Team Management of Skin Rash Associated with Use of Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitors

Katsuhiro Masago[1,2], Fumiko Imamichi[3], Yoshio Masuda[4], Noriko Ariga[3], Kiyomi Fujitomi[3], Yoko Fukumine[3], Kana Hatakenaka[3], Shiro Fujita[1,2], Nobuyuki Katakami[2]

[1]Department of Pathology and Molecular Diagnostics, Aichi Cancer Center, Nagoya, [2]Division of Integrated Oncology, Institute of Biomedical Research and Innovation, [3]Nursing Department, Institute of Biomedical Research and Innovation, [4]Division of Pharmacy, Institute of Biomedical Research and Innovation, Kobe, Japan

Corresponding author: Katsuhiro Masago, MD, PhD

Department of Pathology and Molecular Diagnostics, Aichi Cancer Center, Nagoya, Japan

Tel: +81-52-762-6111; Fax: +81-52-757-4810

E-mail: masago@aichi-cc.jp

ABSRTACT

Objective: The aim of this study was to evaluate the effectiveness of a rash team management intervention designed by certified nurses, medical physicians, and certified pharmacists. The quality of life (QOL) of patients administered epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) was assessed using the dermatology life quality index (DLQI) and Skindex-29 QOL questionnaires. **Methods:** A total of 51 patients with nonsmall cell lung cancer who were treated using EGFR-TKIs were examined between November 1, 2014, and October 31, 2015, at the Institute of Biomedical Research and Innovation in Kobe city, Japan. All the patients were treated daily with erlotinib, gefitinib, or afatinib. The common terminology criteria for adverse events (version 4.0) system were used to grade treatment-induced toxicity events. The multimodality rash management team included nurses, pharmacists, and physicians. The team intervened before the initiation of treatment with EGFR-TKIs and at every visit. Patient QOL characteristics were evaluated using the DLQI and Skindex-29 assessment tools. **Results:** The number of patients with high-grade toxicity decreased when the multimodal approach was used. No grade 3 skin toxicities were recorded in the postintervention cohort. QOL scores for symptoms and feelings (emotions) were impaired in patients who were treated with EGFR-TKIs. **Conclusions:** The rash team management approach may be useful for patients treated with EGFR-TKIs. Specific QOL evaluation tools for the assessment of the effects of a team approach for rash management should be developed.

Key words: Epidermal growth factor receptor, skin toxicity, team management, tyrosine kinase inhibitor

Access this article online

Quick Response Code:

Website: www.apjon.org

DOI:
10.4103/apjon.apjon_33_18

Introduction

Recent advances in biomedical research have provided a greater understanding of the molecular bases of diseases. These advances have had significant effects on the therapeutic interventions for advanced non-small cell lung cancers (NSCLCs) with somatic epidermal growth factor receptor (EGFR) mutations.[1-3] As a receptor tyrosine kinase, EGFR expression is readily inhibited by a series of tyrosine kinase inhibitors (TKIs), including gefitinib,[4] erlotinib,[5] and afatinib.[6]

Previous studies found an inverse relationship between rash toxicities and EGFR-TKI efficacy.[7,8] Skin rash is an indicator of EGFR-TKI-induced EGFR pathway inhibition. However, postmarketing surveillance of approximately 1000 patients who were administered erlotinib in Japan revealed that 8.75% of the patients discontinued medication because of the resulting rash, which is reported in the erlotinib postmarketing, large-scale surveillance study Chugai Pharmaceutical Co., Ltd. leaflet or website. Appropriate management of EGFR-TKI-induced skin rash is critical to ensure dose intensity and maintenance of the patient's quality of life (QOL).

We evaluated the effectiveness of a rash team management strategy designed by certified nurses, medical physicians, and certified pharmacists. We used the dermatology life quality index (DLQI) and Skindex-29 QOL questionnaires to assess the QOL of patients administered EGFR-TKIs. The rash team management approach with specific QOL evaluation tools may be useful for patients treated with EGFR-TKIs.

