# Chapter 10
# Dermatologic Side Effects of Systemic Anticancer Therapy

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**Abstract** Skin, hair, and nails are almost always modified by systemic cancer therapies. These changes can sometimes result in severe adverse events, but most of the patients present with light and moderate skin side effects. Nevertheless, these dermatologic manifestations can significantly impact patients' quality of life, especially in the case of new targeted agents that are sometimes prescribed continuously over long periods of time.

Patients have to be informed in advance about the skin symptoms that might occur during the course of their treatments. Preventive and symptomatic measures can be advised or prescribed that might optimize treatment compliance and improve quality of life.

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Close interaction between oncologists and dermatologist is warranted in order to describe, characterize, and manage the numerous and sometimes new and original skin manifestations of new cancer therapies. In this chapter, we will focus on the side effects associated with new targeted anticancer agents since oncologists and physicians are less informed about this field than they are about skin side effects of classical chemotherapeutic agents.

**Keywords** Cancer treatment • Skin adverse events • Targeted agents • Hand-foot skin reaction • Folliculitis • Keratoacanthomas • Skin squamous cell carcinoma • Hair changes • Paronychia

## Introduction

Abnormalities leading to cell transformation and unrestrained proliferation are usually linked to a deregulation of the normal signaling pathways that control cell differentiation and/or proliferation. New drugs targeting these pathways are being developed. They block more or less specifically one or several enzymes, usually kinases, that are sequentially activated following a chain reaction, from the surface of the cell membrane after binding of a ligand to the corresponding cell surface receptor to the inside of the cell cytoplasm.

Targeted therapies that rely on the specific inhibition of biological events implicated in oncogenic or proliferative processes are now commonly used and still actively being developed. Two types of molecules can be used to inhibit a protein kinase: (1) small molecules designed to inhibit the enzymatic activity of specific kinases (the suffix "–ib" is usually used to name these molecules) and (2) larger molecules, monoclonal antibodies (mAb, suffix "–ab") that bind to ligand or receptors to prevent their interaction and the subsequent pathway activation.

When a skin modification occurs during the course of a cancer treatment, the first question to address is whether this

symptom is related to therapy or not. Indeed, infectious, inflammatory, and specific skin lesions as well as graft-versus-host disease-related rash can also be observed in these patients and have to be identified. Sometimes, the patients are treated with multiple drugs, and it is not easy to know which one is responsible for the skin changes observed.

Second, it is critical to identify the serious hypersensitivity skin reactions that require treatment discontinuation and/or specific management. The signs that suggest the possibility of a DRESS (drug reaction with eosinophilia and systemic symptom), Stevens-Johnson syndrome, or a TEN (toxic epidermal necrolysis) include mucosal involvement, bullous lesions, and the association with clinical or biological systemic symptoms such as elevated temperature, transaminase elevation, or hypereosinophilia.

In this chapter, we will review the skin side effects of anti-EGFR agents, anti-vascular endothelial growth factor (VEGFR), anti-kit, platelet-derived growth factor receptor (PDGFR) and bcr-abl inhibitors, RAF inhibitors, as well as the ones induced by mammalian target of rapamycin (mTOR) inhibitors.

Management of these numerous and various side effects associated with targeted agents will also be addressed, although they are still mostly empirical and rely on expert advices and consensus.

## EGFR Inhibitors

The epidermal growth factor receptor (EGFR) belongs to the family of HER receptors, which comprises four members: HER1 to HER4. HER1/EGFR is expressed by 30–100 % of solid tumors, in which increased activity of this receptor is a poor prognostic factor. Several compounds, small molecule inhibitors or monoclonal antibodies, can specifically block HER1 or HER2 or both. All agents targeting EGFR produce the same spectrum of skin side effects with a direct dose effect.

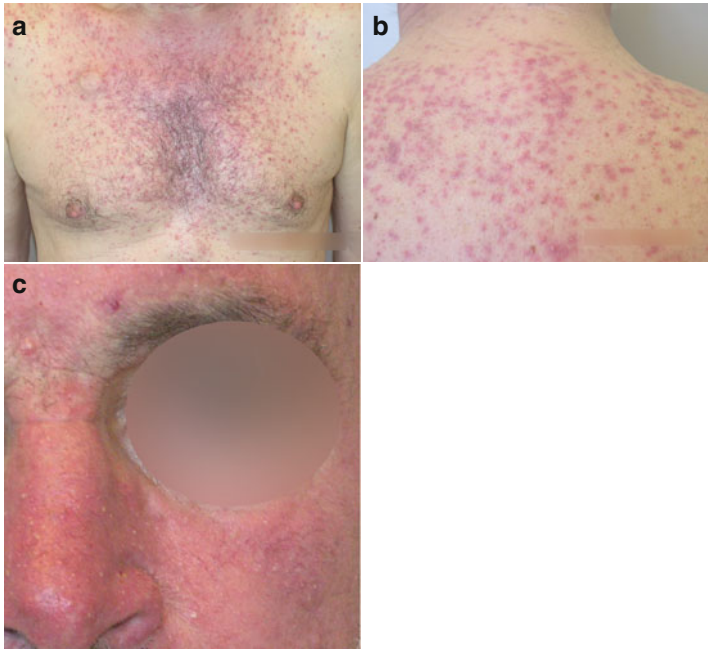


Figure 10.1 Papulopustular rash in a patient treated with EGFR inhibitor on the seborrheic areas of the trunk (**a**, **b**) and face (**c**)

## *Papulopustular Rash/Folliculitis of the Seborrheic Areas*

Papulopustular rash/folliculitis of the seborrheic areas (Fig. 10.1a–c) is the most common, the earliest, and the most impressive skin side effect of anti-EGFR agents, occurring in more than 75 % of patients after 1–2 weeks of therapy [1]. It is often described as acneiform, but in reality differs from an acne because although the lesions are follicular papulopustules located in the seborrheic areas (face, scalp, trunk), no retentional lesions or comedones are present. The severity varies from a few lesions to a profuse eruption that is described as uncomfortable and sometimes even painful by

the patients. Durable pigmented postinflammatory maculae can be observed, especially in patients with pigmented skin.

Pathology shows nonspecific aseptic suppurative folliculitis, but mononuclear cells are recruited at the early stages, before neutrophils are recruited.

The most commonly used classification is the CTCAE (common terminology criteria for adverse events) grading system version 4. Another classification, more adapted to the side effects of anti-EGFR, has been proposed.

Severe rashes (grade 3) occur in less than 10 % of patients [1, 2]. They require local and systemic treatment and sometimes a dose reduction and even temporary treatment discontinuation. A progressive attenuation of the folliculitis is usually observed after several months [3].

The mechanism underlying this folliculitis is related to the critical role of the EGF receptor in epidermal and pilosebaceous follicle homeostasis [4, 5] involving primary cytokines like IL-1α (alpha) and TNFα (alpha) [6].

