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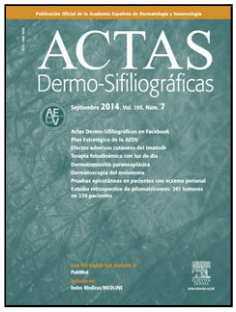

Role of oral tetracyclines in preventing acneiform rash in patients with non–small cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors: a systematic review

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Sección. Review

Role of oral tetracyclines in preventing acneiform rash in patients with non-small cell lung cancer treated with epidermal growth factor receptor tyrosine kinase inhibitors: a systematic review

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Abstract

Introduction: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are the current first-line therapy for non-small cell lung cancer (NSCLC). Acneiform rash is a common adverse effect of this treatment, leading to treatment interruption and affecting the patients' quality of life.

Methods: We conducted a systematic review to assess the role of oral tetracyclines in the prevention of acneiform rash on patients with NSCLC on EGFR TKIs. We conducted a search across Pubmed, Web of Science and Cochrane databases in January 2025. Studies were included if they evaluated prophylactic treatment with oral tetracyclines for acneiform rash in patients with non-small cell lung cancer initiating concomitant epidermal growth factor receptor tyrosine kinase inhibitor therapy.

Results: Two of the 7 selected studies found tetracyclines to reduce all-grade rash – doxycycline (74.2% to 57.2%) and tetracycline (75.6% to 44.5%; $p = 0.046$). Two found tetracyclines did not reduce all-grade rash but were effective in reducing high-grade rash – doxycycline (19% to 4%; $p < 0.001$) and minocycline (28% to 12%; $p = 0.0455$). Single-arm studies reported varying rash incidences rates with minocycline (from 44.8% to 68.3%), inferior to those found in the major trials used for comparison (67% and 77.7%).

Conclusion: Oral tetracyclines appear to reduce the incidence of all-grade acneiform rash or, alternatively, to decrease the incidence of high-grade rash. Preventive treatment for acneiform rash at the initiation of epidermal growth factor receptor tyrosine kinase inhibitor therapy should therefore be considered. Further controlled trials are needed to confirm the efficacy of oral tetracyclines in preventing acneiform rash.

Keywords: Acneiform Rash, Epidermal Growth Factor (EGFR), Non-Small Cell Lung Cancer (NSCLC), Oral Tetracyclines, Prophylactic Treatment, Tyrosine Kinase Inhibitors (TKIs)

Porto, March 2025

Introduction

Lung cancer is the 2nd most common type of cancer worldwide, excluding non-melanoma skin cancer, being the leading cause of dead from cancer. Non-small cell lung cancer (NSCLC) is the most common type of lung cancer [1], accounting for nearly 80% of all lung cancer cases, according to the American Lung Association.

A particular group of NSCLC patients exhibit mutations in the epidermal growth factor receptor (EGFR) and these mutations typically occur in exons 18-21 of the tyrosine kinase domain of the receptor. These sensitizing mutations make these EGFR mutated tumors sensitive to the EGFR tyrosine kinase inhibitors (TKIs) [1], making this class of drugs the first-line therapy for EGFR mutated NSCLC.

Although this class of drugs is generally well tolerated, it has some important cutaneous adverse effects, such as acneiform rash, xerosis and paronychia [2] that can significantly affect the patient's quality of life and lead to dose reduction or in more severe cases, treatment interruption, and have a serious impact on the patients' prognosis. In several reported trials with different generation EGFR TKIS, more than 50% of the patients were affected by any grade of acneiform rash, and around 15% with grade > 3 acneiform rash [3,4,5,6]. This rash consists of papules and pustules, often pruritic and painful, most commonly appearing on the scalp, face, neck and upper trunk [7] 1-to-3 weeks into therapy[8]. According to the Common Terminology Criteria for Adverse Event (CTCAE) v5.0, acneiform rash can be categorized into 5 grades. Grades 1 to 5 vary in terms of percentage of body surface area and associated symptoms. Further details on the grading of acneiform rash can be found in the supplementary data. Acneiform rash has a substantial impact on patients' psychosocial well-being, significantly reducing quality of life, and may be associated with secondary skin infections. In severe cases (grade ≥ 3), it can lead to dose modifications in approximately 70% of patients and treatment discontinuation in up to 30%. [9,10].

[1]Abbreviations

The mechanism through which this drugs cause skin toxicity can be explained by the presence of EGFR in epithelial tissues, where it functions in normal cellular processes, such as proliferation, differentiation, and development [11], and its inhibition prevents intracellular phosphorylation, inhibiting further signalling cascades, promoting inflammatory processes that lead to cutaneous toxicity [12, 13].

