Commentary

Treatment strategies of epidermal growth factor receptor inhibitor-induced skin toxicities: pre-emptive or reactive?

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Epidermal growth factor receptor (EGFR) is known to be over-expressed in many different types of cancers, including lung cancer, breast cancer, colorectal cancer, and so on (1). Treatments targeting on EGFR signaling pathway provide better responses in these cancer patients harboring mutations in *EGFR* gene (2,3). However, adverse effects due to these EGFR inhibitors might lead to a poor drug adherence or discontinued usages of these agents (4). Skin toxicities are commonly encountered adverse effects during the treatment of EGFR inhibitors. Four major skin toxicities have been identified, including papulopustular (acneiform) eruptions, xerosis, pruritus, and paronychia. Therefore, management of these skin toxicities has a critical role in reducing patients' discomforts, improving patients' quality of life, maintaining usage of these agents, and further having a better prognosis (5).

Recently, one phase III trial, Pan Canadian Rash Trial (PCRT), provided new insights of management for EGFR inhibitor-induced skin toxicities (6). In brief, this trial enrolled 150 patients and randomly assigned them into three arms: prophylactic treatment arm, reactive treatment arm, and no treatment unless severe arm. In the arm of prophylactic treatment, patients received minocycline 100 mg twice a day for 4 weeks on the initiation of erlotinib therapy. In the arm of reactive treatment, patients were treated at the initiation of skin eruption, while in the arm of no treatment unless severe, patients would only receive treatment when grade 3 toxicity occurred. Under this setting, the trial demonstrated that the incidence of grade 3 skin toxicities was significantly reduced in patients receiving prophylactic or reactive treatment comparing to those with no treatment unless severe, while overall survival was similar among the three arms. However, the incidence of all grades of skin toxicities did not differ. No differences regarding to the incidence and severity of skin toxicities were found between the patients of prophylactic treatment and of reactive treatment except that time to maximal rash and duration of treatment were longer in prophylactic arm. These results were not surprising and were mostly consistent with other previous studies (7,8). Nevertheless, the characteristics of this study made it not easily being overlooked. First, this trial was the first phase III trial evaluating the treatments on EGFR inhibitor-induced skin toxicities. Second, the trial was composed of three treatment arms. Direct comparisons of these arms in one study were lacking before.

Inhibition of EGFR signaling pathway leads to disrupted epidermal differentiation and exacerbated follicular and interfollicular inflammation (9). Minocycline and doxycycline have been well-known for their anti-inflammatory property (10) and have been shown for their efficacy in treating EGFR inhibitor-induced skin toxicities (7,8). Obviously, anti-inflammatory activity of minocycline and doxycycline is through different pathway from EGFR. Thus, they could reduce the severity but fail to lower the incidence of EGFR-induced skin toxicities.

When to start the treatment is one of the major questions in treating EGFR inhibitor-induced skin toxicities. Direct comparisons between preventive and reactive treatments had only been seldom addressed in the literature before. One phase II trial, skin toxicity evaluation protocol with panitumumab (STEPP), had compared pre-emptive and reactive treatments in 95 patients with metastatic colorectal cancer receiving panitumumab (11). The pre-emptive

regimen in that study included not only doxycycline but also skin moisturizers, topical steroids, and sunscreen and the regimen was used for 6 weeks. The incidence of grade 2 or more skin toxicities was significantly reduced in the pre-emptive treatment group (29%) comparing to the reactive treatment group (62%). This result seems to contradict with that of PCRT.

Some differences in the settings between the two trials may partially explain this discrepancy. First, patients enrolled in the two trials had different cancers and received different EGFR inhibitors. Classes of EGFR inhibitors might impact the incidence of skin toxicities (12). However, direct comparisons regarding to the influences of skin toxicities from different classes of EGFR inhibitors between monoclonal antibodies and tyrosine kinase inhibitors are still lacking. Second, the regimens used in pre-emptive or prophylactic treatment were different in these two trials. In STEPP, the regimen contained topical steroids, skin moisturizers, sunscreens, and doxycycline. These agents may improve skin integrity, avoid exogenous harmful stimuli, reduce skin inflammation, and further ameliorate skin toxicities. But, in PCRT, only minocycline was used as monotherapy for prophylaxis. This difference could also contribute to the disparity between the results of these two trials.

Duration of the preventive treatment is also a question needed to be addressed. In PCRT, the duration of prophylactic minocycline is 4 weeks. It could be extended or resumed if skin rash developed during or after the prophylaxis period. In STEPP, the duration is 6 weeks. Another recent published phase II trial evaluating the effects of prophylactic doxycycline on patients with non-small cell lung cancer (NSCLC) receiving erlotinib should be emphasized (13). In this trial, the period of prophylaxis is 4 months and could be extended up to 12 months. This trial revealed that the severity of acneiform eruptions was reduced, though the incidence was similar. Of note, the severity of paronychia and the incidence of other skin lesions were also significantly reduced in the prophylactic group. Besides, patients with prophylactic treatment had a significantly higher rate of compliance to EGFR inhibitors, less dose reduction, and less drug interruption over the 12-month treatment period. Although we could not make a conclusion based on these trials, it seems that a longer duration of preventive treatment may reduce the impacts of not only acneiform eruptions but also other skin toxicities, and may improve drug compliance and quality of life.

Another still largely-unknown issue is that whether previous chemotherapy impacts the incidence and severity of EGFR inhibitor-induced skin toxicities. Currently published studies were mainly focused on patients who failed first-line chemotherapies. Nevertheless, EGFR inhibitors may serve as the first-line treatment in patients whose tumors harboring mutations in *EGFR* gene (2,3). The incidence and severity of skin toxicities in these patients receiving EGFR inhibitors as first-line treatment might differ from those who have received chemotherapy before. Chemotherapeutic agents per se can be harmful to cells or tissues with high turn-over rates, including skin. It may make patients more vulnerable to subsequent EGFR inhibitors. To answer this question, further studies are needed.

EGFR inhibitors are increasingly used in treating different kinds of cancers. Skin toxicities are major side effects which should be reduced and overcome. With improvement of knowledge and practice on managing these skin toxicities, patients may have more benefits from the treatment of EGFR inhibitors. It is worthy of further investigations. Although we can not make a conclusion based on the findings of the aforementioned trials, we could assume that pre-emptive treatment may provide some benefits for patients, especially when multi-disciplinary managements are used. However, larger studies with direct comparisons are warranted to confirm this assumption.

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Footnote

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