Interestingly, the occurrence and intensity of this eruption are associated with a better tumor response and overall survival of patients [7]. Several hypotheses can be formulated to explain this correlation. It has been suggested that some polymorphisms of EGFR might be associated with both the appearance of cutaneous signs and better antitumor responses [8]. This toxicity/efficacy correlation could also be explained by better bioavailability of the drug in the skin and the tumor. However, other hypotheses cannot be excluded, such as that of a beneficial effect of the inflammatory/immune reaction in the skin and perhaps also in the tumor.

Management of this eruption relies, as usual, on a good information from the patient prior to treatment initiation as well as on symptomatic topical and/or systemic treatments, depending on the severity of the rash and the impact on the patient [1, 9–11].

Topical treatment, relying on local antibiotics (erythromycin, clindamycin, metronidazole) and copper- and zinc-based antiseptic creams, is usually sufficient in the case of a grade 1 eruption. Patients are allowed and advised to camouflage the

lesions with appropriate nonocclusive makeup (tested as noncomedogenic). Topical corticosteroids are usually effective when antibiotics are not sufficient [12].

Systemic treatment is used when the lesions are extensive, profuse, or poorly tolerated by the patient (grades 2 and 3). Cyclines (doxycycline, 100–200 mg/day) are used as first-line therapy for 4–8 weeks and for longer periods of time, if needed. Cyclines are probably active in this indication through their anti-inflammatory action. Preventive treatment with tetracyclines has been evaluated in some prospective studies. These studies have shown that tetracyclines reduced both the intensity and impact of the eruption, but not the incidence of the rash [13, 14]. Patients should be advised to avoid sun exposure during tetracycline treatment because of the phototoxicity of this class of antibiotics.

Psychological management of patients should not be neglected, and it is critical to regularly tackle questions about the impact of the eruption on their socio-occupational and emotional lives.

Doses of anti-EGFR should be reduced if the skin reaction is severe or if the treatment is poorly tolerated by the patient (grade 3). The folliculitis is dose dependent and rapidly attenuates after the reduction or interruption of treatment. It does not necessarily recur upon resumption of therapy.

## *Paronychia*

Paronychia (Fig. 10.2) is probably the most concerning side effect of EGFR inhibitors since it frequently has functional consequences and its treatment is difficult. It presents as an inflammation of the periungual folds that resembles an ingrowing nail. In fact, it is a pyogenic granuloma that grows on top of the lateral fold of the nail. It more often affects the toes than the fingers, and more specifically the large toes, probably because it is the most frequently traumatized. Paronychia occurs later in the course of the treatment, after at least a month of treatment, and is less frequently observed than the folliculitis. It occurs in 10–25 % of patients [15]. The

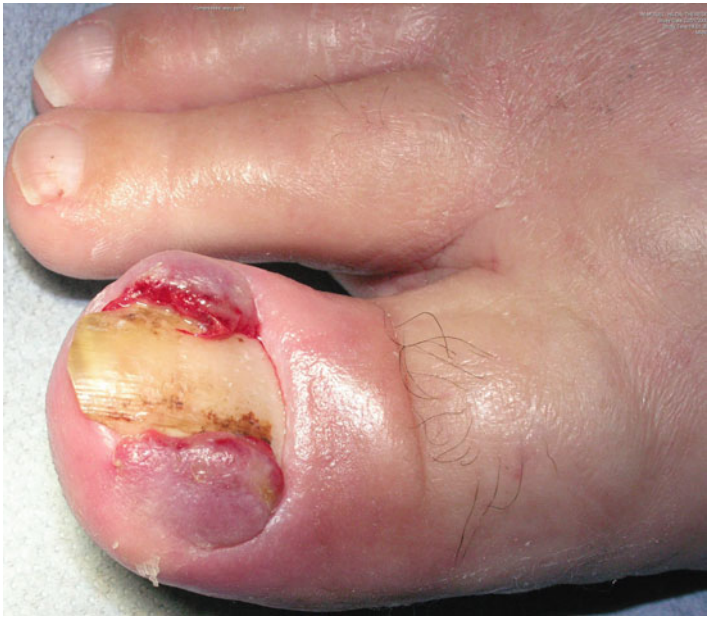

FIGURE 10.2 Paronychia of the right big toe in a patient treated with EGFR inhibitor

impact on daily life can be major, as these lesions are painful and can prevent the patient from wearing shoes and interfere with their walking. As with folliculitis, the lesions are aseptic, but superinfections are common. Management is difficult, and the aim is to reduce the extent of the granulation tissue or even destroy it completely by using either topical corticosteroids that can also be injected in the pyogenic granuloma (close monitoring is important as steroids promote superinfections) or by chemical cautery with liquid nitrogen, silver nitrate, or trichloroacetic acid. Surgical excision followed by the application of phenol can be necessary and is an effective treatment, but it must be performed by experienced physicians. Indeed, it can induce periosteitis if phenol is too vigorously applied. Prophylactic measures such as avoiding friction, traumas, and manipulations and wearing wide, open shoes minimize aggravating factors.

### *Xerosis*

Dry skin is reported in about one-third of the patients after 1–3 months of treatment. It is, in reality, observed in almost all the patients treated with EGFR inhibitors. Xerosis is usually diffuse and easily controlled by emollients. They are more effective if applied after showering, on skin that is still humid. Long, hot baths should be avoided. Xerosis can also predominate on the extremities, where it can result in painful, fissured dermatitis of the finger pulp or heels that can have painful and functional impacts. Vitamin A- or urea-based ointments can help patients.

### *Hair Modification*

Alopecia and a change in hair texture are observed after 2–3 months of treatment in almost all of the patients treated (Fig. 10.3a, b). Alopecia with hair loss in the temporal recesses and the frontal region resembling androgenic alopecia occurs frequently, as does modification of the hair texture, which becomes "straw-like," dry, and fine [1].

Facial hypertrichosis is common, as is eyelash trichomegaly, with fine and wavy eyelashes, after several months of treatment. The eyelashes can curve back toward the conjunctiva and cause keratitis. All these hair side effects are more readily apparent in women, who are inconvenienced more than men by these side effects [16].

Patients can be advised to use hair conditioners, to wax their facial hair, and to regularly trim their eyelashes to prevent conjunctive complications.