First-generation EGFR TKIs, such as erlotinib and gefitinib are characterized by their dose-dependent toxicity resulting from the reversible inhibition of wild-type (WT) EGFR [11]. The second-generation EGFR TKIs, such as afatinib and dacomitinib, bind irreversibly to EGFR and are associated with a higher incidence rate and severity of adverse events vs the recommended doses of first-generation EGFR TKIs [14]. The third generation EGFR TKI, osimertinib, is an irreversible EGFR-TKI and is selective for both EGFR and T790M resistance mutations with activity in the central nervous system (CNS)

[1]CNS – Central Nervous System , CTCAE – Common Terminology Criteria for Adverse Events, EGFR – Epidermal Growth Factor Receptor , ESMO – European Society for Medical Oncology , G≥2 – Grade 2 or higher, G2 – Grade 2 , G3 – Grade 3, NSCLC – Non-Small Cell Lung Cancer, PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses, QoL – Quality of Life , RCT – Randomized Controlled Trial RoB 2 – Cochrane Risk-of-Bias Tool for Randomized Trials, RoBANS 2 – Risk of Bias Assessment Tool for Nonrandomized Studies, TKI – Tyrosine Kinase Inhibitor, WT – Wild-Type

[15]. It is known for causing less dermatologic side effects vs 1st- and 2nd-generations, as it spares WT EGFR [11].

Reactive and preventive measures can act upon these dermatological adverse effects. Some of the preventive measures stablished in the 2021 ESMO clinical practice guidelines for dermatological toxicities related to anticancer agents include avoiding skin irritation with frequent washing with hot water, anti-acne drugs, disinfectants and excessive sun exposure, skin care measures with alcohol free moisturisers and sun protection products and finally, pharmacological measures with oral tetracyclines such as doxycycline and minocycline and, optionally, concomitant treatment with topical corticosteroids, as their benefit is still under discussion[16]. According to these guidelines, these measures reduce the incidence of grade 2 or higher (≥ G2) acneiform rash. In this systematic review, we aimed to evaluate the role of prophylactic oral tetracyclines in reducing the incidence of acneiform rash of any grade in patients with non‑small cell lung cancer receiving epidermal growth factor receptor tyrosine kinase inhibitors. Secondarily, we assessed the impact of acneiform rash on dose reduction and treatment discontinuation and examined whether prophylactic oral tetracycline therapy influences these outcomes.

Methods

Eligibility criteria

This study included randomized controlled trials (RCTs), prospective open-label trials and single-arm prospective studies The language in which it was written was restricted to English. The search was limited to studies published from 2005 through 2025, as the first scientific evidence supporting the efficacy of epidermal growth factor receptor tyrosine kinase inhibitors in the treatment of non–small cell lung cancer emerged around 2003. Since then, both their clinical use and the body of evidence have evolved substantially. Accordingly, a 20-year time frame was considered appropriate and sufficiently comprehensive for the purposes of this study. The studies were included if they had patients with NSCLC who were about to initiate treatment with EGFR TKIs (erlotinib, gefitinib, afatinib, dacomitinib, osimertinib) and were starting at the same time, a preventive treatment with oral tetracyclines due to the appearance of acneiform rash. Studies in which the primary or secondary endpoint was the incidence of acneiform rash were included, whereas studies evaluating exclusively topical preventive treatments were excluded. The primary outcome assessed was the incidence of acneiform rash of any grade.

Search Strategy

A search across the scientific databases PubMed, Cochrane and Web of Science was conducted on January 2025, by 2 authors, using the following terms: "(Prophylactic Treatment OR Preventive treatment OR Pre-emptive treatment) AND Epidermal Growth Factor Receptor-Tyrosine Kinase Inhibitor AND (Skin Toxicities OR Acneiform eruption OR Acneiform Rash) AND Non-small Cell Lung Cancer". Additionally, citations from relevant articles were read as well. A screening phase was conducted by both authors, reading the title and abstract of all extracted articles from the search. From there, all screened articles were assessed for eligibility and were fully read. Those that met the inclusion criteria were included in the review.

Data collection

Data extracted from each study included the incidence of acneiform rash of any grade and of grade 2 or higher, for both the control and intervention arms, which were subsequently compared. Three included studies lacked a control arm; therefore, the incidence of acneiform rash of any grade in these studies was analyzed and compared with rates reported in major clinical trials, including ARCHER 1050[17] and LUX-Lung 8 [18]. Acneiform rash of any grade was defined as grade 0 to 5 rash and encompassed various reported terms, including acneiform rash,[19] rash/acne,[20] skin rash,[21] rash and dermatitis acneiform,[22] rash/folliculitis,[23] and rash.[24],[25] In addition, data were collected on the proportion of patients who required dose reduction or treatment discontinuation of epidermal growth factor receptor tyrosine kinase inhibitor therapy, as well as intervention characteristics, including oral tetracycline dosage, duration of prophylactic treatment, type of epidermal growth factor receptor tyrosine kinase inhibitor used, and its dosage.

Risk of bias

To assess the quality of included trials 2 different tools were used. The version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) was applied to assess the risk of bias of the RCTs and the prospective open-label trials with both control and experimental groups and version 2 of The Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS 2) for the non-randomized, prospective single-arm trials.

Results

Study selection

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) process was followed and the exclusion of the studies at each stage are shown in the flowchart (Figure 1). A total of 55 articles were retrieved from this search and 5 more after reading the citations of relevant articles. After reading title and abstract, a total of 47 articles were excluded, 9 articles were fully read and assessed for eligibility and finally 7 were included in the review. The excluded trials [26][27] appeared to meet all the inclusion criteria; however, they included both NSCLC and GI cancer patients, and treatment with both EGFR TKIs and anti-EGFR monoclonal antibodies, such as cetuximab, without reporting cancer type‐specific results, thereby precluding further analysis.

