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REVIEW ARTICLE

Dermatological Toxicity Associated with Targeted Therapies in Cancer: Optimal Management

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Abstract Targeted therapies have developed rapidly over the last few years in the field of oncology thanks to a better understanding of carcinogenesis. They target pathways involved in signal transduction (EGFR, HER2, HER3, HER4, FLT3, RAS, RAF, MEK, KIT, RET, mTOR, SRC, EPH, SCF), tumor angiogenesis (VEGFR, TIE2), and tumor microenvironment (PDGFR, FGFR). They rarely cause the systemic adverse reactions generally associated with chemotherapy, but frequently cause disabling and specific skin toxicity. The impact on patient quality of life can be important both in terms of symptoms caused and of potentially aesthetic consequences. Inappropriate management can increase the risk of dose reduction or discontinuation of the cancer treatment. In this review, we will discuss skin toxicity associated with the main drug classes—EGFR, BRAF, MEK, mTOR, c-KIT, CTLA4, and SMO inhibitors, and anti-angiogenic agents. Targeted therapy-induced skin toxicities will be detailed in terms of symptoms, frequency, evolution, complications, and topical and oral treatments in order to improve their diagnosis and management.

Key Points

Cutaneous toxicity is often the most frequent observed with the main targeted cancer therapies (EGFR, BRAF, MEK, mTOR, c-KIT, CTLA4, and SMO inhibitors, and anti-angiogenic agents)

It is rarely considered as severe, but can deeply impact quality of life and lead to dose decrease or premature discontinuation of treatment

Dermatologists, oncologists and hematologists who manage these patients must therefore be able to identify, prevent and manage these cutaneous adverse reactions

1 Introduction

The introduction of targeted therapies, based on a better understanding of the molecular changes involved in cancer development and progression, has marked a turning point in the field of oncology. Targeted therapies are divided into two main types—the monoclonal antibodies, administered intravenously, which target the extracellular domain of cell surface receptors and play a role in cell activation, and the tyrosine and serine threonine kinase inhibitors (TKI), small molecules administered orally, which inhibit the kinase activities of some intracellular enzymes. These treatments rarely cause the systemic adverse reactions generally associated with chemotherapy, but frequently cause skin and skin appendage toxicity. Their symptoms may be non-specific, as for xerosis, which is induced by all treatment

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types, or class-specific, as for papulopustular rash. These adverse reactions should be appropriately managed since they may impact the anti-cancer treatment process and also patient quality of life [1]. It is therefore essential that this toxicity is rapidly identified and managed. The dermatologist plays a key role at this level, together with the oncologists.

In this review, we will detail, for each therapeutic class, the molecules with their indication, as well as the symptoms and systemic and topical therapeutic management of their associated skin toxicity. We will present the epidermal growth factor receptor (EGFR), v-raf murine sarcoma viral oncogene homolog B (BRAF), mitogen/extracellular signal-regulated kinase (MEK), mammalian target of rapamycin (mTOR), v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (c-KIT), breakpoint cluster region-abelson (BCR-ABL), and cytotoxic T-lymphocyte-associated protein 4 (CTLA4), smoothened (SMO) inhibitors, and anti-angiogenic agents. The main dermatological toxicities observed are summarized in Table 1 according to the type of adverse event, and their medical management is summarized in Table 2. Grading of toxicity was made according to the National Cancer Institute—Common Terminology Criteria for Adverse Events (NCI-CTCAE) V4.0 throughout article.

2 Epidermal Growth Factor Receptor (EGFR) Inhibitors

Skin toxicity is the most common EGFR inhibitor (EGFRi)-induced toxicity and affects more than 80 % of patients. It requires EGFRi dose adaptation in about 20 % of patients, reaching 50 % when used in combination with radiotherapy [1]. It mainly includes a frequent and early papulopustular rash, frequent and delayed skin barrier alteration, and, more rarely and later, skin appendage involvement.

2.1 Molecules and Indications

Four molecules specifically target the EGFR (or human EGFR-1, HER-1)—cetuximab, panitumumab, erlotinib, and gefitinib. Two molecules target several receptors belonging to the HER family—lapatinib and afatinib. Their characteristics and indications are presented in Table 3.

2.2 Papulopustular Rash or EGFR Inhibitor-Induced Folliculitis

Papulopustular rash must be differentiated from acne because its clinical presentation and pathophysiology are totally different [2, 3]. It is very common, affecting 50–80 % of patients depending on the molecules, and has been reported with all EGFRi [1, 4]. Its severity is dose-dependent and correlated with the tumor response for several tumors [1, 4]. It is characterized by papules and aseptic pustules centered by a follicle, generally occurring on an erythema (Fig. 1a) [4]. The lesions are monomorphic but may coalesce into inflammatory plaques and form crusts. Comedones are absent. Pruritus or pain is frequently associated. The lesions are located on the seborrheic areas—midface region with sparing of the periorbital region and upper trunk (typical V-shaped location) [Fig. 1b, c]. The scalp and neck are frequently affected, and the pubis and limbs may also be involved. No palmoplantar or mucosal involvement has been reported. Its evolution is stereotyped—early onset, within 2 weeks after treatment initiation, maximum intensity within 1–4 weeks then tendency to spontaneously improve. These lesions always disappear in a few weeks after EGFRi cessation but they may leave sequellar hyperpigmentation, telangiectasias or xerosis [5]. The main aggravating factors of papulopustular rash include concomitant radiotherapy, sun exposure, and poor skin hydration.

Differences in terms of symptoms have been reported depending on the EGFRi molecule—papulopustular rash is more intense and severe with the antibodies (cetuximab, panitumumab) and erlotinib than with gefitinib or lapatinib [2, 6]. In clinical practice, panitumumab seems responsible for a slightly different clinical picture, often with less inflammatory and pustular lesions and more persistent telangiectasic and erythematous plaques.

