

REVIEW ARTICLE

Cutaneous Side Effects of New Antitumor Drugs

Clinical Features and Management

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SUMMARY

Background: Many new antitumor drugs have been approved in recent years. Their side-effect profiles are distinct from those of older drugs, and their adverse effects are sometimes highly specific, particularly with respect to the skin.

Methods: This article is based on articles retrieved by a selective search in Medline and the database of the American Society of Clinical Oncology (ASCO), as well as on the authors' personal experience.

Results: Cutaneous adverse effects are among the more common adverse effects of new antitumor drugs: they occur in up to 34% of patients receiving multikinase inhibitors, up to 90% of those receiving selective tyrosine kinase inhibitors (such as EGFR or mutant BRAF inhibitors), and up to 68% of those receiving immunotherapeutic agents (such as CTLA4 inhibitors). These adverse effects can be correlated with therapeutic benefit, but they can also be treatment-limiting because of their severity or visibility.

Conclusion: The recognition and proper management of cutaneous adverse effects is an important part of treatment with new antitumor drugs.

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Increased understanding of the pathogenesis of malignant tumors has paved the way for the development of new drugs for medical tumor therapy. In addition to cytotoxic drugs, drugs with specific molecular targets (so-called “targeted therapies”) and new immunological therapeutic approaches are being implemented. Since an increasing number of patients with different types of tumors are being treated with these drugs, doctors from various disciplines are now faced with dealing with the associated adverse events.

The new mechanisms of action of these drugs can lead to clinically unusual and novel adverse events that are associated with the specific targeted structure or mechanism, representing a major therapeutic challenge. In addition to other organs, such adverse events also occur in the skin. Cutaneous adverse events are in fact often in the forefront, for example those that occur with epidermal growth factor receptor (EGFR) inhibitors and mutated BRAF gene inhibitors. These events can lead to changes in dose or treatment modality modification due to their severity, painfulness, and/or psychological discomfort. At the same time, the incidence of cutaneous adverse events can be associated with positive treatment response, as observed for EGFR inhibitors. Optimizing management of these cutaneous adverse events is therefore crucial for the implementation and success of tumor drug therapy for many patients.

This article summarizes current knowledge regarding the presentation and management of cutaneous adverse events of medical tumor therapy. It is based on the evaluation of a selective analysis of published articles from the Medline database, publications from the American Society of Clinical Oncology (ASCO), and the authors' experience. The data relating to the frequency of cutaneous adverse events, in particular, was based on the current Summary of Product Characteristics and controlled studies. However, since few randomized controlled studies of prophylaxis and treatment of cutaneous adverse events are available, recommendations with a weaker evidence base (such as case reports and expert recommendations) have to be used.

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Intensity and time-course of the most common cutaneous adverse events during EGFR inhibition

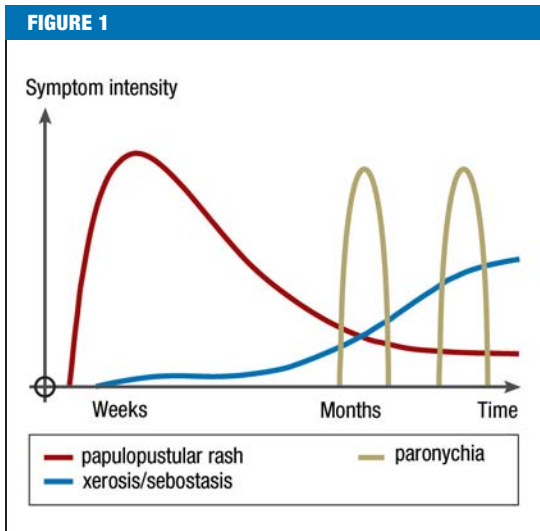


Figure 2: Papulopustular rash during treatment with the EGFR-inhibitor cetuximab

EGFR Inhibitors

EGFR is expressed in many types of solid tumors. Its activation promotes cell proliferation, cell mobility, angiogenesis, and metastasis, but inhibits apoptosis (1).

Tumor therapy uses monoclonal antibodies directed against the extracellular EGFR domains (e.g., cetuximab and panitumumab) or low-molecular-weight, orally administered inhibitors of the intracellular EGFR tyrosine kinase (e.g., erlotinib, gefitinib, and lapatinib), either for monotherapy or in combination with chemoradiotherapy (2).