Methods

Patients

A total of 51 patients with NSCLC treated with EGFR-TKI were examined between November 1, 2014, and October 31, 2015, at the Institute of Biomedical Research and Innovation, Kobe city, Japan. The patients were treated daily with erlotinib (150 mg/day initial dose), gefitinib (250 mg/day initial dose), or afatinib (50 mg/day initial dose). Resulting toxicities were graded using the common terminology criteria for adverse events (CTCAE) version 4.0 system, details of which are posted on National Cancer Institute's Web Site (www.nih.gov). The study protocol was approved by the Institute of Biomedical Research and Innovation Research Ethics Committee.

Rash treatment

The multimodality rash management team of nurses, pharmacists, and physicians informed each patient about the potential associated side effects before initiating treatment with an EGFR-TKI. Oral minocycline, a topical alclometasone dipropionate and difluprednate ointment, and a betamethasone valerate lotion with a moisturizing agent were prescribed before initiation of treatment with an EGFR-TKI. Alclometasone dipropionate was used for the face; difluprednate, for the body; and betamethasone valerate, for the scalp. Oral minocycline was used when the effect of a topical agent was unsatisfactory. Team intervention was performed during every follow-up visit (typically 1 week, 2 weeks, 4 weeks, and then every 4 weeks after beginning the treatment with the EGFR-TKI). Each intervention included a precise assessment of any rash using the CTCAE system by nurses before a medical examination by the attending physician and a review of the patient education information by nurses and pharmacists.

Dermatology life quality index and Skindex-29 quality of life assessments

The DLQI was developed in 1994.[9] This index was the first dermatology-specific QOL instrument to be developed. It consists of a simple, validated, 10-question questionnaire. In this study, each question was graded from 0 to 3, with a possible resulting total score ranging from 0 (no effect of skin disease on QOL) to 30 (maximum effect on QOL).

The Skindex-29 questionnaire was used to determine the frequency (never, rarely, sometimes, often, and all the time) during the previous 4 weeks at which the patient experienced the effect described in each item. The symptoms domain included 7 items; the emotional domain, 10 items; and the functioning domain, 12 items. All responses were transformed into a linear scale that ranged from 0 (no effect) to 100 (effect experienced all the time) points. The Skindex scores were reported as three scaled scores. Each score corresponded to one of the three domains. A scale score was the mean value of a patient's responses to the items included in a given domain.[10]

We administered the first set of the two QOL questionnaires to the preintervention cohort between November 1, 2014, and February 28, 2015, (i.e., before any patients met with the rash management team). The two questionnaires were administered to the postintervention cohort between September 1, 2015, and October 31, 2015, after the patients had received the intervention.

Results

All the patients were Japanese. The preintervention cohort consisted of 18 female (56.3%) and 14 male patients (43.7%). Nineteen patients received erlotinib. Eight patients were treated with afatinib. The remaining patient was treated with gefitinib. Analysis of the preintervention cohort EGFR mutation status revealed 15 patients with

exon 19, 14 patients with L858R, and three patients with other (2 G719A and 1 L861Q) deletions. The postintervention cohort consisted of 15 male (55.6%) and 12 female patients (44.4%). Eleven patients received afatinib treatment. Nine patients were treated with erlotinib. The remaining patient received gefitinib treatment. In the postintervention cohort, 17 patients had an exon 19 deletion, 9 had an L858R deletion, and 1 had a G719S deletion.

The results of the CTCAE skin toxicity grading are presented in Table 1. The number of patients with high-grade toxicity was decreased in the postintervention cohort as compared with the preintervention cohort. No grade 3 skin toxicities were found in the postintervention cohort.

The total scores and scores in the six categories (symptoms and feelings, daily activities, leisure, work or studying, personal relationship, and treatment) of the DLQI are presented in Table 2. The total scores and results for the three categories (symptoms, functions, and emotions) of the Skindex-29 instrument are presented in Table 3. No statistically significant changes in scores were found in the eight patients in both the pre- and postintervention cohorts,

but the total mean DLQI score ranged from higher to lower for afatinib, erlotinib, and gefitinib, respectively. The total median Skindex-29 score also ranged from higher to lower for afatinib, erlotinib, and gefitinib, respectively. The Skindex-29 results indicated that the score for emotion improved in the patients treated with erlotinib or afatinib. These QOL scores indicated that symptoms and feelings were impaired in the patients who received treatment with EGFR-TKIs.