The appearance of crusts may correspond to a severe form of papulopustular rash with dry exudates, or to a bacterial or viral superinfection. Clinical signs of superinfection include a change in clinical appearance (meliceric crusts, polymorphic lesions) and in patient symptoms (pain, pruritus). A bacterial swab must be performed on a pustule without ulceration [7]. In case of doubt between a superinfection and severe papulopustular rash, a dermatologist's opinion is necessary.

The initiation of a prophylactic treatment with doxycycline 100 mg daily or lymecycline 300 mg daily together with EGFRi helps reduce the frequency of severe papulopustular rash (grade 2–3) [1, 4, 8–12]. It will be discontinued after 6 weeks in the absence of lesions or after their disappearance. A moisturizer to preserve the lipid film, skin hydration, and skin microbioma associated with suitable mild cleansing gels (pH 5.5) should be prescribed in combination with the drugs. Patients should avoid sun exposure and use physical photoprotection such as clothing, and sunscreen with a sun protection factor (SPF) of at least 30. Skin irritants should be avoided, especially those containing alcohol, exfoliating agents, or face masks.

Table 1 Summary of the main targeted therapy-induced dermatological toxicities classified by type of involvement

Type of involvement	Type of toxicity	Causative molecules	Common targets of the causative molecules	% of patients affected
Skin involvement	Folliculitis	Cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, axitinib	EGFR	50–80
		Selumetinib, trametinib	MEK	>75
		Everolimus, temsirolimus	mTOR	25–75
		Vandetanib	VEGFR, EGFR, RET	UNK
	Rash	Vemurafenib, dabrafenib	BRAF	>75
		Imatinib, dasatinib, nilotinib, ponatinib, bosutinib	c-KIT, BCR-ABL, PDGFR	50
		Sorafenib, sunitinib, pazopanib, regorafenib, vandetanib, axitinib	VEGFR	<50
		Ipilimumab	CTLA4	20–30
		Vismodegib	SMO	10
	Xerosis, pruritus	Cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, axitinib	EGFR	100 after 6 months
		Vemurafenib, dabrafenib	BRAF	Rare
		Selumetinib, trametinib	MEK	>30
		Everolimus, temsirolimus	mTOR	>30
		Imatinib, dasatinib, nilotinib, ponatinib, bosutinib	c-KIT, BCR-ABL, PDGFR	10–20
		Sorafenib, sunitinib, pazopanib, regorafenib, vandetanib, axitinib	VEGFR	10–20
		Vismodegib	SMO	10
	Keratinocyte proliferation: papilloma, cyst, keratoacanthoma, cSCC	Vemurafenib, dabrafenib	BRAF	30–80
		Sorafenib	RAF, VEGFR, PDGFR, FLT3, KIT, RET	<10
	Hand–foot skin reaction	Axitinib	EGFR	UNK
		Vemurafenib, dabrafenib	BRAF	<20
		Sorafenib, sunitinib, axitinib, pazopanib, regorafenib, vandetanib	VEGFR	10–70
	Periorbital edemas	Selumetinib, trametinib	MEK	10–50
		Everolimus, temsirolimus	mTOR	15–35
		Imatinib, dasatinib, nilotinib, ponatinib	c-KIT, BCR-ABL, PDGFR	60–85
		Sunitinib, pazopanib	VEGFR, KIT, PEGFR	<25
	Photosensitivity	Vemurafenib, dabrafenib	BRAF	30–50
		Imatinib	c-KIT, BCR-ABL, PDGFR, SCF, DDR, CSF	Rare
		Vandetanib	VEGFR, EGFR, RET	30
	Eruptive nevi	Vemurafenib, dabrafenib	BRAF	Rare
		Sorafenib	RAF, VEGFR, PDGFR, FLT3, KIT, RET	Rare
Ungual involvement	Paronychias, pyogenic granulomas	Cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, axitinib	EGFR	10–25
		Selumetinib, trametinib	MEK	UNK
		Everolimus, temsirolimus	mTOR	UNK
		Imatinib	c-KIT, BCR-ABL, PDGFR, SCF, DDR, CSF	UNK
		Vandetanib	VEGFR, EGFR, RET	UNK

Table 1 continued

Type of involvement	Type of toxicity	Causative molecules	Common targets of the causative molecules	% of patients affected
Hair involvement	Alopecia	Cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, axitinib	EGFR	50
		Vemurafenib, dabrafenib	BRAF	Rare
		Selumetinib, trametinib	MEK	UNK
		Imatinib, dasatinib, nilotinib, ponatinib	c-KIT, BCR-ABL, PDGFR	10
		Sorafenib, sunitinib, pazopanib, regorafenib, vandetanib, axitinib	VEGFR	<25
		Vismodegib	SMO	40–60
	Hypertrichosis	Cetuximab, panitumumab, erlotinib, gefitinib, lapatinib, axitinib	EGFR	100
		Selumetinib, trametinib	MEK	UNK
Mucosal involvement	Mucositis, stomatitis	Everolimus, temsirolimus	mTOR	15–50
		Dasatinib	c-KIT, BCR-ABL, PDGFR	16
		Sorafenib, sunitinib, pazopanib, regorafenib, vandetanib, axitinib	VEGFR	20–45
Cutaneous and hair involvement	Pigmentation disorders	Imatinib, dasatinib, nilotinib	c-KIT, BCR-ABL, PDGFR	15–40
		Sunitinib, pazopanib	VEGFR, KIT, PEGFR	25–45

cSCC cutaneous squamous cell carcinoma, *UNK* unknown, *EGFR* epidermal growth factor receptor, *MEK* mitogen/extracellular signal-regulated kinase, *mTOR* mammalian target of rapamycin, *VEGFR* vascular endothelial growth factor receptor, *RET* rearranged during transfection, *BRAF* v-raf murine sarcoma viral oncogene homolog B, *c-KIT* v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, *BCR-ABL* breakpoint cluster region-Abelson, *PDGFR* platelet-ferived growth factor receptor, *CTLA4* cytotoxic T-lymphocyte-associated protein 4, *SMO* smoothened, *FLT3* fms-related tyrosine kinase 3, *SCF* stem cell factor, *DDR* discoidin domain receptor, *CSF-1R* colony stimulating factor receptor 1

