ORIGINAL ARTICLE

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

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Background: Rash is a common epidermal growth factor receptor inhibitor—induced toxicity that can impair quality of life and treatment compliance.

Objective: We sought to evaluate the efficacy of doxycycline in preventing erlotinib-induced rash (folliculitis) in patients with non-small-cell lung cancer.

Methods: This open-label, randomized, prospective, phase II trial was conducted in 147 patients with locally advanced or metastatic non-small-cell lung cancer progressing after first-line chemotherapy, randomized for 4 months with erlotinib alone 150 mg/d per os (control arm) or combined with doxycycline 100 mg/d (doxycycline arm). Incidence and severity of rash, compliance, survival, and safety were assessed.

Results: Baseline characteristics of the 147 patients were well balanced in the intent-to-treat population. Folliculitis occurred in 71% of patients in the doxycycline arm and 81% in the control arm (P = .175). The severity of folliculitis and other skin lesions was lower in the doxycycline arm compared with the control arm. Other adverse events were reported at a similar frequency across arms. There was no significant difference in survival between treatment arms.

Limitations: The open-label design of the study and the duration of the treatment with doxycycline are limitations.

Conclusion: Doxycycline did not reduce the incidence of erlotinib-induced folliculitis, but significantly reduced its severity. (J Am Acad Dermatol http://dx.doi.org/10.1016/j.jaad.2016.01.019.)

Key words: doxycycline; erlotinib; folliculitis; non-small-cell lung cancer; rash.

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The oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor erlotinib (Tarceva, Roche, Basel, Switzerland) is an established second-line monotherapy for advanced non-small-cell lung cancer (NSCLC) in patients with disease progression after first-line platinum-based therapy.[1-3] Erlotinib improves outcomes in patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen,[4] and it was approved recently as first-line treatment for patients with advanced EGFR mutation–positive NSCLC.[5,6] Erlotinib is generally well tolerated and improves tumor-related symptoms and quality of life (QoL).[4,7]

CAPSULE SUMMARY

- Erlotinib-induced folliculitis is a common side effect of epidermal growth factor receptor–targeted agents.
- Doxycycline reduced the severity of erlotinib-induced folliculitis in patients with non-small-cell lung cancer after failure of first-line chemotherapy.
- Prevention of rash is important to improve compliance with treatment to maximize the clinical benefits of epidermal growth factor receptor–targeted therapy.

The most common side effect of EGFR-targeted agents is skin toxicity, including rash (folliculitis or acneiform rash/papulopustular eruption), xerosis, paronychial inflammation, pruritus, hair/eyelash growth disorders, and ocular disorders.[8-10]

Folliculitis—usually mild or moderate—has been reported in 76% of patients treated with erlotinib.[4,8]

The onset of EGFR inhibitor–induced rash usually occurs approximately 1 week after treatment initiation, reaching maximal intensity after 2 to 3 weeks,[9] and symptoms may persist or recur with longer-term treatment,[11] impairing patient QoL and compliance, leading to dose reduction, treatment delay, or withdrawal.[8] In clinical practice, it is important that rash is managed effectively to maximize the benefits of EGFR-targeted therapy.[4]

Oral tetracyclines are potentially effective in the prevention of rash because of their anti-inflammatory effect and activity against *Staphylococcus aureus*, and reduce rash severity in combination with EGFR inhibitors.[12-15]

Here we report the results of a trial conducted to evaluate the efficacy and safety of tetracycline doxycycline in preventing erlotinib-induced folliculitis in patients with advanced NSCLC.

METHODS

Study design

This open-label, randomized, prospective, phase II trial (CYTAR), carried out in 23 sites in France, assessed the efficacy of doxycycline in preventing erlotinib-induced folliculitis during the first 4 months of treatment in patients with NSCLC who failed first-line chemotherapy for advanced disease.

Patients were randomized to erlotinib 150 mg/d per os plus doxycycline (Tolexine Gé Bailleul Biorga Laboratoires, Paris, France) 100 mg/d per os (doxycycline arm), or erlotinib 150 mg/d per os alone (control arm) in a 1:1 ratio. Randomization was centralized via a dedicated Internet site.

Preventive doxycycline treatment started on the day of randomization (day 0) and continued for 4 months and up to 12 months at the investigator's discretion. Erlotinib started on day 1 and was administered for 12 months or until disease progression or unacceptable toxicity, and could be extended beyond 12 months per standard clinical practice. Evaluations were carried out at 14 and 28 days, and 2, 4, 7, 10, and 12 months.

Patients were treated until completion of the posttreatment follow-up period (up to 1 month after the last treatment), death, withdrawal of consent, or loss to follow-up. The maximum duration of patient follow-up was 13.5 months. In both arms, the investigator could treat folliculitis grade 2 or higher (according to National Cancer Institute [NCI]–Common Terminology Criteria for Adverse Events [CTCAE], version 3.0) as appropriate.

NCI–CTCAE criteria specify that a rash involving less than 50% of the body surface area with symptoms is a grade 2, involving greater than or equal to 50% of the body surface area with symptoms is a grade 3, and a more generalized, exfoliative rash is a grade 4.[16]

Patients

Eligible patients were aged 18 years or older, with histologically or cytologically confirmed inoperable locally advanced or metastatic (stage IIIB/IV) NSCLC, and had failed first-line platinum-based chemotherapy. Other inclusion criteria were measurable disease according to Response Evaluation Criteria in Solid Tumors, a set of rules assessing the change in tumor burden (from complete response to disease progression) based on standardized tumor measurements.[17]

Patients had to be graded Eastern Cooperative Oncology Group (ECOG) performance status less than 2 (this scale from 0 [fully active] to 4 [completely disabled] is used by health care professionals to assess how the disease is progressing, how the