

The SERIES Clinic: An Interdisciplinary Approach to the Management of Toxicities of EGFR Inhibitors

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A variety of cancers depend on abnormal signaling through the epidermal growth-factor receptor (EGFR) for their malignant behavior, which has led to the approval of several agents by the US Food and Drug Administration focused on this pathway. Erlotinib (Tarceva) and cetuximab (Erbix) are two such agents, and many more are under development.¹

Although these targeted therapies are devoid of hematopoietic and nonspecific toxicities common with conventional chemotherapy, they are characterized by the development of dermatologic reactions, which occur in the majority of patients. These reactions include a papulopustular rash (45%–100% of patients), xerosis (7%–35%), pruritus (8%–35%), periungual inflammation (12%–16%), and alopecia (14%–21%).^{1–3} Adverse events also occur in the eyes (12%–14%), with a subset of patients developing trichomegaly,⁴ conjunctivitis, and keratoconjunctivitis sicca,^{5,6} which can result in significant ocular discomfort and potential visual blur. The importance of these reactions is underscored by the psychologic and physical distress to the patient, by data suggesting that the severity of the rash may predict clinical outcome,^{7,8} and by the need in certain cases for EGFR-inhibitor dose decrease or discontinuation due to intolerance.

There are no established guidelines in the dermatologic or ophthalmologic literature for the treatment of these reactions. We present a case of a patient who developed a rash to the EGFR-inhibitor erlotinib and was promptly referred to an interdisciplinary clinic established to address these reactions, leading to improved quality of life and continued anticancer therapy.

Case

A 55-year-old female was diagnosed with non-small-cell lung cancer with distant disease involving the brain and bone. Based on her metastatic status and after discussion of various therapeutic

options with the patient, erlotinib was initiated at 150 mg daily as a single agent.

Three days after the onset of rash (7 days after erlotinib initiation), the primary hematology/oncology team called the SERIES (Skin and Eye Reactions to Inhibitors of EGFR and kinases) Clinic. The patient was scheduled for an appointment and within 2 days was thoroughly evaluated and screened for other skin and eye conditions. She complained of a burning sensation on her face and pruritus on the scalp and upper body. On physical exam, confluent erythematous perifollicular pustules were observed on her glabella, nose, nasolabial folds, and chin (Figure 1, left).

The SERIES team made a diagnosis of EGFR inhibitor-induced papulopustular cutaneous reaction of moderate intensity. Therapy was initiated with doxycycline 50 mg twice daily and topical pimecrolimus (Elidel). Within 5–7 days, there was a marked decrease in pruritus on the scalp and the burning sensation on the face. In addition, the pustular lesions on the face became crusted and dry. The patient was seen at a 2-week follow-up by a SERIES Clinic dermatologist. At this time, the patient reported no facial tenderness, and an exam showed resolution of pustules, with only residual erythematous macules on the face (Figure 1, right). She was very satisfied with her improvement in appearance and, more importantly, that she would be able to continue on erlotinib ther-

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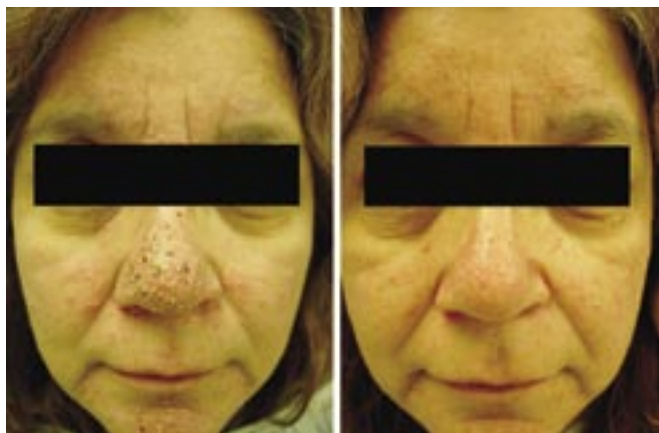


Figure 1 Skin Reaction to EGFR Inhibitor

Patient presented after erlotinib therapy with confluent pruritic pustules on the glabella, nose, and chin (left). After 2 weeks of doxycycline 50 mg twice daily and topical pimecrolimus twice daily, there was marked improvement, with no pustules and only residual macules with no pruritus (right).

apy, which demonstrated significant antitumor response on a computed tomography scan performed 4 weeks later.