## kit and bcr-abl Inhibitors: Imatinib, Nilotinib, and Dasatinib

Imatinib (Gleevec, Novartis, New York, NY, USA), nilotinib (Tasigna, Novartis, New York, NY, USA), and dasatinib (Sprycel, Bristol-Myers Squibb, New York, NY, USA) inhibit c-kit,

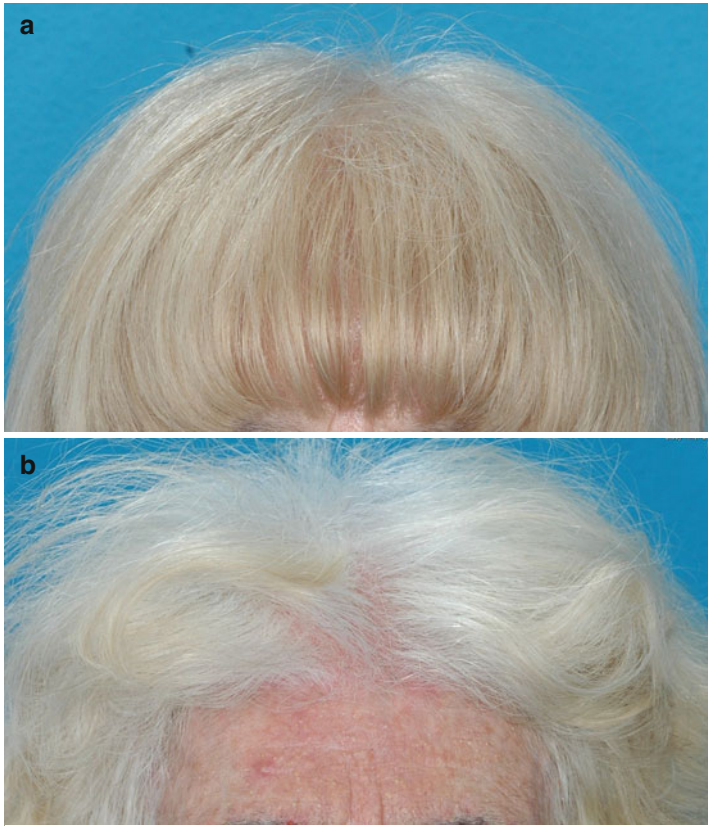


FIGURE 10.3 Hair modification. Photo taken before (**a**) and 3 months after (**b**) initiation of treatment with anti-EGFR therapy

PDGFR, and the bcr-abl fusion protein, characteristic for chronic myeloid leukemia (CML). The c-kit receptor (CD117) is activated by mutation in the majority of gastrointestinal stromal tumors (GIST), and the bcr-abl protein is the product of the translocation between chromosomes 9 and 22 found in chronic myeloid leukemia (CML). PDGFRα (alpha) is involved in hypereosinophilic syndrome, and TEL-PDGFRβ (beta) is involved in chronic myelomonocytic leukemia (CMMoL). The loop, PDGFR/PDGFR, is involved in dermatofibrosarcoma.

Overall, these three drugs are well tolerated, and although skin manifestations are the most frequent nonhematologic AEs, they are rarely severe and usually do not require treatment interruption.

## *Imatinib (Gleevec)*

More information is available for imatinib than for other, more recent drugs targeting kit or PDGFR. Dermatologic manifestations of imatinib are common but rarely severe, with a prevalence ranging from 9.5 to 69 % [17–23].

Edema, predominating on the face and more visible on the periorbital areas in the morning and inferior parts of the body in the evening, is reported in 63–84 % of cases and appears, on average, 6 weeks after initiation of treatment [19–24]. It can be severe, with substantial weight gain and even pleural and/or peritoneal effusions or cerebral edema [25]. The pathophysiology is unclear and is thought to be due to a modification of interstitial fluid homeostasis linked to PDGFR inhibition [1].

Maculopapular eruptions are described in up to 50 % of the patients and appear, on average, 9 weeks after the initiation of therapy [19, 24]. They are usually mild to moderate, self-limiting, or easily manageable with antihistamines or topical steroids [23]. Pathological studies demonstrate nonspecific perivascular mononuclear cell infiltrates [19, 24]. More severe eruptions (grades 3 and 4) have rarely been reported [19].

Several well-documented cases of Stevens-Johnson syndrome have been published [26–31] as well as several cases of acute generalized exanthematous pustulosis [32, 33] and a case of DRESS (drug reaction with eosinophilia and systemic symptoms) [34].

Nilotinib-associated rash is reported in 17–35 % of the patients, pruritus in 13–24 %, alopecia in 10 %, and xerosis in 13–17 %. The majority of the cases are mild to moderate and dose dependent [35, 36].

The most frequently reported dermatologic side effects reported with dasatinib are localized or diffuse maculopapular rashes (13–27 %) that are often associated with pruritus (11 %) [15].

Exacerbations of psoriasis or psoriasiform eruptions have also been described [19, 37] as well as follicular pustular eruptions similar to pustular psoriasis [37] or eruptions resembling pityriasis rosea [38, 39].

Several cases of palmoplantar hyperkeratoses and nail dystrophies have also been reported [40].

Lichenoid eruptions, sometimes associated with mucosal erosive or lichenoid intrabuccal lesions, have been reported [41–47]. They usually present as red-purple papular lesions localized symmetrically on the trunk and limb.

Pigmentary changes (Fig. 10.4) – localized or diffuse pigmentation modifications – have been frequently reported with imatinib, and rare cases have been reported with dasatinib and nilotinib. Homogeneous depigmentation has been observed, particularly in patients with pigmented black or tanned skin (phototypes 5–6), with a reported prevalence of 16–40 % [19, 48, 49]. Conversely, cases of hyperpigmentation or even repigmentation of the skin and hair have been reported [19, 50, 51]. These pigmentary changes are reversible upon treatment discontinuation and might be due to the inhibition of c-kit, whose involvement in melanogenesis via the transcription factor MITF is well established [52, 53].

Several other various skin manifestations have been reported such as urticaria, neutrophilic dermatosis, vascular purpura [54], pseudolymphoma [55], and photosensitive eruptions [19, 56].

Eruptions and edema seem to be dose dependent. Indeed, the prevalence of drug eruptions increases with the daily dosage [19, 21]. This suggests pharmacologic and not immunologic mechanisms in the development of this type of manifestation [57].

With dasatinib, mucosal involvement has also been reported with mucositis and stomatitis in 16 % of the patients [58, 59].

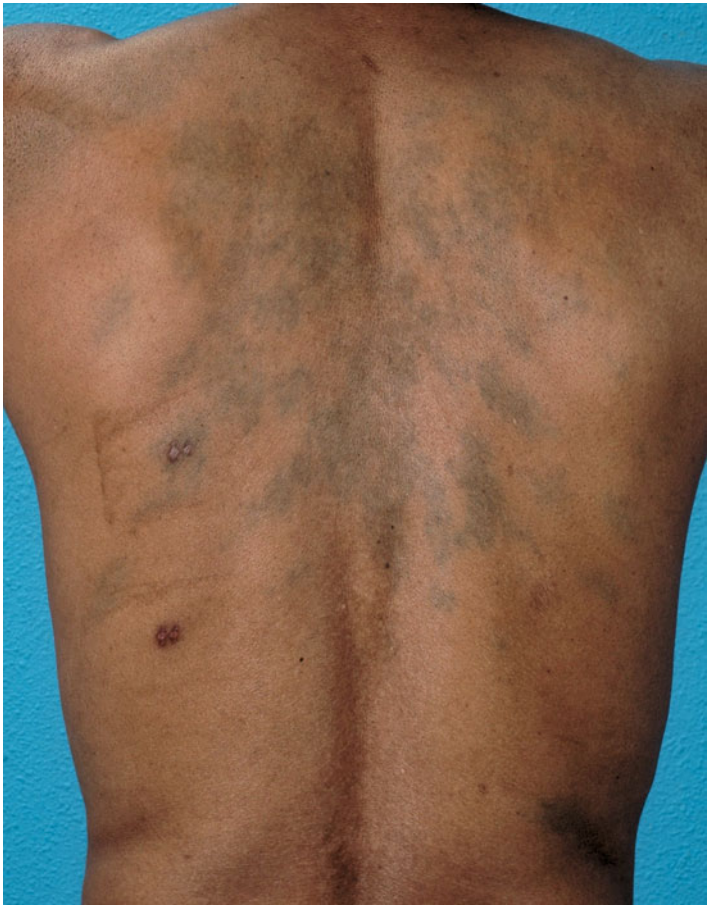

Figure 10.4 Hyperpigmented maculae in a patient treated with imatinib

## *Management*

Moderate periorbital edema does not require any treatment. Diffuse and/or severe edema can be alleviated by electrolyte monitoring and diuretics.