Discussion

This study demonstrates the usefulness of the multimodal rash team management intervention for patients treated with an EGFR-TKI. The incidence of grade 3 skin toxicity was reduced in the postintervention cohort. QOL scores tended to improve in the patients treated using the rash management team approach, especially those for emotion. These findings are similar to those of a prospective Phase III trial.[11] In other words, compared with management by only the attending physician, team management enabled early detection of skin side effects and appropriate intervention for skin rash.

EGFR-TKIs are generally less toxic than conventional cytotoxic agents. However, EGFR-TKIs are associated with some TKI-specific adverse events, including skin toxicities, which require careful management. Adverse skin reactions occur in >50% of patients administered EGFR-TKIs because EGFR is expressed on skin cells and EGFR-TKIs inhibit wild-type EGFRs[12] on skin.[13-15] These adverse skin effects are rarely life-threatening, but the skin rash may affect the QOL by causing physical discomfort and psychological distress. These negative patient experiences may lead to dose reduction or discontinuation of the EGFR-TKI treatment. Racca *et al.* found that cooperation between oncological and dermatologic specialist's results in correct identification and treatment of EGFR cutaneous side effects. This intervention would improve the QOL of

Table 1: Common Terminology Criteria for Adverse Events grading of skin toxicities in patients treated using epidermal growth factor receptor-tyrosine kinase inhibitors before and after intervention by a rash management team

Details of skin toxicities	Rash acneiform (%)	Dry skin (%)	Paronychia (%)	Pruritus (%)
Preintervention				
Grade 1	19 (59.3)	10 (31.3)	5 (15.6)	16 (50.0)
Grade 2	4 (12.5)	15 (46.9)	3 (9.4)	3 (9.4)
Grade 3	1 (3.1)	3 (9.4)	4 (12.5)	1 (3.1)
Postintervention				
Grade 1	13 (48.1)	11 (40.7)	5 (18.5)	9 (33.3)
Grade 2	5 (18.5)	9 (33.3)	2 (7.4)	0
Grade 3	0	0	0	0

Table 2: Dermatology life quality index scores for patients with treated using epidermal growth factor receptor-tyrosine kinase inhibitors before and after intervention by a rash management team

DLQI (*n*)	Total average (range) (0-30)	Symptoms and feelings (0-6)	Daily activities (0-6)	Leisure (0-6)	Work or studying (0-3)	Personal relationship (0-6)	Treatment (0-3)
Preintervention							
Total (32)	3.281 (0-19)	1.333 (0-5)	0.9 (0-5)	0.5 (0-6)	0.167 (0-3)	0.033 (0-1)	0.438 (0-2)
Gefitinib (5)	1.6 (0-4)	1 (0-3)	0	0.2 (0-1)	0	0	0.4 (0-1)
Erlotinib (19)	3.526 (0-19)	1.353 (0-5)	1.118 (0-5)	0.647 (0-6)	0.177 (0-3)	0.059 (0-1)	0.368 (0-2)
Afatinib (8)	3.75 (0-9)	1.5 (0-3)	1 (0-3)	0.375 (0-1)	0.25 (0-2)	0	0.625 (0-2)
Postintervention							
Total (*n*=27)	3.556 (0-13)	1.370 (0-4)	1.074 (0-6)	0.704 (0-3)	0	0.074 (0-1)	0.333 (0-2)
Gefitinib (7)	2.143 (0-8)	1 (0-2)	0.571 (0-2)	0.286 (0-2)	0	0	0.286 (0-2)
Erlotinib (9)	3.778 (1-8)	1.444 (1-3)	0.889 (0-3)	1 (0-3)	0	0.111 (0-1)	0.333 (0-1)
Afatinib (11)	4.273 (0-13)	1.546 (0-4)	1.546 (0-6)	0.727 (0-3)	0	0.091 (0-1)	0.346 (0-1)
DLQI: Dermatology Life Quality Index							