Included trials

We included a total of 7 trials in our systematic review. All the trials tested for the preventive treatment with oral tetracyclines—4 with minocycline, 2 with doxycycline and 1 with tetracycline—in patients with NSCLC on EGFR TKIS, such as erlotinib, afatinib and dacomitinib. Table 1 illustrates the characteristics of the included studies.

Quality of included trials

The results of the risk of bias assessment using version 2 of the Cochrane risk-of-bias tool for randomized trials (RoB 2) and version 2 of The Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS 2) are shown in Figures 2 and 3, respectively.

The studies assessed through RoB2 had an overall low risk of bias. *Deplanque et al.[23]*, *Arrieta el al.[24], and Melosky et al.[25]*, are open-label trials with a higher risk of observer bias. The single-arm studies, assessed through RoBANS2, have inevitably a

higher risk of confounding due to the lack of a comparable control group. Furthermore, they have a higher risk of observer bias due to their open label nature.

Synthesis of the Results

In 4 of the included trials, the incidence rate of all-grade rash was evaluated and compared between the experimental group on preventive therapy with oral tetracyclines for acneiform rash and the control group, without any form of preventive therapy. The prophylactic intervention was initiated at the start of the EGFR TKI therapy in all trials. The duration of prophylactic therapy until the evaluation of skin toxicities varied across trials (from 4 to 16 weeks), and it is showed individually for each trial in Table 1.

Doxycycline in the dosage of 100mg twice daily was effective preventing the acneiform rash in *Lacouture et al.*[22] in patients on dacomitinib, reducing the incidence rate of all-grade rash from 74.2% in the control group to 57.2% in the doxycycline group, and with a relative risk of rash and dermatitis acneiform of 0.62 and 0.39, respectively. The G≥2 rash incidence rate reported in the control group was 31% and in the doxycycline group, 16.1%. In the study by Deplanque et al,[2 3] among patients receiving erlotinib with prophylactic doxycycline 100 mg daily, the difference in the incidence of all-grade rash between the control group and the doxycycline group was not statistically significant (81% vs 71%; P = .18). Doxycycline decreased the rate of severe rash, with an incidence rate of grade 3 (G3) rash of 19% in the control arm and 4% in the doxycycline arm ($p < 0.001$). These results are shown in Table 2.

Tetracycline, in the dosage of 250 mg administered twice daily reduced the incidence rate of any grade rash (75.6% vs 44.5%; p = 0.046) and G≥2 rash (35.6% vs 15.6%; p = 0.030) in *Arrieta et al.*[24] in patients on afatinib. These results are shown in Table 3.

For minocycline in the dosage of 100 mg twice daily, *Melosky et al.*[25] did not find a reduction in the incidence rate of all-grade rash in patients on erlotinib between the prophylactic treatment arm and the control arm (82 vs 84%; p = 0.8769). However, the incidence rate of G3 rash was significantly different between the control arm and the prophylactic treatment arm (28% and 12%, respectively; p = 0.0455).

Minocycline, 100 mg daily was the prophylactic treatment of the single-arm prospective studies included in this review. Prophylactic treatment was initiated at the same time as the EGFR TKI therapy in all these trials. *Okajima et al.*[20] and *Ichiki et al.*[21] assessed prophylactic treatment with minocycline in patients on afatinib. They found incidence rates of all-grade rash of 50% and 44.80%, respectively, and an incidence rate of G≥2 rash of 20% and 3.4%, respectively. The incidence rate of all-grade rash in the *Lux-Lung 8* [18] trial was 67% and the incidence rate of G≥2 was 6%. This was a trial with patients with NSCLC on afatinib in whom no prophylactic measures for skin adverse effects were taken.

Iwasaku et al.[19] tested prophylactic treatment with 100 mg of minocycline in patients on dacomitinib. The incidence rate of all-grade rash was 68,3% (26.8% for G≥2). In the *ARCHER 1050* [17] trial, the incidence rate of all-grade rash in patients on dacomitinib and without any form of prophylactic treatment for dermatologic adverse effects was 77,7% (25,3% for G≥2). The results regarding minocycline are shown in Table 4.

Furthermore, dose reduction and treatment discontinuation were analyzed across the studies and the data is shown in Tables 5 through 6. The available data were somewhat heterogeneous. In 3 randomized clinical trials,[22-24] information on dose reductions was reported for both the control and intervention groups, without specification of the underlying cause. Dose reduction was higher in the control group vs the experimental group in *Deplanque et al.*[23] [43% vs 25% (p = 0.02)]. In *Arrieta et al.*[24], however, dose reduction was lower in the control group vs the experimental group [46.6% vs 53.4% (p = 0.378)], as well as in *Lacouture et al.*[22] (24.2% vs 28.8%). In the study by Melosky et al,[25] the percentages of dose reduction and treatment discontinuation were not reported. In the single-arm studies, we found that in *Iwasaku et al.*[19], dose reduction occurred in 19,5% of patients due to skin toxicities, and in 14,6% of these due to acneiform rash. In the study by Okajima et al,[20] dose reduction occurred in 58.7% of patients for all causes, with 13% attributable to acneiform rash. In the study by Ichiki et al,[21] an overall dose reduction rate of 62% was reported, without further specification.

