Contents lists available at ScienceDirect

Respiratory Investigation

journal homepage: www.elsevier.com/locate/resinv

Original article

Clinical impact of minocycline on afatinib-related rash in patients with non-small cell lung cancer harboring epidermal growth factor receptor mutations

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ARTICLE INFO

Article history:
Received 21 February 2017
Received in revised form
20 September 2017
Accepted 15 November 2017

Keywords:
Afatinib
Rash
Minocycline
Tetracycline
Epidermal growth factor inhibitor

ABSTRACT

Background: The management of skin toxicity is crucial for efficient afatinib treatment, but the role of tetracycline class antibiotics (TCs) in managing these rashes is relatively unknown.

Methods: We reviewed the clinical records of patients who were administered afatinib for the treatment of non-small cell lung cancer harboring epidermal growth factor receptor mutations between October 2014 and November 2016. Twenty-five patients, who received TCs for the management of afatinib-related skin disorders, were enrolled.

Results: Minocycline was administered orally to participants. Afatinib-related toxic effects, such as rash, diarrhea, and paronychia, were observed in 92%, 92%, and 40% of cases, respectively. Although 24% of diarrhea and 4% of paronychia cases were rated grade 3 or higher, no severe cases of rash were observed during afatinib treatment. Of the 18 afatinib dose reductions, 14 (78%), three (17%), and one (6%) resulted from diarrhea, paronychia, and stomatitis, respectively; no patients required a dose reduction because of rash. When minocycline treatment started, 21 patients (84%) had a rash of grade 1 or less, and three patients had a grade 2 rash. A response to afatinib was observed in 18 patients (72%) and the median duration of afatinib administration was 501 days. An adverse event related to minocycline (grade 1 nausea) was observed in one patient.

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https://doi.org/10.1016/j.resinv.2017.11.009

Please cite this article as: Goto A, et al. Clinical impact of minocycline on afatinib-related rash in patients with non-small cell lung cancer harboring epidermal growth factor receptor mutations. Respiratory Investigation (2017), https://doi.org/10.1016/j.resinv.2017.11.009

Conclusions: A large proportion of the study patients started minocycline before grade 2 rash development and the severity of afatinib-related rash was lower than that previously reported. Oral TCs may be beneficial, especially if started early.

1. Introduction

The introduction of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) dramatically altered the treatment strategy for metastatic non-small cell lung cancer (NSCLC) harboring EGFR mutations. Three EGFR-TKIs (gefitinib, erlotinib, and afatinib) are currently available in Japan as first-line therapies. A recent randomized phase II trial demonstrated that afatinib, which irreversibly inhibits human EGFR (HER) 1, 2, and 4 signaling, exerted superior anticancer efficacy to that of gefitinib [1], whereas another study did not reveal differences in the efficacy between gefitinib and erlotinib in NSCLC harboring EGFR mutations [2]. In contrast, more frequent and severe reports of toxicity, especially involving the skin, may limit the benefits of afatinib in clinical practice [1,3–5].

Topical antibiotics or topical corticosteroids are generally recommended for the initial treatment of mild cases (grade 1) of EGFR inhibitor-related skin rash. If the rash is more severe (grade 2 or higher), oral antibiotics, mainly tetracycline class antibiotics (TCs), which include tetracycline, doxycycline, and minocycline, should be prescribed in accordance with several guidelines and recommendations [6–12]. However, most clinical trials about EGFR inhibitor-related skin rashes have been small, and recommendations are made largely based on expert opinion. Although recent phase III trials showed that the treatment of grade 2 erlotinib-related rash with topical clindamycin and corticosteroids, with or without oral minocycline, suppressed skin rash expansion compared with control treatment [13], there are no clear directions for the treatment of EGFR inhibitor-related skin rash.

The prophylactic use of oral antibiotics is one of the most promising strategies for the suppression of EGFR inhibitor-related rash. Lacouture *et al.* reported that the prophylactic oral doxycycline administration over 6 weeks suppressed the severity of a rash related to erlotinib for 6 weeks, although there was no difference in rash frequency [14]. The severity of rashes related to afatinib at 4 weeks was also suppressed by a 4-week prophylactic administration of oral tetracycline [15]. Although phase III trials with prophylactic oral minocycline treatment for 4 weeks did not suppress the maximum severity of erlotinib-related rashes during the whole erlotinib treatment period [13], these trials indicated that oral TCs suppressed EGFR inhibitor-related rash at least for the duration of their administration [8,15].

Blocking EGFR signaling results in rashes through the induction of chemokine (C-C motif) ligand 2 (CCL2), CCL3, CCL5, CCL18, chemokine (C-X-C motif) ligand 9 (CXCL9), CXCL10, interferon-α, and interferon-β, which result in the inflammation and stimulation of an immune reaction via the recruitment of neutrophils, lymphocytes, and monocytes [16–18]. Although the mechanism of the suppressive role of TCs in EGFR inhibitor-related rash is unclear, it can be largely explained by the reported anti-inflammatory and immune-modifying effects, including inhibition of neutrophil and lymphocyte recruitment [19–24]. Therefore, there is a possibility that TCs could be more effective in the early phase of the rash, before the disruption of the skin structure.

Thus, we conducted a retrospective investigation of patients who received afatinib and TCs to analyze the frequency and severity of afatinib-related skin toxicities, and the timing and duration of TC administration.

2. Material and methods

2.1. Patient population

We retrospectively reviewed the clinical records of patients who were administered afatinib for the treatment of pathologically proven NSCLC harboring EGFR mutations between October 2014 and November 2016. Of the 34 patients treated with afatinib, we analyzed the data of 25 patients who were administered TCs for the management of afatinib-related skin disorders. The Seirei Mikatahara General Hospital ethics committee approved this study on 11 January, 2017 (#16–45). Study information for participation was publicly disclosed.

2.2. Efficacy and toxicity

The efficacy of afatinib was determined according to the Response Evaluation Criteria for Adverse Events (RECIST) version 1.1. To assess the toxicity, presence, and severity of skin disorders, a retrospective evaluation of paronychia, diarrhea, liver enzyme elevation, appetite loss, nausea/vomiting, stomatitis, and pneumonitis was conducted. The severity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

2.3. Statistical analysis

The median duration of afatinib treatment and minocycline treatment was estimated by using the Kaplan-Meier method. All statistical analyses were computed by using JMP version 5.01a (SAS Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

The patient characteristics are shown in Table 1. Among the 25 enrolled patients, 23 (92%) had performance status (PS)

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