If a papulopustular rash occurs, treatment with tetracyclines should be initiated or continued at the same doses as in prophylaxis, at least until complete disappearance of the lesions, and mild to strong topical corticosteroids may be applied at night. Treatment is administered on the affected areas until symptom disappearance [4, 13]. Dermocosmetic care should be continued in the morning to repair the skin barrier. If a superinfection occurs, treatment with tetracycline should be transitorily switched to an appropriate anti-infective treatment, such as amoxicillin or pristinamycin, and corticosteroids should be discontinued. If a grade 3 papulopustular rash occurs, treatment with EGFRi should be discontinued then restarted at the recommended doses after disappearance of the lesions. Collaboration between the dermatologist and the oncologist is important in case of failure of the first-line dermatological therapy.

2.3 Alteration of the Skin Barrier

The alteration of the skin barrier is characterized by skin dryness, known as xerosis, which can be complicated by painful fissures and pruritus. It appears gradually within the first month of treatment and persists until its discontinuation [4]. After 6 months, all patients experience xerosis, and 30 % experience pruritus and fissures [14]. Xerosis and pruritus are mainly located on the limbs, palms, and soles, and areas initially affected by the papulopustular rash [4]. The fissures are mainly located on the fingers, nail-folds, and heels (Fig. 2). Risk factors include advanced age, atopic dermatitis, and past cytotoxic treatments having impaired the skin barrier [4].

Xerosis and pruritus are treated with emollients and suitable cleansing gels of pH 5.5 [15]. Skin irritants such as perfumes, products containing alcohol, household products, heat, and excessive sun exposure should be avoided [4]. Gloves should be used when handling skin irritants. Fissures may be improved using skin glues, such as cyanoacrylate, and hydrocolloid dressings, which are often difficult to apply in these locations, or healing creams [4]. Antihistamines are ineffective. Treatment with EGFRi may be continued without dose adjustment.

2.4 Involvement of Skin Appendages

2.4.1 Nail Changes

Nail changes are less common, affecting 10–30 % of patients, starting 1–2 months after treatment initiation [2]. Their most common form is paronychia, which affects

Table 2 Medical management of the most frequent dermatologic toxicities caused by targeted therapies

Type of toxicity	Targeted therapy responsible	Specific prevention measures	Treatment
General preventive measures for all systemic anticancer therapy		Emollients, 1 application per day Mild cleansing gels (pH 5.5) Sun prevention: clothing, sunscreen (SPF 30 or more) Avoid skin irritants	
Papulopustular rash	EGFRi, MEKi, mTORi, an anti-angiogenic agent (vandetanib)	Tetracyclines (doxycycline 100 mg/day or lymecycline 300 mg/day)	Tetracyclines (doxycycline 100 mg/day or lymecycline 300 mg/day) Mild to strong topical corticosteroids at night on symptomatic lesions Appropriate anti-infective treatment in case of superinfection
Erythematous rash	BRAFi, MEKi, mTORi, cKITi, anti-angiogenic agents, CTLA4i	None	Reinforced general preventive measures Oral corticosteroids for severe cases with ipilimumab
Photosensitivity	BRAFi, an anti-angiogenic agent (vandetanib)	Strict photoprotection, including behind windows: clothing and sunscreen with both anti-UVB and UVA filters	Emollients
Fissures	EGFRi, MEKi	Avoid skin trauma (manual work without gloves, tight shoes, etc) Gloves when handling skin irritants	Skin glues (cyanoacrylate) Hydrocolloid dressings Healing creams
Paronychia	EGFRi, MEKi, mTORi	Avoid cutting nails short Avoid skin trauma (manual work without gloves, tight shoes, etc) Gloves when handling skin irritants	Discuss tetracyclines (doxycycline 100 mg/day or lymecycline 300 mg/day) Very strong corticosteroids at night until disappearance of erythema or pain Appropriate anti-infective treatment in case of superinfection
Hand–foot skin reactions	BRAFi, anti-angiogenic agents	Emollients Large and comfortable shoes Gloves when handling skin irritants Debridement of hyperkeratosis Orthopedic insoles in case of bad foot positioning	Increased use of emollients, favoring topical urea- or salicylic acid-based keratolytic agents, possibly under occlusion at night Avoid mechanical debridement Strong to very strong topical corticosteroids for inflammatory forms Pain management
Stomatitis	MTORi, anti-angiogenic agents	Treatment of infectious dental sources	Good oral hygiene Avoid irritants Mouthwashes Topical corticosteroids Local anesthetics in case of intense pain Appropriate anti-infective treatment in case of infection
Edema	MEKi, mTORi, cKITi, two anti-angiogenic agents (sunitinib, pazopanib)	None	Diuretic therapy in severe forms