The majority of eruptions are easily managed with antihistamines and topical treatments, emollients, and/or corticosteroids and do not require treatment discontinuation. However, since most of the reported side effects are dose dependent, in the case of severe or persistent manifestations uncontrolled by symptomatic treatments, a dose reduction can be done. Obviously, in cases of severe and potentially life-threatening dermatologic adverse effects, treatment should be discontinued and not reintroduced.

## Antiangiogenic Agents: Sorafenib, Sunitinib, and Pazopanib

Small molecule kinase inhibitors like sorafenib (Nexavar, Bayer, Wayne, NJ, USA), sunitinib (Sutent, Pfizer, New York, NY, USA), and pazopanib (Votrient, GlaxoSmithKline, Philadelphia, PA, USA) are antiangiogenic agents targeting VEGF receptors (VEGFR) as well as additional receptors like PDGF receptors, kit, Flt3, and RAF (for sorafenib). They are indicated in the treatment of renal cell cancer, hepatocellular carcinoma, or GIST. Antiangiogenic small molecule inhibitors have various and numerous adverse effects; however, mucocutaneous manifestations are usually the most preeminent of them and frequently impact quality of life of the patients, often threatening compliance to treatment [1, 60, 61]. On the other hand, another antiangiogenic agent, bevacizumab (Avastin, Genentech, South San Francisco, CA, USA), which is a monoclonal antibody binding VEGF and preventing its binding to its receptors, has few cutaneous side effects.

Some adverse effects, like hand-foot skin reaction, genital rash, and subungual splinter hemorrhages, are common to the three compounds sorafenib, sunitinib, and pazopanib. Some other manifestations are more specifically observed with one or two of these drugs, as is the case for keratoacanthomas and squamous cell carcinoma of the skin, which occurs only in association of sorafenib and not with sunitinib or pazopanib.

## *Hand-Foot Skin Reaction*

Hand-foot skin reaction (HFSR) is frequent and usually occurs during the first weeks of treatment. It affects 10–63 % of patients treated with sorafenib (with 2–36 % of grade 3 severity) [62–68], 10–28 % of patients treated with sunitinib (4–12 % of grade 3) [69–71], and 11 % with pazopanib (2 % grade 3) [72–74].

It is different from the hand-foot syndrome seen with classical chemotherapies like capecitabine, 5-fluorouracil (5-FU) (Fig. 10.5), pegylated doxorubicin, or cytarabine chemotherapy [75–77]. With VEGFR inhibitors, the lesions are predominantly located on pressure or friction areas (metatarsal heads, heels, sides of the feet, metacarpophalangeal joints) and rapidly become hyperkeratotic (Fig. 10.6). With classical chemotherapies, hand-foot lesions are not limited to pressure areas and the lesions are inflammatory, erythematous, and possibly desquamative for several weeks. Hyperkeratosis can also occur but later after the beginning of the treatment. Hand and feet inflammation can also be seen with antiangiogenic agents, with erythema, desquamation, and even bullous lesions. An erythematous ring surrounding the hyperkeratotic lesions is also quite common [1, 60, 78]. The HFSR is classically bilateral and symmetrical [79]. Areas of preexisting hyperkeratotic lesions seem to confer a predisposition for painful sole involvement [79, 80]. While not life-threatening, HFSR can be very painful, interfering with everyday activities such as walking or holding objects. Prodromal subjective symptoms with mild tingling and numbness of the hands and feet are frequent [78].

The main pathological abnormalities observed in HFSR are keratinocyte degeneration with a perivascular lymphocytic infiltrate and sometimes eccrine squamous syringometaplasia [79, 81, 82]. Sequential pathological modifications found during the course of the treatment are changes in the stratum spinosum/stratum granulosum during the first month and then in the superior layers of the epidermis, in the stratum corneum with hyperkeratosis, and focal parakeratosis after the first month [82].

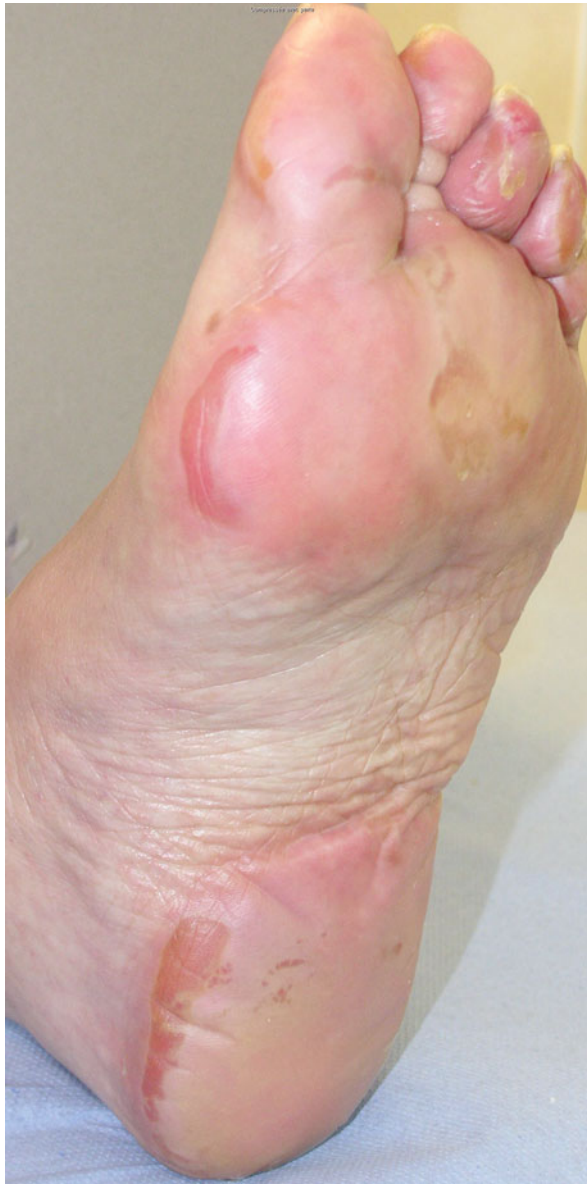

Figure 10.5 Grade 3 hand-foot skin reaction of a patient treated with 5-fluorouracil