Data of treatment discontinuation was available in *Iwasaku et al.*[19], occurring in 22.2% of patients due to disease progression; in *Okajima et al.*[20], occurring in 13% of patients due to G4 transaminase elevation, G3 ileitis, G2 paronychia, G2 decrease appetite and G2 diarrhoea, and in *Lacouture et al.*[22] occurring in 22.7% of patients from the control group and 18.2% of patients from the experimental group, without specification of the cause.

Discussion

Summary of evidence

This systematic review included a total of 7 trials, all testing for the prevention of skin toxicities with oral tetracyclines in patients with NSCLC on EGFR TKIs.

Among the 4 trials comparing a control arm with an oral tetracycline arm, 2 demonstrated a significant reduction in the incidence of all-grade rash with oral tetracyclines. In the remaining 2 trials, the difference in all-grade rash incidence between groups was not statistically significant; however, prophylactic treatment was associated with a reduced incidence of severe rash. All comparative trials reported oral tetracyclines to be well tolerated. In the single-arm studies, the overall incidence of all-grade rash was lower than that reported in the major comparator trials, ARCHER 1050[17] and LUX-Lung 8[18]. Oral tetracyclines were also well tolerated in these studies.

Regarding dose reduction and treatment discontinuation, the heterogeneity of the results makes it difficult to analyze any possible patterns.

We can state that there is a significant percentage of patients who undergo dose reduction when on EGFR TKIs and an important part is due to skin toxicities, such as acneiform rash. Thus, dose reduction is a real issue with this therapy. Regarding the impact of tetracyclines in dose reduction, one trial found that the group exposed to oral tetracyclines had less dose reductions and 2 found the control group to have less dose reductions, so we cannot securely state that oral tetracyclines reduce the percentage of dose reduction in these patients.

Treatment discontinuation is also an important issue. It occurs in a significant percentage of patients. In our review, 1 trial found that in patients on prophylactic treatment with oral tetracyclines there was a smaller percentage of treatment discontinuation vs the control group.

When a patient is starting treatment with an EGFR TKI, the possibility of developing a rash, and even a severe rash is > 50% and 15% respectively. Reducing the chances of this event should be a priority for the physician since these adverse effects have such an impact on patients' lives and can strongly affect treatment adherence. Taking into consideration that oral tetracyclines are well tolerated by patients, starting an oral tetracycline concomitantly with EGFR TKI treatment should be considered by their physicians.

Limitations

This study is a systematic review without meta-analysis, which has on its own several limitations. A meta-analysis was not performed because of heterogeneity in the extracted data and insufficient data for pooling. This decision inevitably limited the statistical power of the review – a qualitative analysis was performed, making it harder to identify overall trends or even the size of the effects across the studies. The studies included had different outcome measures and different primary and secondary endpoints, making it challenging to draw definitive conclusions; our interpretation is more prone to bias vs a meta-analysis, since conclusions depend on a qualitative assessment rather than statistical aggregation; there is no formal assessment of heterogeneity without the meta-analysis that could provide this assessment through statistical tests such as I^2; publication bias was not assessed either; finally, without the meta-analysis it is harder to generalize our conclusions, making it harder for physicians to rely on them.

Moreover, our trials assessed prophylactic treatment with different oral tetracyclines – 4 with minocycline, 2 with doxycycline and 1 with tetracycline-, and the dosage of each antibiotic also deferred from minocycline – 50 mg twice daily, 100 mg daily and 100 mg twice daily-, doxycycline – 100 mg daily and 100 mg twice daily –, and tetracycline 250 mg twice daily. This heterogeneity makes it difficult to assess the true preventive effect of oral tetracyclines, producing confounding by type of tetracycline and its dosage and performance bias.

Furthermore, 3 of our included studies were single-arm prospective studies, and we have no control group to draw comparisons and conclusions. We qualitatively analyzed and compared the incidence rate of all-grade rash with major trials such as ARCHER1050 [17] and Lux-Lung 8 [18]. The absence of direct comparisons limits the ability to attribute differences in rash incidence solely to the intervention rather than to potential confounding factors, such as patient characteristics. Moreover, comparisons with major trials may involve dissimilar populations, which could influence outcome incidence and result in overestimation or underestimation of the effect of prophylactic oral tetracycline treatment.

Aside from dose reduction and treatment discontinuation, the impact on QoL would have been an interesting parameter to analyze. However, only 2 of our studies had QoL data, which is the reason why we decided to not include this parameter. Regarding dose reduction and treatment discontinuation, the heterogeneity of the collected data did not allow us to draw clear conclusions.

In addition, in our search we did not find any study or trial testing for the preventive therapy of acneiform rash or any form of skin toxicity in patients on osimertinib, which is currently the first-line therapy for EGFR mutated NSCLC.