SPF sun protection factor, *UVA* ultraviolet A, *UVB* ultraviolet B

10–25 % of patients [2–4]. It is characterized by the rapid onset of a painful longitudinal inflammatory ridging, frequently associated with serous discharge at the junction between the nail and the lateral subungual fold. It usually affects several fingers, preferentially on the feet, thumbs, and fingers subjected to trauma, and resolves more or less rapidly at EGFRi cessation. It can be complicated by bacterial or fungal superinfection which should be suspected in case of more intense and throbbing pain and increase in discharges and crusts. In this case, a bacterial swab must be performed. A pyogenic granuloma may complicate paronychia. It manifests as a benign vascular proliferation with non-epithelialized red soft mass easily bleeding on contact (Fig. 3). A dermatological opinion is

Table 3 Characteristics and indications of targeted therapies grouped by therapeutic class

Therapeutic class	Type of inhibitor	Name	Indications	Targets
EGFRi	Ab	Cetuximab (Erbitux®)	CRC, squamous cell carcinoma of the head and neck	EGFR
		Panitumumab (Vectibix®)	CRC	EGFR
	TKI	Erlotinib (Tarceva®)	NSCLC, pancreas cancer	EGFR
		Gefitinib (Iressa®)	NSCLC	EGFR
		Lapatinib (Tyverb®)	Breast cancer	EGFR, HER2
		Afatinib (Giotrif®)	NSCLC	EGFR, HER2, HER3 and HER4
RAS-RAF-ERK pathway				
BRAFi	TKI	Vemurafenib (Zelboraf®)	Melanoma	BRAF
		Dabrafenib (Tafinlar®)	Melanoma	BRAF
MEKi	TKI	Trametinib (Mekinist®)	Melanoma	MEK
		Selumetinib	Melanoma	MEK
		Cobimetinib	Melanoma	MEK
		Binimetinib	Melanoma	MEK
PI3 K-AKT pathway				
mTORi	TKI	Everolimus (Afinitor®)	Breast cancer, neuroendocrine tumors of pancreatic origin, kidney cancer	mTOR
		Temsirolimus (Torisel®)	Kidney cancer, mantle cell lymphoma	mTOR
Cytoplasmic kinases				
c-KIT, PDGFR, BCR-ABL inhibitors	TKI	Imatinib (Glivec®)	CML, ALL, myelodysplastic and myeloproliferative syndromes, hypereosinophilic syndromes, chronic eosinophilic leukemia, GIST, dermatofibrosarcoma protuberans	c-KIT, BCR-ABL, SCF, DDR1 and 2, CSF-1R, PDGFRα and β
		Dasatinib (Sprycel®)	CML, ALL	BCR-ABL, c-KIT, SRC, EPH, PDGFRβ
		Ponatinib (Iclusig®)	CML, ALL	BCR-ABL, RET, FLT3, c-KIT, FGFR, PDGFR, VEGFR
		Nilotinib (Tasigna®)	CML	BCR-ABL, PDGFRα and β, c-KIT, EPH
		Bosutinib (Bosulif®)	CML	BCR-ABL, c-KIT, PDGFR
Anti-angiogenic agents	Ab	Bevacizumab (Avastin®)	CRC, breast cancer, NSCLC, kidney cancer, epithelial ovarian cancer, epithelial cancer of the fallopian tubes and primary peritoneal cancer	VEGF
	TKI	Sorafenib (Nexavar®)	HCC, kidney cancer	RAF, VEGFR2 and 3, PDGFRβ, FLT3, KIT, RET
		Sunitinib (Sutent®)	GIST, kidney cancer, pancreatic neuroendocrine tumors	VEGFR1, 2 and 3, PDGFα and β, KIT, RET, FLT3
		Pazopanib (Votrient®)	Kidney cancer, soft tissue sarcoma	VEGFR1, 2 and 3, PDGFα and β, c-KIT
		Regorafenib (Stivarga®)	CRC	VEGFR1, 2 and 3, TIE2, KIT, RET, RAF-1, BRAF, PDGFR, FGFR
		Vandetanib (Caprelsa®)	Medullary thyroid cancer	VEGFR2 and 3, EGFR, RET
		Axitinib (Inlyta®)	Kidney cancer	VEGFR1, 2 and 3
Other pathways				
CTLA4 inhibitor	Ab	Ipilimumab (Yervoy®)	Melanoma	CTLA4
Smoothened inhibitor	TKI	Vismodegib (Erivedge®)	Basal cell carcinoma	SMO

TKI tyrosine kinase inhibitor, *Ab* antibodies, *CRC* colorectal cancer, *NSCLC* non-small cell lung cancer, *CML* chronic myeloid leukemia, *ALL* acute lymphoblastic leukemia, *GIST* gastrointestinal stromal tumors, *HCC* hepatocellular carcinoma, *EGFR* epidermal growth factor receptor, *HER* human epidermal growth factor receptor, *BRAF* v-raf murine sarcoma viral oncogene homolog B, *MEK* mitogen/extracellular signal-regulated kinase, *mTOR* mammalian target of rapamycin, *c-KIT* v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, *BCR-ABL* breakpoint cluster region-Abelson, *SCF* stem cell factor, *DDR* discoidin domain receptor, *CSF-1R* colony stimulating factor receptor 1, *PDGFR* platelet-derived growth factor receptor, *SRC* V-src sarcoma (Schmidt-Ruppin A-2) viral oncogene homolog, *EPH* ephrin receptor, *RET* rearranged during transfection, *FLT3* fms-related tyrosine kinase 3, *FGFR* fibroblast growth factor receptor, *VEGFR* vascular endothelial growth factor receptor, *TIE2* tyrosine kinase with immunoglobulin and EGF homology domains 2, *CTLA4* cytotoxic T-lymphocyte-associated protein 4, *SMO* smoothened