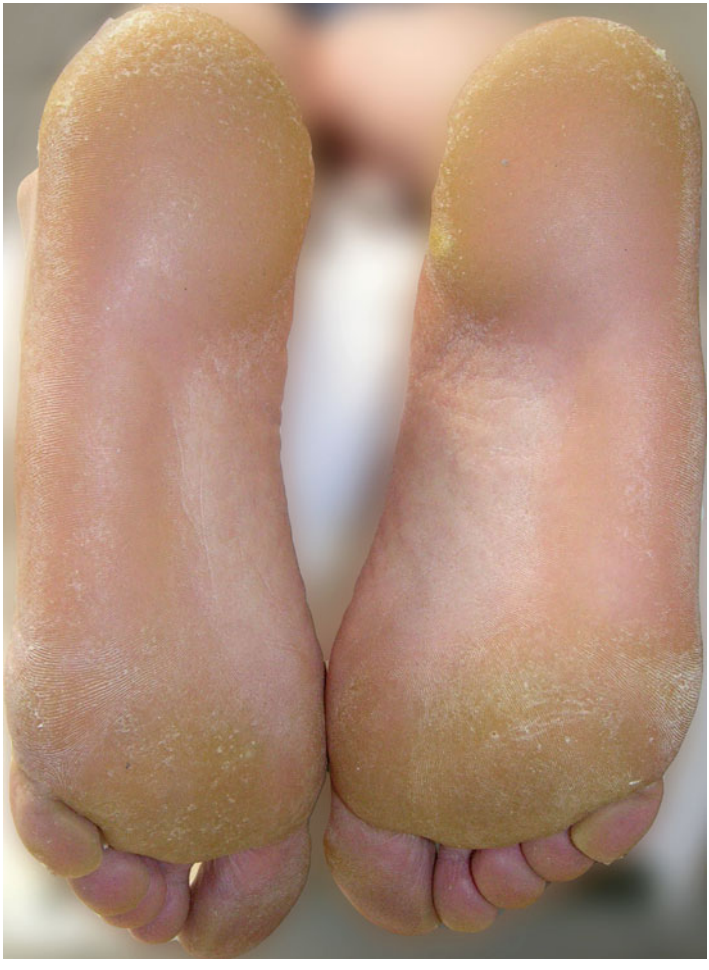

Figure 10.6 Grade 1 hand-foot skin reaction in a patient treated with sorafenib

## Management

HFSR is clearly dose dependent and may improve with dose reductions or treatment interruptions. Management has not yet been evaluated by controlled studies and is currently

based on prescribers' experience and advice by experts' consensus [83]. Guidance can be split into preventive measures and management strategies.

## Preventive Measures

The patients must be clearly informed that an HFSR might occur; ideally, they should have their hands and feet examined prior to treatment initiation. A podiatric examination and preventive treatment of preexisting hyperkeratotic areas by mechanical or chemical keratolytic measures (topical 10–50 % urea, 2–5 % salicylic acid ointments) seem helpful. Emollients can be used to prevent dryness and cracking. Prescription of orthopedic soles may also be helpful in patients with unbalanced sole pressure areas.

Patients should be advised to wear comfortable and flexible shoes and to avoid rubbing and trauma. As a memory aid, these measures can be referred to as the "3C" approach: control calluses, comfort with cushions, and cover with cream [83].

## Treatment

Treatment is based on symptomatic measures and dose adjustment. Therapeutic measures are proposed according to the three HFSR severity grades NCI-CTCAE classification V4:

- Grade 1: Supportive measures include using moisturizing creams, keratolytic agents such as 40 % urea, and/or creams or ointments containing 1–10 % salicylic acid on the callused areas. Cushioning of the affected regions with gel- or foam-based shock absorber soles and soft shoes is recommended. Treatment is maintained at the same dosage.
- Grade 2: The same symptomatic measures as for grade 1 should be initiated promptly; potent topical corticosteroids (clobetasol) can be prescribed on inflammatory lesions for a few days. Analgesic treatment should be considered, if needed. A dose reduction of 50 % should be considered until the HFSR returns to grade 0 or 1, particularly in the event of a second episode of grade 2 HFSR. If

toxicity resolves to grade 0 or 1, reescalation to the initial dose should be done. Decision whether to reescalate the dose after the second or third occurrence of grade 2 HFSR should be based on clinical judgment and patient preference. If toxicity does not resolve to grade 0 or 1 despite dose reduction, treatment should be interrupted for a minimum of 7 days and until toxicity has resolved to grade 0 or 1. When resuming treatment after dose interruption, treatment should begin at reduced dose. If toxicity is maintained at grade 0 or 1 at reduced dose for a minimum of 7 days, initial dose should be given.

- Grade 3: Symptomatic measures as described for grade 2 HFSR should be prescribed as well as antiseptic treatment of blisters and erosions. Treatment should be interrupted for a minimum of 7 days and until toxicity has resolved to grade 0 or 1. When resuming treatment after dose interruption, treatment should begin at a reduced dose. If toxicity is maintained at grade 0 or 1 at reduced dose for a minimum of 7 days, initial dose should be given again. On the second occurrence of grade 3 HFSR, decision whether to reescalate dose should be based on clinical judgment and patient preference. The same principle applies for the decision whether to discontinue therapy after the third occurrence of grade 3 HFSR.

No systemic therapy has demonstrated any beneficial effect until now.

## *Subungual Splinter Hemorrhages*

Ranging from 3 to 70 %, depending on the series, subungual splinter hemorrhages occur with the three compounds (sorafenib, sunitinib, pazopanib), but their frequency is often underestimated because of their asymptomatic nature. They appear as painless longitudinal black lines beneath the distal part of the nail plate in the first weeks of therapy. They can be clinically identical to those observed in certain systemic diseases such as rheumatoid arthritis, systemic lupus, or Osler's

endocarditis, but they are not associated with distant embolic or thrombotic processes, unlike these conditions. Inhibition of the VEGF receptor coupled with local microtraumas could explain the symptom. They disappear progressively at the end of treatment and do not require any treatment [78, 80, 84].