There is, however, an ongoing phase II trial [28] assessing the impact of enhanced management of patients on oral tetracyclines – doxycycline and minocycline – on first-

line amivantamab, an anti-EGFR and anti-MET antibody that seems to have an even bigger risk of skin toxicity.

Conclusions

Acneiform rash is among the most common side effects of EGFR TKI therapy, affecting the patients' quality of life and leading to dose reduction or even treatment discontinuation when the rash is severe. Oral tetracyclines, which are generally well tolerated, appear to reduce the incidence of all-grade rash or, alternatively, to decrease the incidence of high-grade rash. Preventive treatment for acneiform rash at the initiation of epidermal growth factor receptor tyrosine kinase inhibitor therapy should therefore be considered.

The 2021 ESMO clinical practice guidelines on the management of dermatological toxicities associated with anticancer therapies shed light on the importance of addressing this issue when initiating therapy with EGFR TKIS, stating that these measures can decrease the incidence rate of G>2 rash [16]. Given the heterogeneity of the included trials and their results, further investigation through prospective, controlled studies is needed to clarify the role of prophylactic oral tetracyclines in reducing the incidence of all-grade rash and to inform the development of robust guidelines and protocols for the prevention of skin toxicity, thereby supporting broader implementation of these preventive measures.

Furthermore, we acknowledge that more recent studies on the upcoming and first-line therapies are required to confirm the safety and efficacy profile of oral tetracyclines in the prevention of acneiform rash, as well as its impact on the percentage of dose reduction and treatment discontinuation.

References

[1] Miao D, Zhao J, Han Y, Zhou J, Li X, Zhang T, et al. Management of locally advanced non-small cell lung cancer: State of the art and future directions. Cancer Commun (Lond). 2024 Jan;44(1):23-46. doi: 10.1002/cac2.12505. Epub 2023 Nov 20. PMID: 37985191; PMCID: PMC10794016.

[2] Zhao Y, Cheng B, Chen Z, Li J, Liang H, Chen Y, et al. Toxicity profile of epidermal growth factor receptor tyrosine kinase inhibitors for patients with lung cancer: A systematic review and network meta-analysis. Crit Rev Oncol Hematol. 2021 Apr;160:103305. doi: 10.1016/j.critrevonc.2021.103305. Epub 2021 Mar 20. PMID: 33757838.

[3] Wu YL, Zhou C, Hu CP, Feng J, Lu S, Huang Y, et al. Afatinib versus cisplatin plus gemcitabine for first-line treatment of Asian patients with advanced non-small-cell lung cancer harbouring EGFR mutations (LUX-Lung 6): an open-label, randomised phase 3 trial. Lancet Oncol. 2014 Feb;15(2):213-22. doi: 10.1016/S1470-2045(13)70604-1. Epub 2014 Jan 15. PMID: 24439929.

[4] Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. Lancet Oncol (2012) 13:239–46. doi: 10.1016/S1470-

[5] Soria JC, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, et al; LUX-Lung 8 Investigators. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous

cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2015 Aug;16(8):897-907. doi: 10.1016/S1470-2045(15)00006-6. Epub 2015 Jul 5. PMID: 26156651.

[6] Cheng Y, Mok TS, Zhou X, Lu S, Zhou Q, Zhou J, et al. Safety and efficacy of first-line dacomitinib in Asian patients with EGFR mutation-positive non-small cell lung cancer: Results from a randomized, open-label, phase 3 trial (ARCHER 1050). Lung Cancer. 2021 Apr;154:176-185. doi: 10.1016/j.lungcan.2021.02.025. Epub 2021 Feb 23. PMID: 33721611.

[7] Obradovic J, Todosijevic J, Jurisic V. Side effects of tyrosine kinase inhibitors therapy in patients with non-small cell lung cancer and associations with EGFR polymorphisms: A systematic review and meta-analysis. Oncol Lett. 2022 Dec 23;25(2):62. doi: 10.3892/ol.2022.13649. PMID: 36644136; PMCID: PMC9827468.

[8] Gorji M, Joseph J, Pavlakis N, Smith S. Prevention and management of acneiform rash associated with EGFR inhibitor therapy: A systematic review and meta-analysis. Asia-Pac J Clin Oncol. 2022;18:526–539. https://doi.org/10.1111/ajco.13740

[9] Balagula Y, Garbe C, Myskowski PL, Hauschild A, Rapoport BL, Boers-Doets CB, et al. Clinical presentation and management of dermatological toxicities of epidermal growth factor receptor inhibitors. Int J Dermatol. 2011 Feb;50(2):129-46. doi: 10.1111/j.1365-4632.2010.04791.x. PMID: 21244375.

[10] Lacouture ME, Anadkat MJ, Bensadoun RJ, Bryce J, Chan A, Epstein JB, et al; MASCC Skin Toxicity Study Group. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer. 2011 Aug;19(8):1079-95. doi: 10.1007/s00520-011-1197-6. Epub 2011 Jun 1. PMID: 21630130; PMCID: PMC3128700.