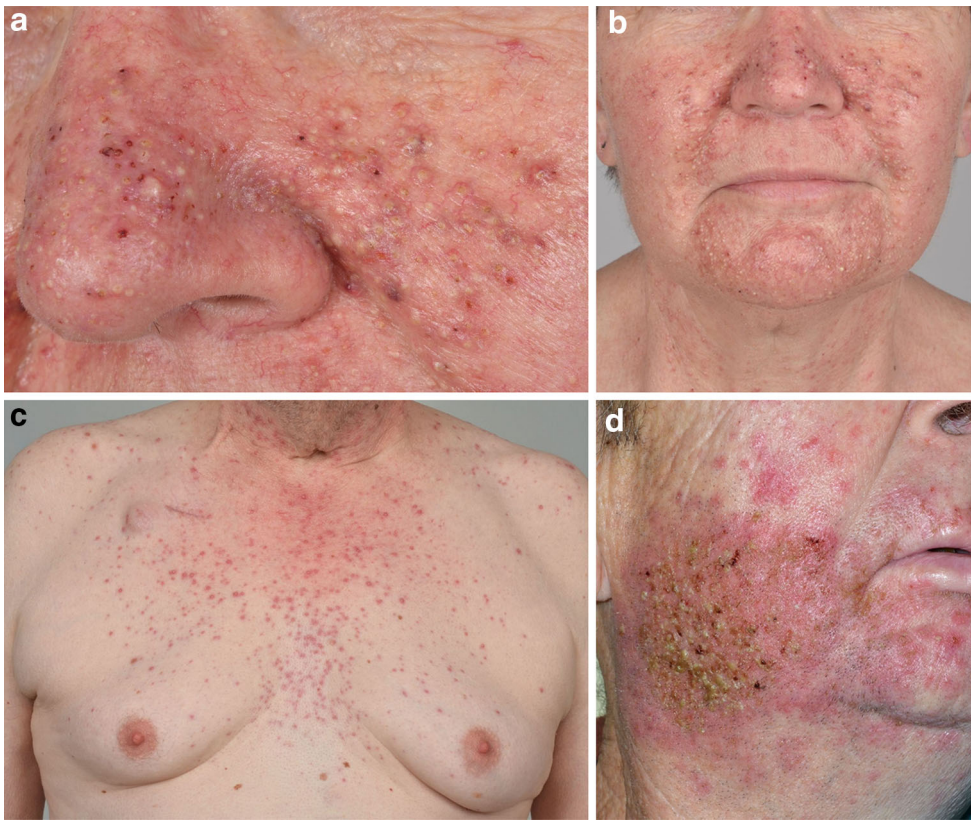

Fig. 1 Epidermal growth factor receptor inhibitor-induced papulopustular rash: monomorphic papular lesions (**a**) located at the midface sparing the periorbital region (**b**) and at the chest with V-shaped appearance (**c**). Increase in papulopustular rash with confluent and crusted lesions in the radiotherapy field (**d**)

indicated for severe paronychia, or those suspected of superinfection or in case of pyogenic granuloma.

The other nail changes described include a slow growth, onycholysis (distal nail detachment), and fragile and brittle nails.

Prevention advice should be given at the time of EGFRi initiation [4]—not cutting the nails flush, avoiding skin trauma associated with manual work or wearing tight shoes, and wearing gloves when handling skin irritants. If paronychia occurs, very strong topical corticosteroids should be applied at night until disappearance of the erythema and pain, in the absence of superinfection signs, associated with daily disinfection [4]. Treatment with tetracyclines at the same doses as for papulopustular rash may be discussed [13]. If a superinfection occurs, tetracyclines should be switched to a suitable antibiotic, such as amoxicillin or pristinamycin, or based on culture results. The nails should be cut straight but not short even if the clinical picture is similar to that of a benign ingrown toenail as it promotes the chronicity of paronychia. Podiatry care should be practiced only after dermatological opinion and by transmitting strict instructions along these lines. Pyogenic granulomas require a dermatological opinion to discuss the use of treatments such as surgery with partial nail avulsion, matricectomy and cauterization, silver nitrate, electrocoagulation, or intralesional injections of corticosteroids, depending on the impact on quality of life, burden, number of digits involved, and prognosis. Treatment with EGFRi may be discontinued in case of superinfection or pyogenic granuloma.

2.4.2 Hair Changes

The occurrence of hair changes is very common 2–3 months after treatment initiation [2, 4], with the most classical form being eyelash trichomegaly, characterized by curly, thick, and long lashes (Fig. 4). Hair changes are almost inevitable after more than 3–6 months of treatment, and may be complicated by mechanical conjunctivitis with lacrimation, related to eyelash friction on the cornea, and sometimes worsened by xerophthalmia [5]. The increase in hair density and thickness may also be observed on the eyebrows, cheeks, and upper lip in women. Conversely, minor to mild alopecia, reversible upon treatment discontinuation, is observed in 50 % of patients (Fig. 5). A change in hair texture, which becomes thin, shiny, curly, and difficult to manage, is also present in the majority of patients after 3–6 months of treatment [3, 4].

Eyelashes may be cut in case of trichomegaly. Bleaching, non-irritating hair removal, and the use of eflornithine may be recommended for disturbing facial hypertrichoses [4]. These anomalies do not require EGFRi discontinuation.