Table 3: Skindex-29 score in patients with treated with epidermal growth factor receptor-tyrosine kinase inhibitors before and after intervention by a rash management team				
Skindex-29 (*n*)	Overall median (0-100)	Symptoms (0-100)	Functions (0-100)	Emotions (0-100)
Preintervention				
Total (32)	16.380	21.429	10.417	16.25
Gefitinib (5)	5.172	17.857	0	2.5
Erlotinib (19)	17.241	21.429	10.417	15
Afatinib (8)	19.397	23.214	14.583	22.5
Postintervention				
Total (*n*=27)	15.517	25	10.417	12.5
Gefitinib (7)	8.621	25	4.1667	10
Erlotinib (9)	15.517	21.429	10.417	12.5
Afatinib (11)	21.551	25	20.833	20

patients with metastatic colorectal cancer treated with an anti-EGFR monoclonal antibody and cetuximab-containing regimen.[16] Few studies have been performed to determine whether similar results occur in patients with NSCLC treated with EGFR-TKIs.[17] However, during recent years, team management intervention designed by certified nurses, medical physicians, and certified pharmacists, with the goal of reducing diarrhea and rash severity, has become more common in Japan.

These skin rashes are difficult to resolve using appropriate management because of the characteristics of EGFR-TKIs, which inhibit wild-type EGFR expression.[18] However, a Phase III trial revealed that preemptive skin treatment reduced the incidence of skin-specific toxicities of ≥ grade 2 and resulted in less QOL impairment.[11] Our study also revealed that skin-specific toxicities of ≥ grade 2 were not present in the postintervention cohort. This result indicates that appropriate management of skin rashes may improve treatment compliance in patients receiving EGFR-TKIs.

Joshi *et al.* reported that EGFR-TKI-related skin toxicities affect the QOL score evaluated using the Skindex-16 instrument.[19] To achieve good treatment compliance, maintaining good QOL is highly important in patients receiving EGFR-TKIs. However, no appropriate methods have been established to evaluate the degree to which skin condition affects patient QOL during TKI therapy. We used the DLQI and Skindex-29 instruments for evaluation of skin QOL because their usefulness as QOL assessment and treatment evaluation tools in patients with acne has previously been reported.[12,20] The study revealed no statistically significant changes in the QOL scores evaluated using the DLQI or Skindex-29 questionnaires between the pre- and post-intervention cohorts. However, these QOL scores were impaired according to the degree of wild-type EGFR inhibition owing to the half maximal inhibitory concentration of each TKI. Symptoms and

feelings (i.e., emotions) were impaired in the patients treated with an EGFR-TKI, which may indicate the usefulness of these QOL tools for evaluation of the current status of patients treated with an EGFR-TKI. Specific QOL evaluation tools that can be used to evaluate factors that vary during the rash management process should be developed.

Limitations

This study had several limitations. The study design included a small sample size and was retrospective in nature. Completion of QOL questionnaires was inconvenient for tumor-bearing patients. Prospective evaluation of repeated QOL scores in a large number of patients treated with EGFR-TKIs should be performed. This type of evaluation may be more likely after the development of a more specific QOL questionnaire.

Conclusion

This study revealed that the incidence of grade 3 skin toxicities was reduced in the postintervention cohort. Symptoms and feelings (i.e., emotions) were impaired in the patients treated with an EGFR-TKI. A rash team management may be useful for these patients, and premedication education may be particularly beneficial. Specific QOL evaluation tools that assess the effects of rash management should be developed.

Conflicts of interest

There are no conflicts of interest.