[11] Singh M, Jadhav HR. Targeting non-small cell lung cancer with small-molecule EGFR tyrosine kinase inhibitors. Drug Discov Today. 2018 Mar;23(3):745-753. doi: 10.1016/j.drudis.2017.10.004. Epub 2017 Oct 12. PMID: 29031620.

[12] Kozuki T. Skin problems and EGFR-tyrosine kinase inhibitor. Jpn J Clin Oncol. 2016 Apr;46(4):291-8. doi: 10.1093/jjco/hyv207. Epub 2016 Jan 29. PMID: 26826719; PMCID: PMC4886131.

[13] Nanba D, Toki F, Barrandon Y, Higashiyama S. Recent advances in the epidermal growth factor receptor/ligand system biology on skin homeostasis and keratinocyte stem cell regulation. J Dermatol Sci. 2013 Nov;72(2):81-6. doi: 10.1016/j.jdermsci.2013.05.009. Epub 2013 Jun 13. PMID: 23819985.

[14] Hsu WH, Yang JC, Mok TS, Loong HH. Overview of current systemic management of EGFR-mutant NSCLC. Ann Oncol. 2018 Jan 1;29(suppl_1):i3-i9. doi: 10.1093/annonc/mdx702. PMID: 29462253.

[15] Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al; AURA3 Investigators. Osimertinib or Platinum-Pemetrexed in EGFR T790M-Positive Lung Cancer. N Engl J Med. 2017 Feb 16;376(7):629-640. doi: 10.1056/NEJMoa1612674. Epub 2016 Dec 6. PMID: 27959700; PMCID: PMC6762027.

[16] Lacouture ME, Sibaud V, Gerber PA, van den Hurk C, Fernández-Peñas P, Santini D, et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. Prevention and management of dermatological toxicities related to anticancer agents:

ESMO Clinical Practice Guidelines☆. Ann Oncol. 2021 Feb;32(2):157-170. doi: 10.1016/j.annonc.2020.11.005. Epub 2020 Nov 25. PMID: 33248228.

[17] Cheng Y, Mok TS, Zhou X, Lu S, Zhou Q, Zhou J, et al. Safety and efficacy of first-line dacomitinib in Asian patients with EGFR mutation-positive non-small cell lung cancer: Results from a randomized, open-label, phase 3 trial (ARCHER 1050). Lung Cancer. 2021 Apr;154:176-185. doi: 10.1016/j.lungcan.2021.02.025. Epub 2021 Feb 23. PMID: 33721611.

[18] Soria JC, Felip E, Cobo M, Lu S, Syrigos K, Lee KH, et al; LUX-Lung 8 Investigators. Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label randomised controlled phase 3 trial. Lancet Oncol. 2015 Aug;16(8):897-907. doi: 10.1016/S1470-2045(15)00006-6. Epub 2015 Jul 5. PMID: 26156651.

[19] Iwasaku M, Uchino J, Chibana K, Tanzawa S, Yamada T, Tobino K, et al. Prophylactic treatment of dacomitinib-induced skin toxicities in epidermal growth factor receptor-mutated non-small-cell lung cancer: A multicenter, Phase II trial. Cancer Med. 2023 Jul;12(14):15117-15127. doi: 10.1002/cam4.6184. Epub 2023 Jun 3. PMID: 37269194; PMCID: PMC10417098.

[20] Okajima M, Miura S, Watanabe S, Tanaka H, Ito K, Ishida T, et al. A prospective phase II study of multimodal prophylactic treatment for afatinib-induced adverse events in advanced non-small cell lung cancer (Niigata Lung Cancer Treatment Group 1401). Transl Lung Cancer Res. 2021 Jan;10(1):252-260. doi: 10.21037/tlcr-20-649. PMID: 33569309; PMCID: PMC7867768.

[21] Ichiki M, Wataya H, Yamada K, Tsuruta N, Takeoka H, Okayama Y, et al. Preventive effect of kampo medicine (hangeshashin-to, TJ-14) plus minocycline against afatinib-induced diarrhea and skin rash in patients with non-small cell lung cancer. Onco Targets Ther. 2017 Oct 24;10:5107-5113. doi: 10.2147/OTT.S145613. PMID: 29123409; PMCID: PMC5661491.

[22] Lacouture ME, Keefe DM, Sonis S, Jatoi A, Gernhardt D, Wang T, et al. A phase II study (ARCHER 1042) to evaluate prophylactic treatment of dacomitinib-induced dermatologic and gastrointestinal adverse events in advanced non-small-cell lung cancer. Ann Oncol. 2016 Sep;27(9):1712-8. doi: 10.1093/annonc/mdw227. Epub 2016 Jun 10. PMID: 27287210; PMCID: PMC6279098.

[23] Deplanque G, Gervais R, Vergnenegre A, Falchero L, Souquet PJ, Chavaillon JM, et al; CYTAR investigators. Doxycycline for prevention of erlotinib-induced rash in patients with non-small-cell lung cancer (NSCLC) after failure of first-line chemotherapy: A randomized, open-label trial. J Am Acad Dermatol. 2016 Jun;74(6):1077-85. doi: 10.1016/j.jaad.2016.01.019. Epub 2016 Mar 4. PMID: 26946985.