## *Erythematous Rash*

Various erythematous rashes are observed with these three compounds – in 13–24 % of cases with sunitinib [85, 86], in 10–60 % with sorafenib [78, 85, 87], and in 6–8 % with pazopanib [72–74]. They usually appear during the first weeks of treatment. They are usually minor, relatively asymptomatic maculopapular eruptions, but can sometimes be more severe and diffuse. They can predominate on the face, as is often the case in the first weeks of sorafenib therapy, where a mild erythematous and desquamative facial rash, resembling seborrheic dermatitis, is frequently observed [78]. Rashes can disappear spontaneously despite continued treatment, but temporary discontinuation of therapy may be necessary in some cases. A case of erythema multiforme has been published [88], and signs of severity such as mucosal involvement, epidermal detachment, and general signs (fever, elevated hepatic enzymes) that can be associated with severe manifestations, toxic epidermal necrolysis, or a DRESS syndrome should always be evaluated

## *Hair Modification*

Largely underreported in the literature, hair modifications are almost always associated with these drugs. It can be only a minor texture change, with hair usually becoming dryer and curlier. Alopecia occurs in 21–44 % of patients on sorafenib [78, 89]. It occurs slightly less frequently with sunitinib (5–21 %) and pazopanib (8–10 %). [72–74] It is usually moderate and develops gradually after several weeks or months. It can be associated with loss of hair in other hairy regions (trunk, arms, pubis).

It is not unusual to see hair growing back even though patients are still on therapy with sorafenib. New-grown hair is usually curlier than it was before treatment.

Reversible hair depigmentation is seen frequently with sunitinib (7–14 %) [85, 90, 91] and pazopanib (27–44 %) [72, 73]. With sunitinib, which is given 4 weeks on and 2 weeks off, characteristic discoloration can occur, with successive depigmented bands related to periods of treatment and normally pigmented bands associated with periods off treatment [91, 92]. The underlying mechanism of the depigmentation is thought to be a melanogenesis defect resulting from the inhibition of the c-kit pathway; however, this must not be a direct effect of kit inhibition since other kit inhibitors, such as imatinib, dasatinib, or nilotinib, do not induce such systematic hair depigmentation.

### *Xerosis*

The skin becomes dryer with these treatments [1, 78], and symptomatic emollient treatments are usually efficient.

### *Genital Rash*

Genital rash with erythematous, desquamative psoriasiform, or lichenoid lesions can be observed in the genital areas of both male and female patients (Fig. 10.7) [61, 93]. Lesions can involve the vulvar or scrotal areas and extend to the inguinal region. It can occasionally result in phimosis. Histological analysis, when performed, revealed a psoriasiform or lichenoid pattern. Such genital rashes have been observed with sorafenib, sunitinib, and pazopanib [62]. Their real incidence is unknown. Careful and systematic questioning is necessary. Treatment with topical steroid can be proposed after ruling out a bacterial or fungal infection. A temporary dosage modification is sometimes necessary, resulting in a rapid improvement of the symptoms.

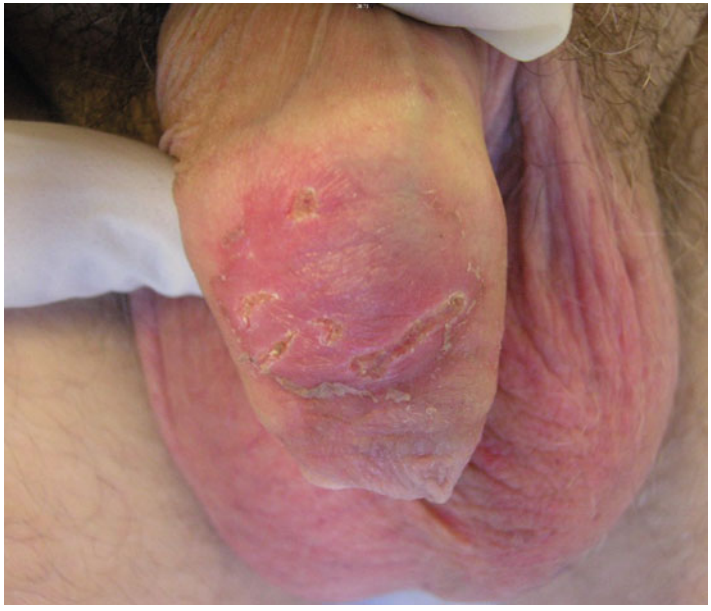

FIGURE 10.7 Genital rash in a patient treated with sunitinib

## *Mucositis*

Mucositis is characterized by painful inflammation and ulceration of the mucous membranes lining the digestive tracts, whereas stomatitis more specifically refers to inflammation of the mucosae lining the mouth, and cheilitis, to inflammation of the lips. These side effects can give rise to pain and difficulty with speaking or eating. Stomatitis and cheilitis have been reported in 19–35 % of sunitinib-treated patients and 19–26 % of sorafenib-treated patients [71, 78, 85, 94], usually during the first weeks of treatment. They are dose dependent and can require dose modifications [85].

## *Adverse Effects Specifically Related to Sunitinib*

### Skin Discoloration

A yellow appearance of the skin is seen with sunitinib. It is rapidly reversible and decreases during the 2 weeks off treatment. It is probably due to the bright yellow color of the drug itself [1].

### Facial Edema

A mild to moderate facial edema is seen in 4.5–24 % of patients treated with sunitinib [95]. Hypothyroidism, which is a frequent complication of sunitinib, can exacerbate this edema.

### Xerostomia

Xerostomia is commonly seen with sunitinib and can result in difficulty with speaking and eating as well as in the occurrence of tooth cavities and vulnerability to mouth infection.

## *Adverse Effects Related Specifically to Sorafenib*

### Eruptive Nevi

In patients treated with sorafenib, several cases of eruptive nevi have been observed on the face, trunk, or limbs, including the palmoplantar areas [89, 96]. Pathologically, the lesions that were biopsied presented as junctional nevi. Because of the pro-senescence effect of BRAF protein in wild-type BRAF cells [97, 98], it can be hypothesized that these nevi eruption could be linked to an "anti-senescence effect" with the appearance and the development of subclinical preexisting nevi.

### Squamous Cell Proliferations: Keratoacanthomas and Squamous Cell Carcinomas

Over the last few years, several cases of skin tumors, keratoacanthomas (KA) (Fig. 10.8), and squamous cell carcinomas

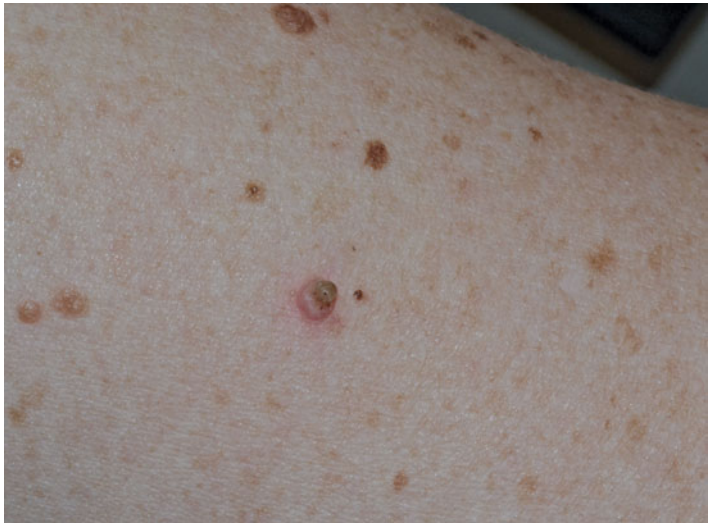

Figure 10.8 Keratoacanthoma in a patient treated with sorafenib

(SCC) have been described during the course of sorafenib therapy [99, 100]. These lesions could be multiple and occurred several weeks to months after initiating the treatment with an estimated incidence of less than 10 %. Beside the contexts of uncommon genetic diseases like Ferguson-Smith or Muir-Torre syndromes, KA is a rare lesion preferentially occurring on sun-exposed areas and presenting as a fast-growing, dome-shaped nodule with a central keratotic crust. It does not give rise to metastases and can occasionally spontaneously regress. Pathologically, it is almost undistinguishable from a well-differentiated SCC, with an exoendophytic proliferation and a crateriform zone of well-differentiated squamous epithelium surrounding a central keratotic plug. The existence of KA is still controversial since for some authors this entity should be assimilated to a well-differentiated form of SCC [101–103]. In contrast to KA, SCC is a real malignant lesion that does not regress spontaneously and can give rise to metastases. It is a frequent skin tumor and most of the time related to sun exposure or to the existence of precancerous lesions like