Unlike conventional chemotherapy, which interferes with RNA and DNA synthesis, EGFR inhibitors have a favorable side effect profile with low hematotoxicity. Since EGFR is also expressed in normal skin and hair follicles, three clinically relevant reaction patterns of skin toxicity are observed following EGFR inhibition, all of which are drug class effects (Figure 1) (3). Frequency, type, and severity of the cutaneous adverse events of EGFR inhibitors vary, depending not only on the therapy duration and the kind of EGFR inhibitor administered, but also on patient-related factors, such as smoker status, immune status, and pharmacogenetic factors like the K-ras mutations that have not yet been clearly defined (4).

The earliest and most common cutaneous adverse events are papulopustular, follicular exanthems, often referred to as skin rashes or as „acneiform“ that, in contrast to acne, does not present with comedones (blackheads). This immunologically mediated and often stigmatizing and painful rash usually occurs initially on the face, chest, and upper back (Figure 2), but can also occur anywhere on the entirety of the skin and the hair regions of the head. The eruption slowly resolves after several weeks, so that usually only moderate erythema and follicular papules remain even after long-term EGFR inhibitor therapy in the absence of dermatological therapy. The severity levels have been classified by the US National Cancer Institute (NCI) in a catalog of common toxicity criteria (CTC) (Table 1), and the progress of the rash can be evaluated using a precise dermatological severity index score (5). Incidence and severity of papulopustular rashes are associated with a better prognosis and are therefore considered to be predictive indicators for the response of a tumor to EGFR inhibitor (4). After discontinuation of EGFR inhibitor, papulopustular lesions usually heal completely. After the onset of massive inflammation, isolated cases of scarring or perifollicular xanthoma have been described (6).

The second group of clinically significant adverse events appear insidiously and gain clinical relevance first after 1 to 2 months of therapy for many patients; these include:

- sebostasis
- epidermal atrophy
- xerosis cutis
- itchy, dry eczema
- vulnerability of the skin to fissures, especially on the fingers, toes, and heels (Figure 1).

TABLE 1

Classification of severity of cutaneous adverse events (as defined by the National Cancer Institute Common Toxicity Criteria, version 4.03)

	Papulopustular (acneiform) rash	Maculo-papular rash	Hand-foot syndrome
Grade 1	<10% body-surface area, with or without symptoms of pruritus or tenderness	<10% body-surface area, with or without symptoms (e.g. pruritus, tightness, or burning)	Minimal skin changes (e.g., erythema, edema, or hyperkeratosis) without pain
Grade 2	10–30% body-surface area, with or without symptoms of pruritus or tenderness; with psychosocial impact; limiting instrumental activities of daily living	10–30% body-surface area with or without symptoms (e.g. pruritus, tightness, or burning), limiting instrumental activities of daily living	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting practical activities
Grade 3	>30% body-surface area, with or without symptoms of pruritus or tenderness; limiting self-care activities of daily living; associated with local superinfection with oral antibiotics indicated	>30% body-surface area with or without associated symptoms; limiting self-care activities of daily living	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care activities
Grade 4	Covering any percent of the body-surface area; with or without symptoms of pruritus or tenderness; associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences		
Grade 5	Death		

The third major group consists mainly of painful periungual inflammation (paronychia) that usually arises from the nail wall and is sometimes associated with abundant formation of granulation tissue (Figure 3). This affects only about 10% to 30% of patients, suggesting the presence of an infectious cofactor. In almost all smears, gram-positive or gram-negative bacteria, and sometimes also *Candida albicans*, are detectable (7).



