Cutaneous adverse effects of targeted therapies

Part I: Inhibitors of the cellular membrane

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Learning objectives
After completing this learning activity, participants should be able to identify the most common cutaneous adverse events associated with targeted therapies; describe the etiopathogenesis of cutaneous adverse effects associated targeted therapies; and recognize clinical features of common cutaneous adverse effects associated with targeted therapies.

Disclosures
None declared.

There has been a rapid emergence of numerous targeted agents in the oncology community in the last decade. This exciting paradigm shift in drug development lends promise for the future of individualized medicine. Given the pace of development and clinical deployment of targeted agents with novel mechanisms of action, dermatology providers may not be familiar with the full spectrum of associated skin-related toxicities. Cutaneous adverse effects are among the most frequently observed toxicities with many targeted agents, and their intensity can be dose-limiting or lead to therapy discontinuation. In light of the often life-saving nature of emerging oncotherapeutics, it is critical that dermatologists both understand the mechanisms and recognize clinical signs and symptoms of such toxicities in order to provide effective clinical management. Part I of this continuing medical education article will review in detail the potential skin-related adverse sequelae, the frequency of occurrence, and the implications associated with on- and off-target cutaneous toxicities of inhibitors acting at the cell membrane level, chiefly inhibitors of epidermal growth factor receptor, KIT, and BCR-ABL, angiogenesis, and multikinase inhibitors. (J Am Acad Dermatol 2015;72:203-18.)

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INTRODUCTION

Key points

- **Targeted therapies offer more precise oncologic treatment options; however, they are not free of adverse effects**
- **Cutaneous adverse effects are among the most frequently encountered, and significantly impact both quality of life and health care economics**

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Abbreviations used:

EGFR: epidermal growth factor receptor
HhSP: hedgehog signaling pathway
VEGFR: vascular endothelial growth factor receptor

- **Dermatologists can provide key input in treatment of patients with targeted cancer therapies**

Virtually all cancers are driven by molecular aberrations that ultimately lead to uncontrolled proliferation. This notion has spurred the development of a spectrum of therapies specifically aimed at the molecular mechanisms contributing to cancer development and progression. The emergence of this class of agents, often referred to as "targeted therapies," offers a promise of more effective treatments tailored to a specific disease and possibly even to an individual patient's cancer.

Although designed to be significantly more "precise" than traditional chemotherapies, targeted therapies frequently induce adverse effects (AEs). Cutaneous toxicities are among the most frequently observed AEs[1] and, when severe or protracted, can result in significant morbidity, requiring dose modification or drug discontinuation.[2] The morbidity can affect patient's quality of life, including patient's physical,[3] emotional,[4] and psychological well-being.[5] In addition, AEs can affect medication adherence, risk of infection, and cancer therapy dosing[6,7] and result in a substantial economic burden[5] and potentially time-exhaustive clinic visits for cancer patients. In one analysis, management of dermatologic toxicities of targeted therapies was estimated at a median of $1920 per patient.[8]

Given the increasing use of targeted therapies, dermatology providers are encountering growing numbers of oncology patients who are experiencing cutaneous side effects of varied pathogeneses and complexity. The resulting need for a dual clinical expertise has led to collaborative efforts between dermatologists and oncologists, including the introduction of supportive oncodermatology fellowship programs.[5] To allow for uniform reporting and proper cataloging of side effects between specialists caring for cancer patients, a standardized grading system has been established,[9] and dermatologic AEs have been stratified accordingly.[10]

In this 2-part review, we address the key skin and skin appendage–related toxicities of the most prominent targeted anticancer therapies and discuss the incidence, pathogenesis, clinical presentations, and management strategies by drug category (Table I). Part I will focus on inhibitors of membrane-associated therapeutic targets (Fig 1), while part II details inhibitors of intracellular signaling pathways and immunotherapies.

EPIDERMAL GROWTH FACTOR RECEPTOR INHIBITORS

Key points

- **Epidermal growth factor receptor inhibitors generate a unique constellation of skin toxicities, including papulopustular eruption, hair and nail changes, mucositis, and photosensitivity**
- **The severity of papulopustular eruption directly correlates with epidermal growth factor receptor inhibitor efficacy and patient outcomes**
- **Prophylaxis and the early management of cutaneous toxicities may prevent dose reduction or dose discontinuation**

Epidermal growth factor receptor (EGFR) inhibitors are among the first families of targeted therapies and are used in the treatment of several malignancies, including colorectal, head and neck, non–small cell lung, and breast cancers.[11] This class of EGFR inhibitors includes monoclonal antibodies to EGFR (eg, cetuximab and panitumumab), small-molecule tyrosine kinase inhibitors specific for EGFR (eg, erlotinib and gefitinib), dual kinase inhibitors of EGFR and HER2 (ie, lapatinib, neratanib, and afatinib), inhibitors of erbB receptors (ie, canertinib), and other less specific multikinase inhibitors (eg, vandetanib). Most agents targeting EGFRs produce a similar spectrum of dermatologic toxicities,[12] as detailed below.

The unique constellation of class-specific cutaneous AEs associated with EGFR inhibition clearly point to the important role of EGFR in epidermal and pilosebaceous homeostasis.[13-15] Indeed, EGFRs are abundantly expressed in the epidermis and its appendages,[16] consistent with the high incidence of AEs induced by EGFR inhibition. Interestingly, EGFR has also been shown to play a putative role in restraining interleukin-1 (IL-1)-dependent inflammatory reactions at the hair follicle level, possibly shedding light on the acneiform papulopustular eruptions[17] seen in conjunction with EGFR blockade. In addition to altering IL-1 and tumor necrosis factor–alfa,[18] EGFR effects on IL-8 have more recently been implicated as a mechanism mediating EGFR-induced AEs.[19] The observed skin toxicities are clearly related to EGFR itself, rather than off-target effects of EGFR inhibitors, because the reversal of EGFR inhibitor–induced receptor