[24] Arrieta O, Vega-González MT, López-Macías D, Martínez-Hernández JN, Bacon-Fonseca L, Macedo-Pérez EO, et al. Randomized, open-label trial evaluating the preventive effect of tetracycline on afatinib induced-skin toxicities in non-small cell lung cancer patients. Lung Cancer. 2015 Jun;88(3):282-8. doi: 10.1016/j.lungcan.2015.03.019. Epub 2015 Mar 28. PMID: 25882778.

[25] 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 Mar 10;34(8):810-5. doi: 10.1200/JCO.2015.62.3918. Epub 2015 Nov 16. PMID: 26573073.

[26] Jatoi A, Rowland K, Sloan JA, Gross HM, Fishkin PA, Kahanic SP, et al. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). Cancer. 2008 Aug 15;113(4):847-53. doi: 10.1002/cncr.23621. PMID: 18543329; PMCID: PMC3918166.

[27] Grande R, Narducci F, Bianchetti S, Mansueto G, Gemma D, Sperduti I, et al. Pre-emptive skin toxicity treatment for anti-EGFR drugs: evaluation of efficacy of skin moisturizers and lymecycline. A phase II study. Support Care Cancer. 2013 Jun;21(6):1691-5. doi: 10.1007/s00520-012-1715-1. Epub 2013 Jan 13. PMID: 23314653.

[28] Janssen Research & Development, LLC Clinical Trial, Janssen Research & Development, LLC; Enhanced Dermatological Care to Reduce Rash and Paronychia in Epidermal Growth Factor Receptor (EGRF)-Mutated Non-Small Cell Lung Cancer (NSCLC) Treated First-line With Amivantamab Plus Lazertinib (COCOON). Unpublished results.

Porto, March 2025

Figure 1. PRISMA Flow-chart.

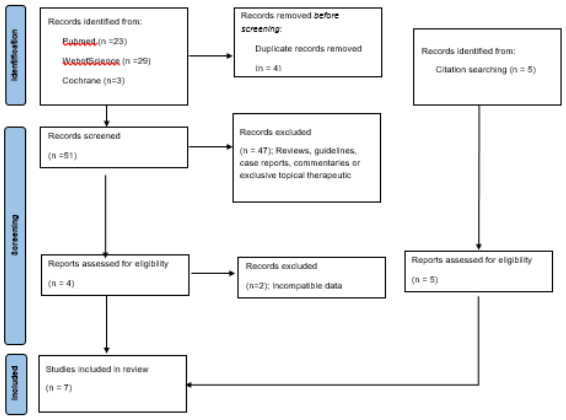

Figure 2. Risk of bias using RoB2.

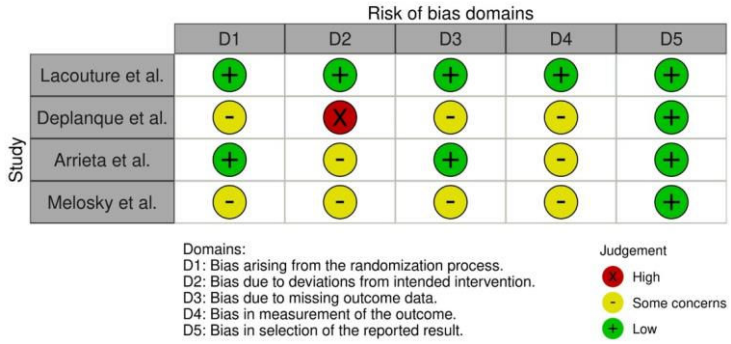

Figure 3. Risk of bias using RoBANS2.

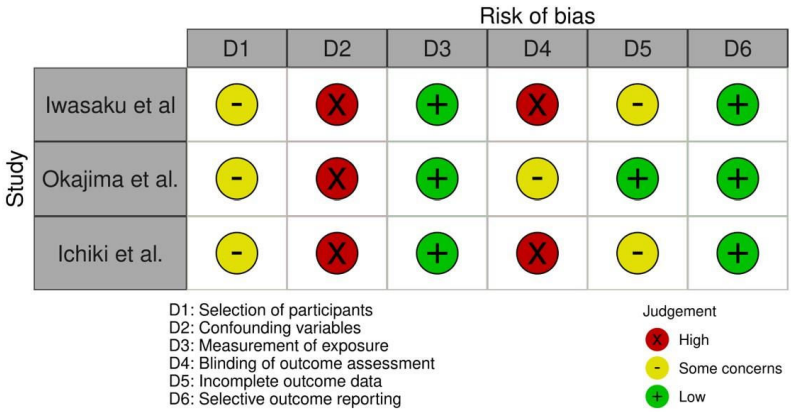

Table 1. Characteristics of included studies. NSCLC, non-small cell lung cancer; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