Figure 3: Paronychia with granulation tissue during treatment with the EGFR-inhibitor cetuximab

The prophylaxis and treatment of adverse events should be adjusted based on the experiential knowledge of the individual situation (2–4). On initiation of an EGFR inhibitor therapy, patients should begin an emollient-based therapy with a topical preparation containing urea and should avoid activities that are mechanically damaging. The rationale for the treatment of a papulopustular rash is based on its similarity to the acne-related skin diseases, especially papulopustular acne and rosacea. Mild cases of papulopustular rashes can be treated with metronidazole or topical erythromycin containing preparations. For moderate cases, a combination of nadifloxacin cream and a topically applied glucocorticosteroid, such as prednicarbate cream, or an oral antibiotic therapy (with tetracycline, minocycline, or doxycycline), have proven effective. For the majority of patients, the papulopustular rash can be satisfactorily treated this way, resolving in either complete healing or regression to a grade 1 rash (Table 1) (4). Currently, prophylactic long-term oral antibiotic medication is not generally recommended (2–4). Patients with severe or unusual manifestations, or skin reactions that do not respond to standard treatment, should be

examined by an experienced dermatologist (4). Fissures on the finger tips or toes can be treated with tetracycline-containing ointment or hydrocolloid dressing or, where appropriate, closed with a cyanoacrylate adhesive.

Paronychia treatment is usually antiseptic, anti-inflammatory, and, depending on the findings, antibiotic or antifungal, although surgical procedures are sometimes required (7).

Multikinase, c-Kit, BRAF, and MEK inhibitors

Targeted therapies can cause cutaneous adverse events that are either specifically related to the drug's mechanism of action or non-specific. Examples of non-specific reactions are maculo-papular rash, itching (often associated with xerosis cutis), and reversible alopecia (Table 2). The trigger factor leading to maculo-papular rashes (Figure 4) can often be identified by the temporal relationship obtained from the medical history and clinical progression. It should be noted that alternative trigger factors, such as infections or other drugs, should also be considered. Test procedures have not yet

TABLE 2

Cutaneous adverse events by targeted therapies (++ very frequent $\geq 10\%$, + frequent $\geq 1\%$, +/- occasionally $\geq 0.1\%$, - seldom/never $<0.1\%$)

Target structure (reference)	Main indications	Substances	Cutaneous adverse events	Frequency
EGFR inhibitors (2, 3, 4)	Carcinomas of lung, pancreas, gastrointestinal tract, breast; squamous cell carcinomas of the head and neck	Erlotinib, gefitinib, lapatinib, cetuximab, panitumumab	Papulopustular rash, perifollicular xanthoma, xerosis cutis/pruritus, eczema craquele, fissures/rhagades, paronychia, hypertrichosis, hair follicle abnormalities	++ +/- ++ + ++ ++ + +
Multikinase inhibitors (8, 9, 13, 14)	Renal cell carcinoma, hepatocellular carcinoma	Sorafenib, sunitinib, pazopanib	Maculo-papular rash, hand-foot syndrome, hair discoloration, skin discoloration, xerosis cutis/pruritus, facial erythema, alopecia, epithelial skin tumors, subungual splinter hemorrhages	++ ++/pazopanib + ++/sorafenib - ++ (only sunitinib) + + + + (only sorafenib) +
BCR/ABL c-kit (15, 17)	Certain leukemia entities, gastrointestinal stromal tumor	Imatinib, nilotinib, dasatinib	Maculo-papular rash, periorbital edema, xerosis cutis/pruritus, light sensitivity, alopecia, pigmentation disorders, pustules/folliculitis	++ ++ (only imatinib) + + + + +/-
Mutated BRAF (15, 16)	In clinical trials, with focus on melanoma	Vemurafenib (PLX4032, RG7204, RO5185426), GSK2118436	Maculo-papular rash, light sensitivity, epithelial skin tumors, alopecia, hand-foot syndrome	++ ++ (only vemurafenib) ++ + +
MEK (17)	In clinical trials, with focus on melanoma	Selumetinib (AZD6244) GSK1120212 CI-1040 (PD184352)	Papulopustular rash, xerosis/pruritus, paronychia, fissures/rhagade	++ + + +

Source: Summary of Product Characteristics and given references

been established for most drugs. Therapy is analogous to the treatment protocols for other drug-induced rashes and depends on the course and severity of the event (Table 1). Topical and systemic glucocorticosteroids can be used, while keeping in mind that dose reduction or discontinuation of the suspected trigger substance may be necessary.

For pruritus, possible triggers should be investigated primarily by analyzing the medical history and clinical examinations. Pruritus is often associated with xerosis cutis, which can be treated with a consistent skin moisturizing regimen.