actinic keratoses, for example. However, the SCC observed during sorafenib therapy do not appear as the typical and most frequently reported SCC. They all exhibit clinical and pathological aspects close to KA and are usually described pathologically as KA-like SCC with nest of atypical cells invading the dermis as well as a crateriform pattern with bulging borders reminiscent of KA. They are not always located on sun-exposed areas [99]. Until now, no metastatic evolution of any SCC induced by sorafenib has been reported, and they rather appear as low-aggressiveness skin tumors.

Looking at the molecules targeted by sorafenib, it could be deduced that this particular side effect was likely to be due to RAF inhibition. Indeed, no KA or SCC has ever been reported with drugs targeting the molecules inhibited by sorafenib in addition to RAF proteins – that is, PDGFR, FLT3, or VEGFR – like sunitinib (VEGFR, KIT, PDGFR, FLT3) or imatinib (kit, PDGFR), for example. This reasoning proved to be correct since similar tumors are now described with the use of two new drugs, presently in development, that efficiently and specifically target RAF proteins and more particularly the mutant form of BRAF: $BRAF^{V600E}$.

BRAF is a serine/threonine kinase, downstream from the RAS proteins and upstream from MEK and ERK on the MAPK (mitogen-activated protein kinase) signaling pathway [104]. This pathway is constitutively activated in several cancers, including melanomas, favoring cell proliferation and survival. It is activated in more than 65 % of melanomas resulting from the recurrent $BRAF^{V600E}$ mutation in 40–50 % of the cases and NRAS mutation in 15–20 % of the cases [105].

The mechanism explaining the appearance of skin tumors with sorafenib and RAF inhibitors is probably due to a paradoxical RAF-MEK-ERK signaling pathway activation via cells that do not harbor the BRAF mutation, especially if the cells have a mutant RAS protein, as was shown recently in several in vitro models [106–110].

Advice is given that patients' skin should be carefully monitored and that KA and SCC should be removed. These lesions should be completely resected, and simple shaving of

the lesions, leading to partial resection only, should not be performed.

In addition to KA and SCC, more or less inflammatory follicular cystic lesions are frequently observed in patients treated with sorafenib: keratosis pilaris [87], microcysts, dystrophic follicular cystic lesions, and perforating folliculitis [78, 87, 99]. Association of these lesions with KA and SCC in the same patients suggests that they could represent various aspects of a wide spectrum of lesions from benign cystic lesions to borderline (KA) and malignant skin tumors (SCC) [99, 109, 110].

## RAF Inhibitors

BRAF is the most frequently mutated protein kinase in human cancer and is the target of several anticancer drugs. The potency and the specificity of BRAF inhibitors available on the market or under clinical development are variable. Sorafenib (Nexavar, Bayer/Onyx) is a pan-RAF inhibitor that also blocks vascular endothelial growth factor receptors (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor-b (PDGFR-b), fms-like tyrosine kinase 3 (FLT3), and kit. Conversely, vemurafenib (Zelboraf, Plexxikon/Roche) is highly selective and very potent BRAF inhibitor that is effective against tumors harboring BRAF mutations and dependent on the RAF/MEK/ERK pathway, like melanoma with V600E *BRAF* mutation.

### *Skin Neoplasms: Papillomas, Keratoacanthomas, Cutaneous Squamous Cell Carcinomas, and Melanomas*

In spite of their variability in terms of BRAF selectivity and clinical activity, all RAF inhibitors are associated with one and the same intriguing cutaneous side effect, which is the emergence of borderline squamous cell neoplasms: skin papillomas (Fig. 10.9), keratoacanthomas (KA), and squamous cell carcinomas (SCC).

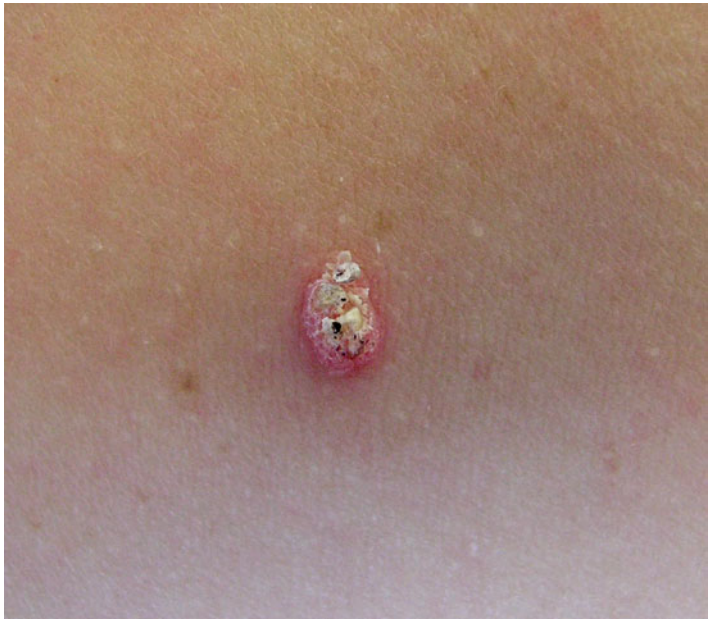

FIGURE 10.9 Skin papilloma in a patient treated with vemurafenib

These paradoxical keratinocyte proliferations arise in less than 10 % of patients treated with sorafenib. They occur much more frequently with vemurafenib, having been described in 15–25 % of the patients [110, 111].

Indeed, vemurafenib frequently induces multiple benign skin tumors resembling human papilloma virus–related papillomas or warts, keratoacanthomas, and cutaneous skin carcinomas during the first weeks or months of treatment. Until now, no metastatic squamous cell carcinoma has been reported, and these skin neoplasms can easily be surgically excised or destroyed.

They are due to a paradoxical activation of the MAPK pathway in keratinocytes associated with BRAF/CRAF heterodimerization and subsequent CRAF activation. Additional somatic events such as a *HRAS* mutation or *EGFR* activation giving rise to MAPK pathway coactivation might be required for full transformation of keratinocytes [109, 112].