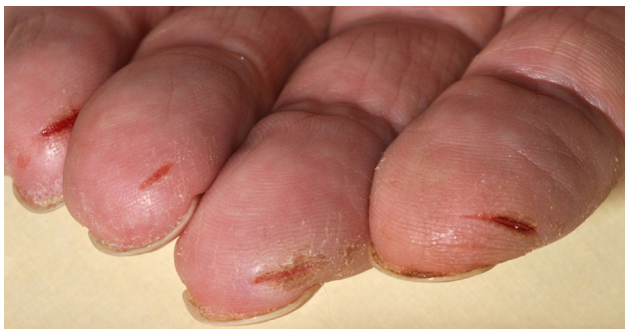

Fig. 2 Fissures of the finger pulps complicating xerosis under epidermal growth factor receptor inhibitor

2.5 Combination of Radiotherapy and EGFR Inhibitors

There is synergistic skin toxicity in combination therapies with EGFRi and radiotherapy (Fig. 1d). A meta-analysis has found a relative risk of developing severe radiodermatitis of 2.38 (95 % CI 1.8–3.2; $p < 0.001$), severe papulopustular rash of 3.01 (95 % CI 2.1–4.6; $p < 0.001$), and severe mucositis of 1.76 (95 % CI 1.5–2; $p < 0.001$) compared with radiation alone [16].

Management depends on the severity of the papulopustular rash and radiodermatitis. To prevent this toxicity, radiotherapy protocols should minimize the radiation dose received on the skin [4, 17]. In case of papulopustular rash or grade 3 or 4 radiodermatitis, both EGFRi and radiotherapy should be discontinued. Emollients and strong topical corticosteroids may be prescribed for dry inflammatory lesions and drying solutions for oozing lesions [4, 13]. Whenever possible, the uninterrupted continuation of radiotherapy will be preferred to that of EGFRi [18].

2.6 Specificities of Multireceptor Inhibitors

Lapatinib-induced cutaneous adverse reactions are less severe and frequent than those induced by the other EGFRi, and rarely require treatment adjustment [17, 19]. A meta-analysis of dermatological adverse reactions to lapatinib found that 58 % of patients treated with monotherapy experienced dermatologic events (55 % had grade 1–2, 3 % had grade 3 and none had grade 4) [17]. The type of adverse reactions experienced is usual but with limited pruritus and skin appendage involvement, and the rash is located on the trunk rather than on the face [17, 20].

Afatinib induces a less well-described skin toxicity but seems very similar to that induced by the other EGFRi in terms of type, severity, and frequency. Pruritus seems particularly common even at low doses in phase 1 trials. Hand–foot skin reactions have also been described with this molecule [21, 22].

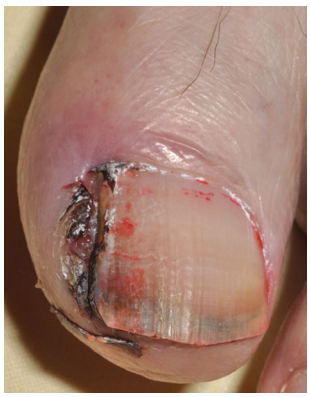

Fig. 3 Paronychia of the left foot thumb complicated by pyogenic granuloma under epidermal growth factor receptor inhibitor

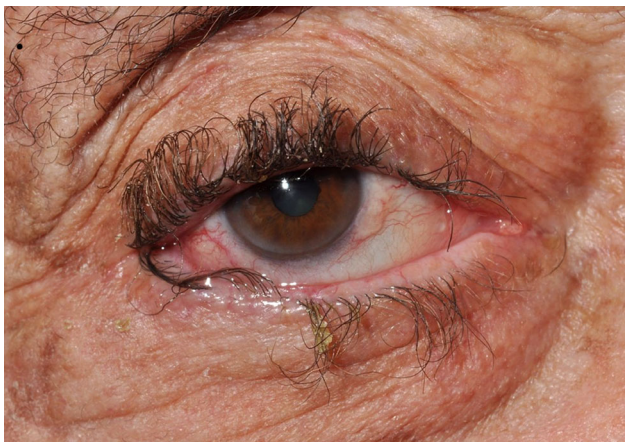

Fig. 4 Eyelash trichomegaly and conjunctivitis under epidermal growth factor receptor inhibitor

3 v-Raf Murine Sarcoma Viral Oncogene Homolog B (BRAF) Inhibitors (BRAFi)

BRAF inhibitor (BRAFi)-induced skin toxicity is very common, affecting almost all patients, but is rarely severe, with only 5 % grade 3 or higher [23, 24]. It mainly includes lesions secondary to keratinocyte proliferation, rash and photosensitivity.

3.1 Molecules and Indications

Two molecules target BRAF—vemurafenib and dabrafenib. Their characteristics and indications are presented in Table 3.

3.2 Keratinocyte Hyperproliferation

There are various skin lesions secondary to keratinocyte hyperproliferation, ranging from skin papillomas, cysts, keratoacanthomas (KA), to cutaneous squamous cell

