Epidermal growth factor receptor inhibitors: A new era of drug reactions in a new era of cancer therapy

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On September 27, 2006 the Food and Drug Administration approved panitumumab (Vectibix) for the treatment of epidermal growth factor (EGF)—expressing metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Interestingly, the first line of the product labeling for panitimumab warns of the dermatologic toxicity associated with its use. In clinical trials, 89% of patients developed dermatologic sequelae, including acneiform rash, paronychia, dry skin, and skin fissures. Severe dermatologic toxicity (National Cancer Institute Common Terminology Criteria for Adverse Events—[NCI-CTCAE] Grade 3 or higher)[1] was observed in 12% of patients, and reported events included abscesses requiring incision and drainage, sepsis, and death.[2]

Panitumumab is the fourth anti-neoplastic agent targeting the epidermal growth factor receptor (EGFR) to be approved since 2003. Along with the 3 other approved therapies targeting this signaling pathway, gefitinib, erlotinib, and cetuximab, this class of drugs exemplifies a new approach in contemporary cancer therapy. The indications for these agents include notoriously difficult-to-treat malignancies, such as metastatic colorectal, pancreatic, and lung cancers. Erlotinib is the first agent in more than a decade to improve survival in combination with chemotherapy in patients with pancreatic cancer.[3] Similarly, cituximab is the first newly approved therapy approved for head and neck cancer in 30 years.[4]

Abbreviations used:

EGF:	epidermal growth factor
EGFR:	epidermal growth factor receptor
NCI-CTCAE:	National Cancer Institute Common Terminology Criteria for Adverse Events

EGFR (ErbB1, HER1) is a member of the ERBB receptor tyrosine kinase family, which also includes ErbB2 (Her2/neu), ErbB3 (HER3), and ErbB4 (HER4). It is a transmembrane glycoprotein that plays an important role in a number of cancers,[5,6] but it is also found on skin cells, including keratinocytes, and cells in the hair follicle, eccrine and sebaceous glands.[7,8] Selective inhibition of EGFR signaling can be mediated by the use of humanized antibodies that bind to the extracellular domain of EGFR (panitumumab, cetuximab), or by small-molecule tyrosine kinase inhibitors which compete with adenosine triphosphate for binding to the tyrosine-kinase domain of the receptor (erlotinib, gefitinib; Fig 1).[9] Because aberrant EGFR signaling due to receptor overexpression, activating mutations, and other causes play a key role in carcinogenesis,[5] these therapies can inhibit tumor growth without incurring many of the systemic toxicities that are associated with conventional chemotherapeutic agents.

The high incidence of EGFR inhibitor—induced cutaneous reactions is not unanticipated in light of the prominent role that EGFR signaling plays in skin homeostasis. Because skin toxicity is a pharmacologic class effect rather than a hypersensitivity reaction, skin involvement has been proposed as a surrogate marker for EGFR inhibition.[10] Along these lines, there is mounting evidence that the presence and severity of rash appear to correlate with tumor response.[11]

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EGFR inhibitor skin changes include alterations in hair growth and texture, paronychial inflammation with and without secondary infection or pyogenic granuloma formation, diffuse xerosis, and desquamation. Typically the most dramatic skin manifestation is a noncomedonal follicle-based papular/pustular eruption involving the head, neck, central area of the chest and back, which may progress to diffuse involvement. These reactions usually develop in the first several weeks of therapy and are more commonly associated with anti-EGFR monoclonal antibodies (cetuximab, panitumumab). Development of skin eruptions does not appear to correlate with duration of therapy, but is dose dependent. The product labeling for cetuximab provides a table of recommended dose reductions should severe skin reactions occur.[12]