This case raises important questions about the management of frequently occurring cutaneous toxicities secondary to anti-EGFR cancer therapy. Although the specificity of these agents circumvents the hematopoietic and generalized side effects typical of conventional chemotherapy, the cutaneous side effects may significantly affect a patient's physical and emotional well-being, as well as have an impact on anticancer drug dose or continued drug administration. Since there are no published data, and no consensus exists on the management of these side effects, the attempts at correcting them are numerous; unfortunately, most of these attempts are ineffective, precluding the potentially minimal side effects of targeted agents.

So when should an oncologist refer a patient on EGFR inhibitors to the dermatologist? Even when a patient is referred to dermatology, a regular appointment may not be available until it is too late, and the patient has suffered morbidity sufficient enough to interrupt antineoplastic therapy. Therefore, it is imperative for dermatologists and ophthalmologists to prioritize these cases to decrease morbidity and enable the continued administration of lifesaving therapy.

An Interdisciplinary Approach to EGFR Inhibitor-Induced Toxicities

The SERIES Clinic was established to detect and treat the frequent cutaneous and ocular reactions that occur secondary to anti-EGFR therapy. Previously, patients treated with these agents would be referred to the Department of Dermatology and/or Ophthalmology once they had failed a therapeutic intervention by the oncologist; by this time, the patient likely would have developed clinically significant reactions requiring EGFR-inhibitor therapy dose decrease or interruption. In spite of receiving high-quality dermatologic and ophthalmologic care, the skin or eye reactions usually would have advanced to

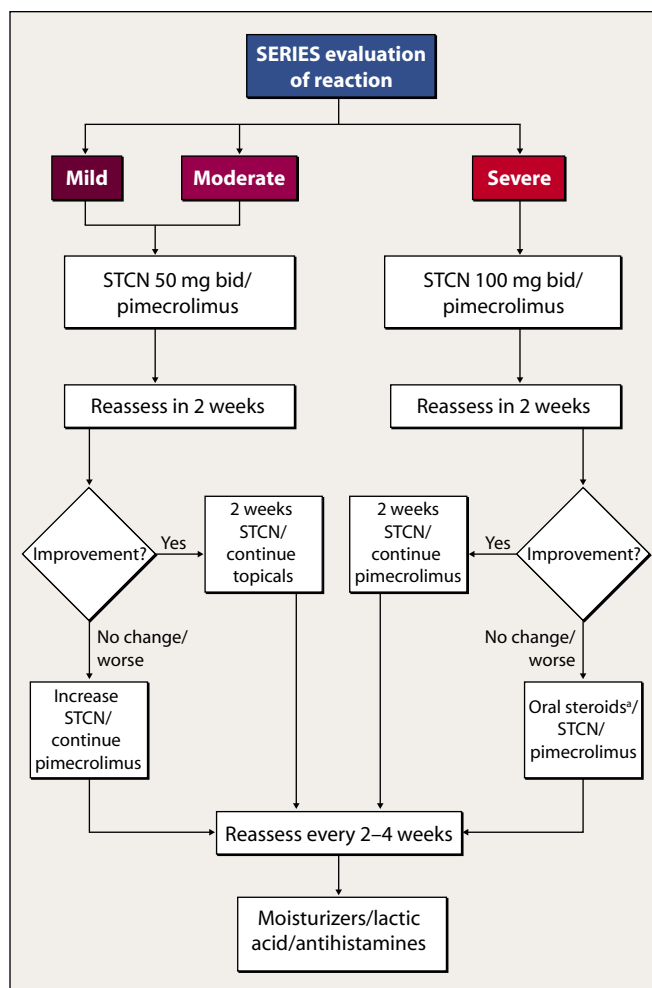


Figure 2 Algorithm for the Management of Cutaneous Toxicities to EGFR Inhibitors

Severity of a papulopustular rash is graded clinically based on symptoms, functioning, and clinical presentation (mild/moderate = NCI-CTCAE grades 1/2; severe = NCI-CTCAE grade 3).

*If no improvement after 2 weeks of oral steroids (prednisone or methylprednisolone), consider reduction or interruption of EGFR inhibitor.