The multikinase inhibitors (MKI) sorafenib and sunitinib often provoke cutaneous side effects that are specifically associated with their mechanisms of action (Table 2). Since these drugs target different kinases, they also have different side effect spectra (8). The most common side effect for both drugs is the hand-foot syndrome (HFS), which differs from the chemotherapy-associated HFS (9). With MKI, a painful, callus-like hyperkeratosis, sometimes with blister-

ing and inflammation in its peripheral region, often appears almost exclusively in the palmoplantar areas, especially those under mechanical stress (Figure 5). This is associated with the inhibition of vascular endothelial growth factor (VEGF) receptors. In contrast, cytostatic-associated HFS that begins within a few days after starting cytostatic therapy displays sensory symptoms (dysesthesia) on the palms and soles, with sharply demarcated erythema sometimes showing edema (Table 1; Figure 6). In grade 3 severity, further symptoms ranging from blistering and desquamation of the stratum corneum, to the development of large-area erosion and ulceration, can also be observed (Table 1) (9, 10). Additional areas that may be affected include the dorsal parts of the hands and feet, intertriginous areas, and skin in contact with tight clothes, suggesting that a possible triggering mechanism is the excretion in sweat of cytostatic or toxic metabolics (9, 10).

Currently, there are few recommendations from controlled studies on the management of MKI- or cytostatic-associated HFS. The guiding principles for

management are based on detailed explanations about the disease and its preventive measures, such as:

- treatment of previously-existing skin conditions (e.g., eczema or fungal infections)
- consistent moisturizing skin care
- avoidance of mechanical stress
- regular removal of sweat with warm water.

Two studies using docetaxel therapy have shown that cooling of the hands and feet, perhaps through reactive vasoconstriction, significantly reduced the frequency and severity of HFS (9). Recent prospective studies have found that treating externally with urea- and lactic acid-containing preparations, or systemically administering vitamin B6, were not beneficial for the prophylaxis of capecitabine-associated HFS (11, 12). Topical glucocorticosteroid-containing preparations are recommended to treat inflammatory lesions on the hands and feet.

In severe cases of HFS, it is recommended that the dose is reduced and the associated therapy is 1 severity, it is usually possible to attempt renewed treatment (9).

Epithelial skin tumors have been described in association with sorafenib treatment; these fall within the clinical and histological spectrum of actinic keratosis, keratoacanthoma, atypical keratoacanthoma, cutaneous squamous cell carcinoma, and, in rare cases, basal cell carcinoma (13–15). In some retrospective case series, the incidence has been estimated at 6% to 7%, but this remains to be verified by prospective studies (13). These epithelial skin tumors have a very good prognosis. Metastasis or local recurrence after surgical removal has not been described, and spontaneous regression is possible, especially after discontinuation of sorafenib therapy (13). The incidence of epithelial skin tumors is likely due to the effect of sorafenib on the tyrosine kinase BRAF, since the MKI sunitinib, which does not target BRAF, is not associated with the development of skin tumors. In contrast, studies in which the highly selective inhibitors of the mutated BRAF, vemurafenib and GSK2118436, were used in malignant melanoma therapies revealed that up to 30% of the treated patients developed epithelial skin tumors (*Table 2*) (15, 16). The skin tumors resulting from sorafenib and selective BRAF inhibitor treatment are clinically, histologically, and prognostically comparable. In light of this, patients treated with sorafenib or a BRAF inhibitor should undergo regular dermatological examinations, and newly developed skin changes should be removed at an early stage and histopathologically examined.

Sunitinib and other blockers of the tyrosine kinase c-Kit often lead to a hypopigmentation of the hair or skin (*Table 2*) (17), likely due to the effects of the receptor on the melanocytes of the hair follicles. The intense yellow discoloration of the skin with sunitinib is due to a metabolite of sunitinib that has a yellow color (8). No treatment is possible for this.

MEK inhibitors inhibit the same signaling pathways as do the EGFR inhibitors and can therefore cause similar cutaneous adverse events (*Table 2*) (18).