Despite the expanded use of the EGFR inhibitors and the high incidence of cutaneous reactions, our understanding of the skin toxicities has not progressed significantly since they were first described in clinical trials. The EGFR is thought to play a key role in epidermal maturation and differentiation, particularly in early life.[13,14] Exactly how inhibition of this key regulator of epidermal and hair follicle control leads to the different skin manifestations is uncertain. Although the pustular eruption typically involves areas of the body predisposed to acne vulgaris, comedonal lesions and histologic changes indicative of increased sebaceous gland activity are not typically observed. Brisk inflammation appears to be a common feature in this eruption, even in the absence of an infectious source or follicular rupture. Busam et al[15] described histologic evidence of a superficial lymphocytic perifolliculitis and suppurative folliculitis in patients treated with cetuximab. Van Doorn et al[16] also characterized the histopathologic findings in patients treated with ZD1839 (gefitinib) as a purulent folliculitis, with dense neutrophilic infiltration of the follicle and absence of the follicular epithelial lining. Epidermal changes are typically more subtle and include a loss of orthokeratosis, irregular epidermal differentiation, and hypogranulosis.

Management of severe skin manifestations has become a significant issue for oncologists, who are left with few alternative cancer treatment options should the medication need to be discontinued, and dermatologists, who lack a treatment algorithm based on evidence-based medicine. Several reviews of the dermatologic side effects associated with anti-EGFR therapy have been published in this *Journal* and elsewhere in the past 18 months.[17-20] To date, however, most reports describing successful treatment for EGFR inhibitor–related skin toxicity have been based on anecdotal experience treating the "pustular eruption." Partial or complete responses to topical metronidazole,[21] benzoyl peroxide,[22] fusidic acid,[22] erythromycin solution,[22] povidone iodine,[22] hexamidine,[22] and retinoids[16,23] have been described. Complete response to a 14-day course of itraconazole was observed in a patient taking erlotinib found to have *Malassezia sympodialis* by tissue culture.[24] Use of oral tetracyclines after failure of topical therapies or in patients with more severe involvement has been advocated by several groups and often results in some improvement.[17,18,20,21] Slow spontaneous improvement has also been reported in cancer trials; however, precise characterization of the nature of the skin involvement is often not provided.[20,25]

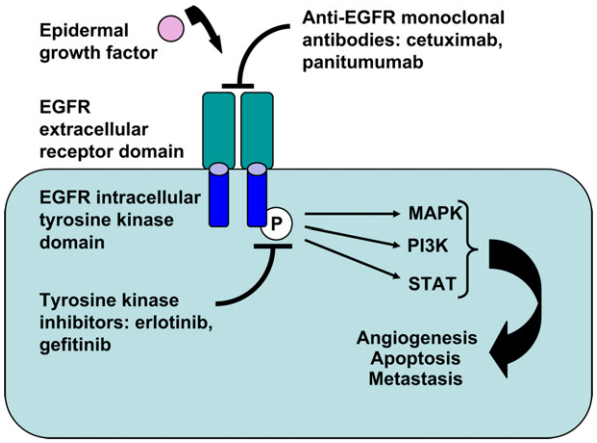

Fig 1. EGFR signaling blockade of the extracellular domain by monoclonal antibodies, or through intracellular inhibition of tyrosine kinase phosphorylation (*P*), results in interruption of signaling to downstream targets, including mitogen-activated protein kinase (*MAPK*), phosphatidylinositol 3-kinase (*PI3K*), and signal transducer and activator of transcription (*STAT*).

In addition to the above agents, topical steroids such as betamethasone 0.05% have been purported to alleviate the pustular rash in some patients.[20] A forum convened in early 2004 to develop consensus management guidelines for EGFR inhibitor–related rash advocated the use of high-potency topical steroids (eg, clobetasol propionate) early in therapy for patients with mild rash, and specifically recommended against conventional topical acne therapies (eg, benzoyl peroxide, topical retinoids).[26] In contrast, the experience of multiple European dermatology and oncology departments published in a review last year advocated the use of topical antibacterial and acne/rosacea agents in patients with mild or moderate rash.[19] In both reviews, the authors concede that treatment recommendations are based on personal experience, emphasizing the need for a standardized evaluation of potential therapies.