Study	Year	Patients	Type of Study	EGFR TKI	Type of cancer	Treatment	Duration (weeks)	Control group	Skin toxicity criteria	Incidence of all-grade rash	Incidence of G≥2 rash
Iwasaku et al.[19]	2023	41	Prospective open label	Dacomitinib	NSCLC	Minocycline 100mg daily	8	Single arm	NCI CTCAE	68.3%	26.8%
Okajima et al.[20]	2021	46	Prospective study	Afatinib	NSCLC	Minocycline 100mg daily, loperamide 2mg daily, topical medium-class steroids, and gargling with sodium azulene	4	Single arm	NCI CTCAE	50.00%	20%
Ichiki et al.[21]	2017	29	Prospective multicenter trial	Afatinib	NSCLC	Minocycline 50mg twice daily and TJ-14 7.5 daily	4	Single arm	NCI CTCAE	44.8%	3.4%
Lacouture et al.[22]	2016	122	RCT	Dacomitinib	NSCLC	Doxycycline 100mg twice daily	4	Placebo	NCI CTCAE	Doxycycline group: 57.2% Control group: 74.2%	Doxycycline group: 16.1% Control group: 31%
Deplanque et al.[23]	2016	147	Prospective open label	Erlotinib	NSCLC	Doxycycline 100mg daily	16	No therapy	NCI CTCAE	Doxycycline group: 71% Control group: 81%	Doxycycline group: 4% Control group: 19%
Arrieta et al.[24]	2015	90	Prospective open label	Afatinib	NSCLC	Tetracycline 250mg twice daily	4	No therapy	NCI CTCAE	Tetracycline group: 44.5% Control group: 75.6%	Tetracycline group: 15.5% Control group: 35.6%

Melosky et al.[25]	2015	150	Prospective open label	Erlotinib	NSCLC	Minocycline 100mg twice daily versus reactive treatment with topical clindamycin plus hydrocortisone	4	No therapy	NCI CTCAE	Minocycline group: 84% Reactive treatment group: 84% Control group: 82%	(G3) Minocycline group: 12% Reactive treatment group: 8% Control group: 28%

Table 2. Reduction in the incidence of acneiform rash with doxycycline

			All-grade rash		G≥2 rash	
Study	EGFR TKI	Doxyxcline dosage	Control Group	Doxycycline group	Control Group	Doxycycline group
Lacouture et al	Dacomitinib	100 mg 2x/day	74.2%	57.2%	31%	16,10%
Deplanque et al	Erlotinib	100 mg/ day	81%	71% (p=0.18)	(G3) 19%	4% (p<0.001)

Porto, March 2025

Table 3. Reduction in the incidence of acneiform rash with tetracycline.

			All-grade rash		G≥2 rash	
Study	EGFR TKI	Minocycline dosage	Control Group	Minocycline group	Control Group	Minocycline group
Arieta et al.	Afatinib	250mg 2x/day	75,60%	44,5% (p=0.046)	35,6%	15,6% (p=0.030)
Jatoi et al.	Gefitinib, Cetuximab, others	500mg/day	76%	70% (p=0.61)	55%	17% (p=0.009)

Table 4. Reduction in the incidence of acneiform rash with minocycline.

			All-grade rash		G≥2 rash	
Study	EGFR TKI	Minocycline dosage	Control Group	Minocycline group	Control Group	Minocycline group
Melosky et al	Erlotinib	100mg 2x/day	82,00%	84% (p=0.9769)	(G3) 28%	12% (p=0.0455)

					Lux-Lung 8	
Study	EGFR TKI	Minocycline dosage	All-grade rash	G≥2 rash	All-grade rash	G≥2 rash
Okajima et al	Afatinib	100mg/day	50%	20%	67%	6%
Ichiki et al	Afatinib	100mg/day	44.80%	3.4%		
					Archer 1050	
Iwasaku et al	Dacomitinib	100mg/day	68.3%	26.8%	77.7%	25.3%

Porto, March 2025

Table 5. Results of dose reduction and treatment discontinuation of single-arm studies.

	% Dose reduction			
	Overall (n)	Due to skin toxicities (n)	Due to acneiform rash (n)	Treatment Discontinuation
Iwasaku et al	-----	19,5 % (8)	14.6% (6)	22.2% (9)
Okajima et al	58,7% (27)	-----	13% (6)	13% (6)
Ichiki et al	62% (18)	-----	-----	-----

Table 6. Results on dose reduction and treatment discontinuation of RCTs.

	% Dose reduction (n)		% Treatment Discontinuation (n)	
	Control Group	Experimental Group	Control Group	Experimental Group
Lacouture et al	24.2 % (16)	28.8 % (19)	22.7 % (15)	18.2 % (12)
Deplanque et al	43%	25% [p=0.02]	-----	-----
Arrieta et al	46.6%	53.4% [p=0.378]	-----	-----

Porto, March 2025

Appendix

Appendix A

Skin and subcutaneous tissue disorders					
CTCAE Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
Rash acneiform	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10 - 30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL; papules and/or pustules covering > 30% BSA with or without mild symptoms	Papules and/or pustules covering >30% BSA with moderate or severe symptoms; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated	Life-threatening consequences; papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated	Death
Definition: A disorder characterized by an eruption of papules and pustules, typically appearing in face, scalp, upper chest and back.					
Navigational Note: -					

Appendix A. Grades of acneiform rash according to National Cancer Institute Common Terminology Criteria for Adverse Events

Porto, March 2025