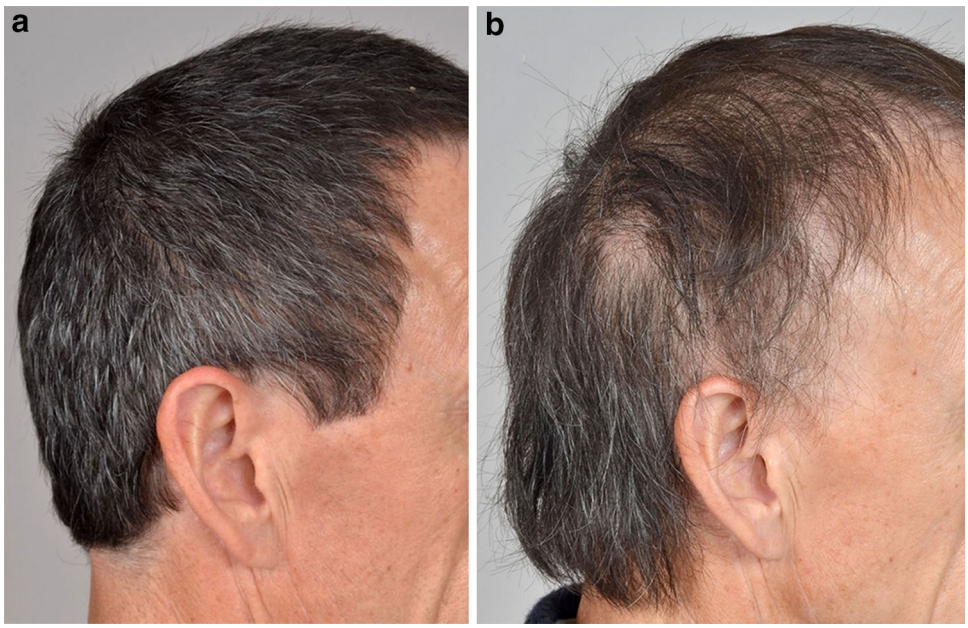

Fig. 5 Alopecia and change in hair texture which became thin and curly after 6 months of epidermal growth factor receptor inhibitor

carcinoma (cSCC) [Fig. 6a–e] [24, 25]. Papillomas occur in up to 80 % of patients treated with vemurafenib and 50 % of patients treated with dabrafenib, and KA and cSCC occur in 15–25 % of both of them [25–28]. The use of BRAF and MEK inhibitors (MEKi) in combination, being currently assessed, decreases their incidence [25, 26]. Skin papillomas can take several aspects—they can mimic viral warts, seborrheic keratosis, cutaneous horn, or smooth whitish papule. KA and cSCC usually look like papules centered by hyperkeratosis. The clinical and histopathological aspects of the two latter are close, and their classification is difficult and quite dependent on the pathologist [24]. cSCC are usually well differentiated and no progression towards metastases has been described. Most often, they are eruptive, occurring within a few days before the third month of treatment with BRAFi, but late occurrences have also been reported. Keratinocyte proliferation during a treatment with BRAFi seems to be due to a paradoxical activation of the mitogen-activated protein kinase (MAPK) pathway via v-raf murine sarcoma viral oncogene homolog C (CRAF) in wild-type *BRAF* cells with upstream activation of rat sarcoma (RAS). RAS can be activated by a mutation in 30–70 % of cases, a growth factor receptor, or other molecules. Cofactors such as papillomavirus infection, ultraviolet, pressure, or radiation could be involved [24, 28, 29]. KA and cSCC should be removed for histological analysis. When the lesions are too numerous, KA may be destroyed by liquid nitrogen application but their evolution should be strictly monitored. Close dermatological monitoring is necessary throughout the treatment duration and up to 1 month after its discontinuation.

Hand–foot skin reactions occur in 20–60 % of patients under vemurafenib, of whom less than 5 % experience severe forms [24, 25, 27, 28], and in around 20 % of patients under dabrafenib [29]. It presents as inflammatory hyperkeratotic lesions located on areas of pressure or friction of the hands and feet, sometimes painful but rarely disabling, of the same type as those observed under anti-angiogenic agents. They persist throughout the BRAFi treatment duration, and their treatment is similar to that recommended with anti-angiogenic agents (see Sect. 7.2). A dose adjustment of BRAFi is rarely necessary.

3.3 Rash

The occurrence of a rash is very common, affecting 75 % of patients, but severe forms are experienced in less than 20 % of patients [24, 25, 27]. Rash is typically an erythema predominantly located on the trunk and limbs, often pruriginous. It is characterized by small hyperkeratotic follicular papules, as in keratosis pilaris (Fig. 7). These rashes must not be misdiagnosed, with severe skin reactions also occurring under BRAFi, Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), Stevens–Johnson syndrome, or toxic epidermal necrolysis [24, 30]. Their clinical signs should therefore be identified and explained to patients (see Sect. 10).

3.4 Photosensitivity

Ultraviolet A (UVA) photosensitivity affects 30–50 % of patients under vemurafenib [27, 31, 32]. It is much rarer under dabrafenib, and consists of the occurrence of an erythema and an edema strictly limited to exposed areas

after 10–15 min of sun exposure (Fig. 8) [31]. This toxicity resolves within a few days. It may be very disabling. A very strict photoprotection should be initiated at BRAFi initiation with the use of clothes and sunscreen having both anti-UVB and anti-UVA filters. Patients should be informed about the need to protect themselves, including behind a window which allows UVA to pass.

3.5 Eruptive Nevi and Melanoma

Efflorescence of nevi and change in pre-existing ones seem to occur in 10–20 % of patients, reaching 50 % in case of systematic dermoscopic exploration, mainly within 3 months of drug initiation [24, 28, 33, 34]. More severely, the occurrence of melanomas under vemurafenib has also been published [28, 33–35]. Melanocytic proliferation seems to be mainly explained by paradoxical activation of the MAPK pathway in wild-type BRAF melanocytes, but other pathways such as phosphoinositide-3-kinase/protein kinase B (PI3K/AKT) could also be involved [33, 34]. The implication of coexisting RAS activation is less clear than for keratinocyte proliferation. Close dermatological monitoring is thus necessary throughout the treatment duration.

3.6 Other Toxicities

Other frequent toxicities have been reported, including xerosis possibly complicated by pruritus, curly and brittle hair, slower and thinner growth of scalp and body hair, or even mild alopecia, usually getting better despite drug continuation [24, 25, 27–29, 35, 36]. Painful panniculitis associated with arthralgia have also been reported with BRAFi [37].