Abbreviations: EGFR = epidermal growth-factor receptor; SERIES = Skin and Eye Reactions to Inhibitors of EGFR and kinases; STCN = semisynthetic tetracyclines (doxycycline or minocycline); pimecrolimus = twice daily topical application; NCI-CTCAE = National Cancer Institute's Common Terminology Criteria for Adverse Events

the point where cancer therapy had to be stopped or patients had undergone significant morbidity. Therefore, we decided to minimize these risks by pursuing a strategy of collaboration and early intervention.

In 2005, members of the Departments of Dermatology, Hematology/Oncology, and Ophthalmology of Northwestern University and the Robert H. Lurie Cancer Center, Chicago, Illinois, met to develop a collaborative approach to this problem. The goal was to develop a subspecialty clinic that would increase patient education, early diagnosis, and treatment (Figure 2)⁹⁻¹² of cutaneous and ocular reactions to EGFR inhibitors. An additional objective of the clinic was to establish the foundation

for future research on these poorly understood conditions.

The SERIES Clinic is based in the Department of Dermatology. Additional specialists who have developed an interest in the treatment and understanding of EGFR side effects (ophthalmologists and basic science researchers) are also an integral part of the team. A dermatologist is in charge of providing initial care of toxicities and referring patients to other subspecialists. The ability to provide direct appointment access to the Department of Hematology/Oncology ensures rapid and effective scheduling.

Communication between oncologists and nurses with the dermatologist and ophthalmologist is direct and immediate when patients present with progressive or disabling symptoms that may prompt drug discontinuation. Whereas most oncologists will refer patients on an as-needed basis, more recently patients have been referred for an early evaluation during EGFR-inhibitor treatment. In cases where toxicities progress rapidly, patients are offered swift access to appointments to avoid delays in diagnosis and treatment. Although early diagnosis and treatment are renewed goals of the subspecialty clinic, many long-term cancer patients experience the development of side effects at different times during treatment, which requires continued interaction with SERIES specialists.

The activities of the SERIES Clinic are focused on patient care, research, and education. Standard guidelines have been developed to ensure consistent and proactive clinical care. At initial evaluation, all patients undergo assessment of skin phenotype and underlying dermatologic diseases, and educational efforts are tailored according to the type of cutaneous reaction (ie, papulopustular rash, periungual inflammation, xerosis). Severity of reactions is determined based on clinical characteristics, patients' symptoms and social functioning (mild, moderate, or severe), and the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE v 3.0).¹³ Patients receive both verbal and written education designed specifically for EGFR inhibitor-induced toxicities regarding early recognition of rash and eye changes, as well as appropriate follow-up. Standardized follow-up intervals, stratified by clinical characteristics, are presented to the patients and relayed to the referring oncologist.

We place emphasis on the need for regular follow-up and early

attention to any new reaction or complication. Should a patient develop a skin or eye toxicity that does not respond to subspecialist treatment or becomes intolerable, the team will contact the oncologist to consider decreasing the EGFR inhibitor dose to permit normal functioning and symptom improvement.

The educational aspect of the clinic is varied. Written materials tailored to the specific need of the EGFR inhibitor population have been developed. Oncology physicians and healthcare personnel are seeking continuing education about the care of the skin and eyes at specialist conferences.

Conclusion

The subspecialty SERIES Clinic has been well received by patients, oncologists, and allied healthcare staff, who cite increased efficiency, improved communication, and the proactive/preventive approach as positive factors. Early education and prompt intervention are the cornerstones of this initiative. The enhanced communication and relationships between dermatologists, ophthalmologists, and oncologists have created new opportunities for patient care, education, and research, with the ultimate goal of lessening the burden of cutaneous and ocular morbidity in cancer patients treated with EGFR inhibitors.

For the patient described in the case study, the early referral by the oncologist to the SERIES Clinic ensured comprehensive dermatologic and ophthalmologic exams and an effective treatment for the rash. Staging of the reaction was performed based on the degree of symptomatic discomfort and clinical findings, and photographs were obtained for follow-up. The patient was worried that her symptoms would interfere with anticancer therapy and also mentioned how she felt relatively well and would have liked to continue her social life but was impeded by her appearance. Therefore, the SERIES team began dermatologic therapy aimed at decreasing the clinically visible lesions as well as the symptoms of the rash, with success in just 2 weeks and no interruption in erlotinib therapy.

The patient is being followed at the SERIES Clinic every 2 weeks, much more frequently than might be required for other disorders (6–12 weeks). She was satisfied with being able to continue her social life and, more importantly, her anticancer EGFR inhibitor therapy.

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