References

1. Gridelli C, de Marinis F, Cappuzzo F, Di Maio M, Hirsch FR, Mok T, *et al.* Treatment of advanced non-small-cell lung cancer with epidermal growth factor receptor (EGFR) mutation or ALK gene rearrangement: Results of an International Expert Panel Meeting of the Italian Association of Thoracic Oncology. Clin Lung Cancer 2014;15:173-81.
2. Shigematsu H, Lin L, Takahashi T, Nomura M, Suzuki M, Wistuba II, *et al.* Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 2005;97:339-46.
3. Ulivi P, Zoli W, Capelli L, Chiadini E, Calistri D, Amadori D, *et al.* Target therapy in NSCLC patients: Relevant clinical agents and tumour molecular characterisation. Mol Clin Oncol 2013;1:575-81.
4. Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, *et al.* Gefitinib plus best supportive

care in previously treated patients with refractory advanced non-small-cell lung cancer: Results from a randomised, placebo-controlled, multicentre study (Iressa survival evaluation in lung cancer). Lancet 2005;366:1527-37.

5. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, *et al.* Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.

6. Yang JC, Wu YL, Schuler M, Sebastian M, Popat S, Yamamoto N, *et al.* Afatinib versus cisplatin-based chemotherapy for EGFR mutation-positive lung adenocarcinoma (LUX-lung 3 and LUX-lung 6): Analysis of overall survival data from two randomised, phase 3 trials. Lancet Oncol 2015;16:141-51.

7. Liu HB, Wu Y, Lv TF, Yao YW, Xiao YY, Yuan DM, *et al.* Skin rash could predict the response to EGFR tyrosine kinase inhibitor and the prognosis for patients with non-small cell lung cancer: A systematic review and meta-analysis. PLoS One 2013;8:e55128.

8. Melosky B, Hirsh V. Management of common toxicities in metastatic NSCLC related to anti-lung cancer therapies with EGFR-TKIs. Front Oncol 2014;4:238.

9. Finlay AY, Khan GK. Dermatology life quality index (DLQI) – A simple practical measure for routine clinical use. Clin Exp Dermatol 1994;19:210-6.

10. Chren MM. The skindex instruments to measure the effects of skin disease on quality of life. Dermatol Clin 2012;30:231-6, xiii.

11. Melosky B, Anderson H, Burkes RL, Chu Q, Hao D, Ho V, *et al.* 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. J Clin Oncol 2016;34:810-5.

12. Newton JN, Mallon E, Klassen A, Ryan TJ, Finlay AY. The effectiveness of acne treatment: An assessment by patients of the outcome of therapy. Br J Dermatol 1997;137:563-7.

13. Harandi A, Zaidi AS, Stocker AM, Laber DA. Clinical efficacy and toxicity of anti-EGFR therapy in common cancers. J Oncol 2009;2009:567486.

14. Giovannini M, Gregorc V, Belli C, Roca E, Lazzari C, Viganò MG, *et al.* Clinical significance of skin toxicity due to EGFR-targeted therapies. J Oncol 2009;2009:849051.

15. Lynch TJ Jr., Kim ES, Eaby B, Garey J, West DP, Lacouture ME, *et al.* Epidermal growth factor receptor inhibitor-associated cutaneous toxicities: An evolving paradigm in clinical management. Oncologist 2007;12:610-21.

16. Racca P, Fanchini L, Caliendo V, Ritorto G, Evangelista W, Volpatto R, *et al.* Efficacy and skin toxicity management with cetuximab in metastatic colorectal cancer: Outcomes from an oncologic/dermatologic cooperation. Clin Colorectal Cancer 2008;7:48-54.

17. Iwata K, Ryota N, Hikita A, Sando M, Suzuki H, Tamiya M, *et al.* Retrospective analysis of the afatinib clinical pathway during the 28-day introductory period-the Japanese style of collaborative drug therapy management (J-CDTM). Gan To Kagaku Ryoho 2015;42:967-72.

18. Cross DA, Ashton SE, Ghiorghiu S, Eberlein C, Nebhan CA, Spitzler PJ, *et al.* AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer. Cancer Discov 2014;4:1046-61.

19. Joshi SS, Ortiz S, Witherspoon JN, Rademaker A, West DP, Anderson R, *et al.* Effects of epidermal growth factor receptor inhibitor-induced dermatologic toxicities on quality of life. Cancer 2010;116:3916-23.

20. Lasek RJ, Chren MM. Acne vulgaris and the quality of life of adult dermatology patients. Arch Dermatol 1998;134:454-8.