Eruptive nevi and thin melanomas have rarely been reported with vemurafenib [113].

They might be related to the same mechanism as keratinocyte proliferation or to an anti-senescence effect of vemurafenib.

The other skin side effects of sorafenib have been reviewed earlier in the antiangiogenic section of this chapter. We will now see the side effects associated with the specific BRAFV600E inhibitor vemurafenib, which is authorized for the treatment of metastatic melanoma after a rapid clinical development reporting a rate of objective response around 50 % and a benefit in terms of overall survival in this population of patients [114–116].

Photosensitivity is frequently observed with vemurafenib in 30–70 % of the patients. It can occur with moderate sun exposure, and patients have to observe strict photoprotection measures: clothes and potent sunscreen with UVA and UVB blockers.

Skin rash, that can present as maculopapular rash or as a keratosis pilaris occur frequently, predominantly on the trunk and the extension parts of the limbs. Rashes are reported in up to 75 % of the patients but rarely impair treatment continuation.

Hair modification and alopecia similar to the ones that are induced by sorafenib are seen.

Hand-foot skin reaction with hyperkeratosis on pressure and rubbing areas, resembling the symptoms observed with VEGFR inhibitors, is associated with vemurafenib, although the symptoms are less severe than those seen with anti-VEGFR and very few patients present with severe inflammatory or bullous lesions (Fig. 10.10). Hyperkeratosis can also be seen on additional skin-rubbing areas like the nipples or the elbows.

Xerosis is reported in 15–20 % of patients and pruritus in 10–30 %.

## mTOR Inhibitors: Everolimus and Temsirolimus

These drugs inhibit the serine/threonine kinase mTOR (mammalian target of rapamycin), inducing downstream dephosphorylation of the mTOR molecular targets and ultimately

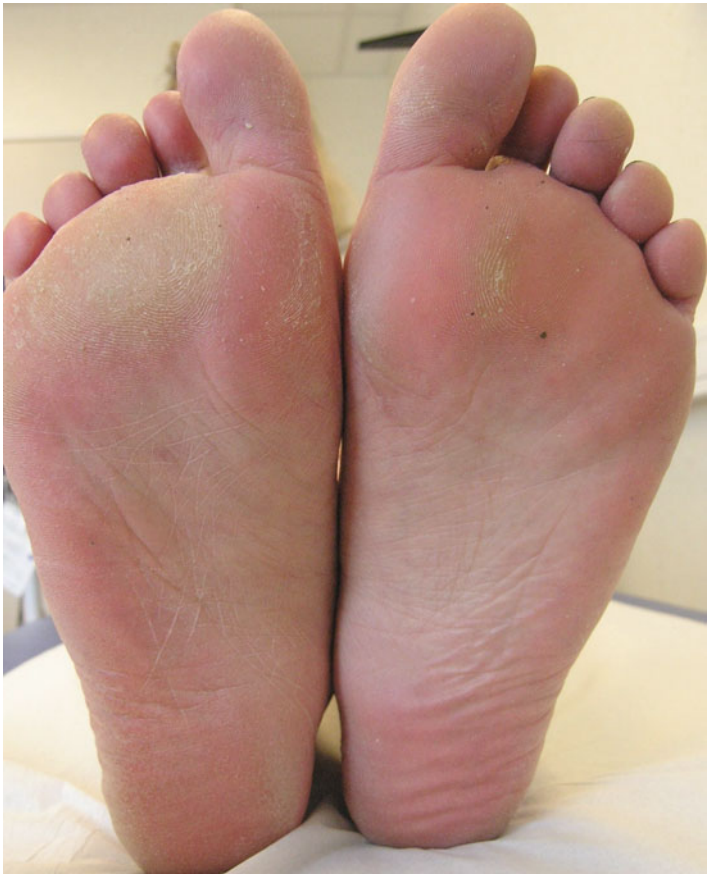

FIGURE 10.10 Grade 2 hand-foot skin reaction in a patient treated with vemurafenib

inhibiting the PI3K/AKT/mTOR signaling pathway. This particular signaling pathway plays a critical role in tumor cell biology, especially in regulating cell growth, survival, and proliferation and apoptosis mechanisms, and is also actively involved in angiogenesis [117–119].

Two compounds are approved in the treatment of advanced or metastatic renal cell cancer: temsirolimus (Torisel, Wyeth,

Madison, NJ, USA) and everolimus (Afinitor, Novartis, New York, NY, USA). These drugs are associated with various side effects, among which mucocutaneous adverse effects are the most frequently represented.

## *Rash*

Skin rash is reported in 25–61 % of patients on everolimus and 43–76 % of patients on temsirolimus. Usually mild to moderate (0–6 % of grade 3 or 4), it appears during the first weeks of treatment. It rarely requires dose modifications or treatment interruption. The rash is not very well characterized and few series provide details on its clinical presentation. However, the rash is described as papulopustular or acneiform eruptions, in 30–40 % of the patients. There are no associated retention lesions (microcysts, blackheads), which distinguishes this rash from a true acne. A nonspecific neutrophilic dermoepidermal infiltrate has been found pathologically. Therapeutic management is currently, and by analogy, based on that proposed for anti-EGFR inhibitors.

## *Stomatitis and Oral Ulcerations*

Stomatitis, mucositis, cheilitis, and oral ulcerations resembling aphthous ulcers are very common with both drugs: in up to 40 % of patients with everolimus and 70 % with temsirolimus [117, 120–126]. These side effects are dose dependent and can sometimes entail a dose reduction or treatment interruption, especially in the case of oral ulceration, which is often very painful and can impact patients' food intake.

Xerostomia is reported in 5–11 % of patients treated with everolimus, and a dysguesia has been observed with both compounds [120, 121, 123–125].

Management of these side effects relies on symptomatic measures: topical or systemic analgesics or topical steroids. However, these palliative measures are frequently not effective enough, and dose modification, or temporary treatment discontinuation, is often necessary.

### *Paronychia/Pyogenic Granulomas*

Nail involvement, sometimes described as nail dystrophy or thickening of the nail table, has been reported sporadically with both compounds in 5–46 % of the cases. Paronychia and/or pyogenic granulomas very similar to the lesions observed with EGFR inhibitors are also observed; their incidence is unknown. Management relies on symptomatic measures similar to the ones proposed for anti-EGFR.

Xerosis and pruritus seem common (20 and 30 %, respectively) and are sometimes associated. Pruritus is observed in 40 % of patients treated with temsirolimus with 1 % of grades 3–4.

Edema is also reported in up to 35 % of the patients [95, 122, 127].

## Summary

Systemic cancer, and especially new targeted agents, induces extremely frequent and various skin manifestations that can significantly impact a patient's quality of life and compliance with therapy. Potentially serious adverse events that can require treatment interruption have to be recognized early. Patients must be informed of the risk before the treatments are initiated, and preventive measures can sometimes be advised. Optimal management of these skin side effects requires close interaction between prescribers and dermatologists.

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