine Treatment of Trichophyton interdigitale Infection in a Child**

We describe for the first time, to our knowledge, a paradoxical reaction to terbinafine treatment in the context of dermatophyte infection due to *Trichophyton interdigitale*.

**Report of a Case**

A child weighing 30 kg and without any comorbidities and allergies and not taking any long-term medications was seen for erythematous, infiltrating, well-demarcated skin lesions located on the face, chest, abdomen, and limbs (Figure, A). Mycological culture yielded growth of *Trichophyton mentagrophytes*. The fungus was identified as *T. interdigitale* by sequence analysis of the internal transcribed spacer and the D1/D2 domains of the large-subunit (26S) rRNA gene within the rDNA cluster using the polymerase chain reaction sequencing described elsewhere. The patient reported frequent contact with stray cats.

Initial treatment included 125 mg of terbinafine once daily. Twelve hours after the first dose, we observed temperature elevation (39°C), chills, malaise, aggravation of inflammatory symptoms including increased erythema, edema, and pustule formation (Figure, B). These changes were accompanied by increased erythrocyte sedimentation rate (47 mm/h), elevated C-reactive protein levels (25.8 mg/L), leukocytosis (white blood cell count, 15.390/uL), eosinophilia (eosinophils, 11%), and high IgE level (7200 μg/L). (To convert C-reactive protein to nanomoles per liter, multiply by 9.524; white blood cells to ×10⁹/L, multiply by 0.001; and IgE to milligrams per liter, multiply by 0.001.) Therapy with terbinafine was discontinued for 3 days and oral prednisone was administered (10 mg/d). Terbinafine therapy was reintroduced at the same dose (125 mg/d) for 6 weeks resulting in a complete resolution of skin lesions.

**Discussion**

Among the very few reports of paradoxical or inflammatory drug-related reactions during treatment of fungal infections are those described for *Cryptococcus neoformans* meningoitis or disseminated paracoccidioidomycosis.

Only 1 report to our knowledge has been published on paradoxical reactions during treatment of dermatophyosis. Nikkels et al described inflammatory flare-up reactions in 5 patients with dermatophyte infection undergoing antifungal therapy.

In the present case, we observed high fever, chills, and malaise within 12 hours of the first dose of antifungal treatment. Elevated temperature was accompanied by intensified inflammation and pustule formation within the area of primary lesions, leukocytosis, eosinophilia, increased C-reactive protein levels, and elevated total IgE levels. The reaction symptoms prompted us to categorize it as the Jarisch-Herxheimer reaction (JHR), a well-recognized paradoxical complication of the treatment of syphilis and other infectious diseases, including leprosy, anthrax, meningococcal meningitis, *Pneumocystis carinii* pneumonia, and African trypanosomiasis.

The present case, while sharing some features with the flare-up reaction described by Nikkels et al, is closer to JHR than the earlier report, and this is supported by 2 facts. First, Nikkels et al observed that the inflammatory exacerbation started 12 to 24 hours after drug intake, while a typical JHR occurs at half this time. Second, while JHR is always characterized by systemic signs (fever up to 39°C, malaise, and chills), these were present only in 2 patients with flare-up reactions (both developed the symptoms 24 hours after drug administration).

Although eosinophilia and elevated total IgE level, as evidenced in our case, may suggest an allergy to terbinafine, successful reintroduction of the drug would negate this. The