Figure 4: Maculo-papular rash during treatment with the multikinase inhibitor sorafenib



Figure 5: Hand-foot syndrome during treatment with the multikinase inhibitor sorafenib

Figure 6:
Hand-foot syndrome
(palmar-plantar
erythrodysesthesia)
during treatment with
pegylated liposome-
encapsulated
doxorubicin



Figure 7: Papular urticarial rash during treatment with the anti-CTLA-4-antibody ipilimumab

Immunotherapy with CTLA-4 blockade

Immunostimulatory cytokines, such as interferon alpha and interleukin-2, have been approved for years as a drug therapy for different tumor diseases (especially for renal cell carcinoma, malignant melanomas, and certain lymphomas and leukemias). They have a well known cutaneous side-effect profile, which includes:

- drug-induced maculo-papular rash
- xerosis cutis and pruritus
- alopecia
- triggering inflammatory skin diseases (such as psoriasis or other autoimmune dermatoses)
- necrosis at the injection site (19).

Currently, cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blockade plays an important role. Two anti-CTLA-4 antibodies, ipilimumab and tremelimumab, are in clinical trials for different tumor types in advanced stages, including malignant melanoma, lung carcinoma, prostate cancer, and renal cell carcinoma. Ipilimumab is at a more developed stage than tremelimumab and was approved in March 2011 in the USA, and in July 2011 in Europe, for the treatment of metastatic melanoma.

CTLA-4 is a surface protein that is expressed by activated T lymphocytes; binding of the antigen-presenting cells by the costimulatory molecules B7-1 and B7-2 leads to the down-regulation of the T cells. Under physiological conditions, this mechanism is important for preventing an excessive T-cell-mediated immune response. In tumor therapy, an enhanced T-cell-mediated immune response is desirable for tumor therapy, provided that it is directed against the structures of the tumor cells. Thus, the two antibodies mentioned above were developed for CTLA-4 blockade in order to enhance the T-cell-mediated anti-tumor immune response. Both substances have a

similar spectrum of side effects. Intervening with the regulatory mechanisms of the T-cell-mediated immune response often leads to excessive immune reactions with respect to autoimmune-related infections, in particular enterocolitis (with the clinical symptom of diarrhea), hepatitis (which is usually first recognized by increased levels of liver enzymes), and hypophysitis (with the clinical symptom of headache) (20–22). These side effects are often severe and may necessitate therapy interruption or discontinuation. Comprehensive algorithms have been developed to manage these side effects (23).

Adverse effects on the skin usually occur in the form of a rash that usually has a macular, maculo-papular, or urticarial morphology (Figure 7) and is often accompanied by severe itching (20, 24). For ipilimumab, these skin lesions have been observed in up to 68% of all treated patients; however, fewer than 5% of these patients develop a severity of grade 3 (Table 1) (22, 23). The rash usually occurs 3 to 4 weeks after administration of ipilimumab but can also occur either very early in therapy or after therapy has ended, and it gets worse after each ipilimumab dose (23). It usually is self-limiting within the first 2 to 3 months of treatment, is well tolerated using topical treatment with glucocorticosteroids and antipruritic compounds (such as ThesitTM), and seldom leads to therapy interruption or discontinuation (23). The prophylactic application of topical steroidal cream is therefore not recommended.

Conclusions

New medical tumor therapies are frequently associated with cutaneous adverse events. Early intervention is critical in treating them. However, unified therapy standards and guidelines based on studies are generally lacking. With early diagnosis and appropriate treatment

based on available evidence, cutaneous adverse effects should not limit the tumor therapy for most patients. Successful management requires not only the efforts of the primary attending physician but also an intense interdisciplinary collaboration involving dermatologists, who are experts on the classification and treatment of cutaneous adverse events.

KEY MESSAGES

- Cutaneous adverse events (AE) in anti-tumor drug therapy are common (up to 34% for multikinase inhibitors, 90% for EGFR inhibitors, and 68% for anti-CTLA-4 antibodies).
- Cutaneous AE in anti-tumor drug therapy may correlate to tumor response.
- Cutaneous AE in anti-tumor drug therapy may be clinically unusual and severe.
- Cutaneous AE in anti-tumor drug therapy require special knowledge in diagnosis and management.
- Cutaneous AE in anti-tumor drug therapy generally are not therapy-limiting if properly managed.

Conflict of interest statement

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