Treatment of Cutaneous Reactions to Epidermal Growth Factor Receptor Inhibitors

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Background: Cutaneous toxicity is the most common adverse effect of anticancer therapy with epidermal growth factor receptor (EGFR) inhibiting agents. In some cases the drug-induced skin rash is severe, interfering with activities of daily living and requiring dose reduction or cessation of EGFR inhibitor therapy. EGFR inhibitor-induced rash is a relatively new clinical entity without established, evidence-based treatment paradigms to inform its management.

Methods: We have treated skin toxicity in EGFR inhibitor-treated patients with the retinoid acitretin, with excellent responses. In order to formally evaluate the utility of this management approach, we designed a pilot trial utilizing acitretin to treat cutaneous reactions to the EGFR inhibitor erlotinib. In this trial, patients with National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Grade 2 rash are treated with low-dose (10 mg/day) acitretin and followed for 12 weeks; we evaluate clinical response (primary outcome) and effect on skin-related quality of life (secondary outcome). In addition, we published a review of EGFR inhibitor-induced cutaneous toxicities, focusing on clinical features, histopathological characteristics, and management of these toxicities, including our own novel treatment algorithm.

Results: Numerous patients have been treated in our clinic with acitretin for EGFR inhibitor-induced skin toxicity. The severity of these cutaneous reactions has ranged from moderate to severe, painful, dose-limiting eruptions. Nearly all of these patients have benefited from acitretin therapy, and more than half have had complete or near-complete responses; management of cutaneous toxicity in these patients has enabled continuation of EGFR inhibitor therapy at full dose. Collectively, our anecdotal experiences suggest a potential role for acitretin in the treatment of cutaneous eruptions associated with EGFR inhibitor therapy. A clinical trial was designed to formally evaluate this hypothesis, and is currently ongoing.

Conclusions: Cutaneous toxicity to erlotinib therapy is extremely common and in severe cases, may limit the clinical utility of a potentially life-sustaining therapy. Most of the current treatment options for EGFR inhibitor-associated skin toxicity have significant limitations, including lack of efficacy and unfavorable side effect profiles. In order to avoid dose reduction, interruption, or discontinuation of antineoplastic therapy in patients experiencing significant cutaneous toxicities to EGFR inhibitors, improved treatment paradigms for management of these cutaneous toxicities are needed. Acitretin may be helpful for management of moderate to severe skin reactions to EGFR inhibitors.

References:
Bibliography

Published abstracts


Poster presentations


Oral presentation


Published manuscripts in peer-reviewed journals

Pomerantz RG, Mirvish ED, Geskin LJ. Cutaneous reactions to epidermal growth factor receptor inhibitors. *Journal of Drugs in Dermatology*, 2010 October; 9(10): 1229-34.


Manuscript in press


Book Chapters


Research Grants

Howard Hughes Medical Institute Research Training Fellowship for Medical Students, 2008-2009 (support for full-time research between second and third years of medical school)

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American Medical Association Seed Grant, 2008-2009
- American Dermatological Association Medical Student Fellowship Grant, 2009
- OSI Pharmaceuticals Research Grant, 2008-present

Summary of Scholarly Activity

Significance of the project

EGFR inhibitors are an important new class of molecular targeting agents for the treatment of a variety of advanced neoplastic diseases. Cutaneous toxicity to EGFR inhibitor agents is extremely common and in severe cases, may limit the clinical utility of a potentially life-sustaining therapy. Clinical trials such as this one are needed to enable the development of evidence-based paradigms for the treatment of EGFR inhibitor-associated skin rashes.

Approaches to project goals

Larisa Geskin, MD, my faculty mentor for this project, has experience treating skin toxicity in EGFR inhibitor-treated patients with acitretin, with excellent responses. I wrote a short manuscript describing one such patient, who developed a severe, painful pustular eruption upon beginning erlotinib therapy for pancreatic cancer; the rash resolved completely with low dose (10 mg/day) acitretin. This was the first reported case of acitretin for treatment of EGFR inhibitor-induced skin toxicity. Subsequently, we designed a prospective study utilizing acitretin to treat cutaneous reactions to the EGFR inhibitor erlotinib, in order to formally evaluate the utility of this management approach. Additionally, I wrote a review of EGFR inhibitor-induced cutaneous toxicities, incorporating the novel management algorithm that is utilized in Dr. Geskin's clinic.

Independence of the student

The novel concept of utilizing acitretin to treat EGFR inhibitor-induced skin reactions was Dr. Geskin's. I wrote the manuscript for our initial case report described above, and worked with Dr. Geskin to design the clinical trial. I wrote the protocol for the trial and subsequently incorporated the modifications requested by the IRB. I also successfully sought funding for this study from the American Medical Association (AMA Seed Grant for Medical Students) and from OSI Pharmaceuticals (grant for investigator-initiated trial), and wrote the grants to both organizations. Additionally, I was the primary author of our review article describing the clinical characteristics and management of EGFR inhibitor-induced cutaneous toxicities.
Project originality

This is the first prospective study to evaluate acitretin, or any oral retinoid agent, for treatment of cutaneous reactions to EGFR inhibitor therapy. The results of this study are expected to provide a new evidence-based treatment option for the management of EGFR inhibitor-associated skin rashes.

Project limitations and possible future directions

This is a pilot study designed to evaluate acitretin in a small number of patients with erlotinib-induced skin rash. Future studies evaluating the efficacy of this approach may be designed as randomized, controlled prospective trials. Additionally, future studies may evaluate patients with skin reactions to EGFR inhibitors other than erlotinib.

Contribution to analytical skills

This work has provided extensive and valuable experience in study design, writing and revising a protocol, the IRB submission process, writing and revising manuscripts, submitting to peer-reviewed journals, identifying appropriate funding sources, and grant writing. I hope that the skills developed through this work will provide grounding for a career in academic medicine and research.

Scholarly Project Paper

Published manuscripts relevant to this work have been uploaded to the Scholarly Project site. In addition, I have attached selected publications related to my work on other concurrent projects.

Addendum

In addition to this study, I have also been working on multiple projects related to Cutaneous T Cell Lymphoma, during my CSTP/Howard Hughes fellowship year and on an ongoing basis throughout medical school. Those projects which led to manuscripts and/or presentations are noted in the bibliography above. Additionally, I have uploaded some of these manuscripts to the Scholarly Project site.