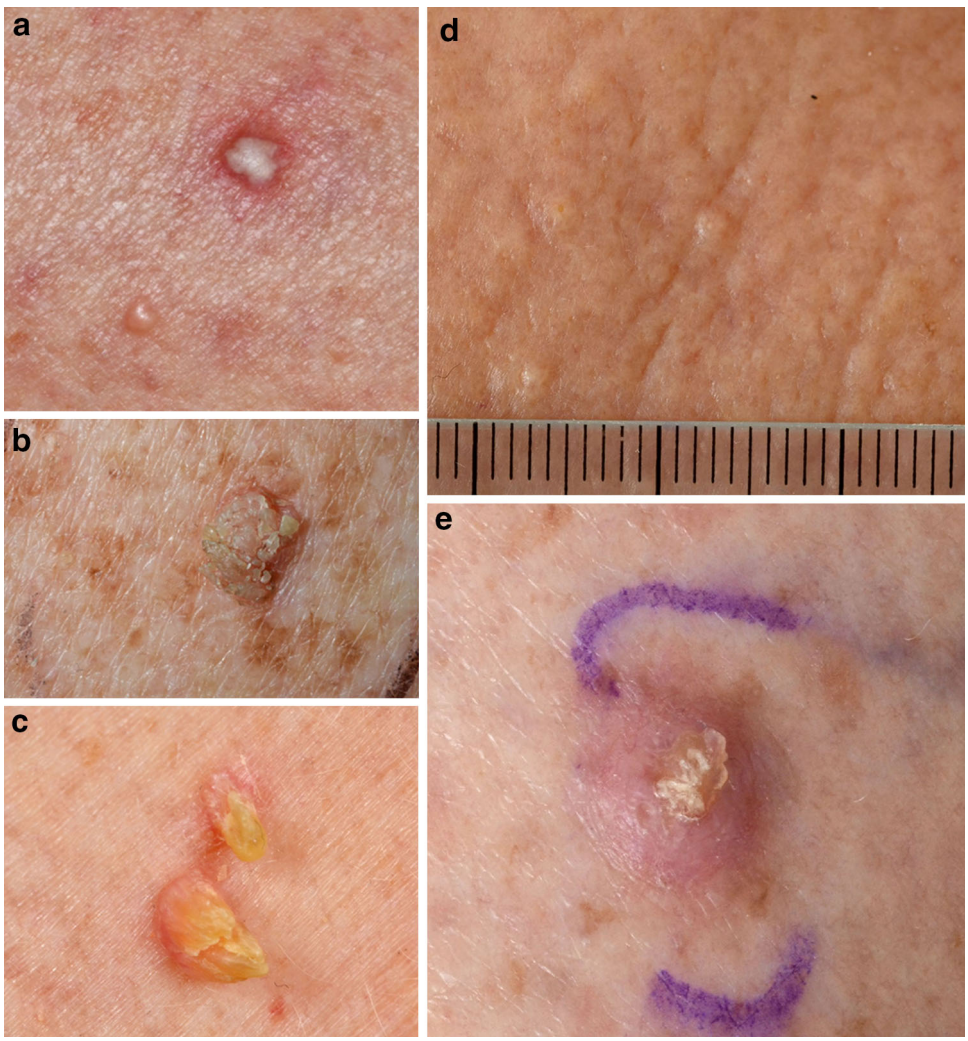

Fig. 6 Lesions secondary to vemurafenib-induced keratinocyte hyperproliferation: papillomas (**a**–**c**), facial cysts (**d**), keratoacanthoma (**e**)

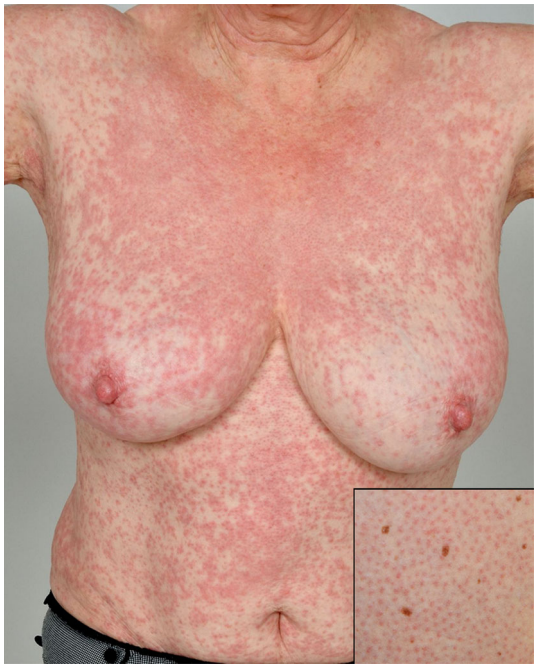

Fig. 7 Rash under vemurafenib with keratosis pilaris-like appearance on magnification

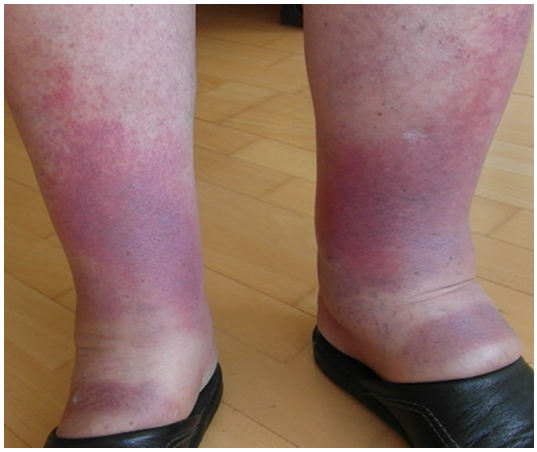

Fig. 8 Photosensitivity under vemurafenib strictly limited to exposed zones

4 Mitogen/Extracellular Signal-Regulated Kinase (MEK) Inhibitors

More than 85 % of patients treated with MEKi experience at least one skin toxicity in clinical trials, being thus the most frequent toxicity and one of the causes of dose-limiting toxicity [23, 25, 38]. Most MEKi-induced skin adverse reactions are similar to those described under EGFRi [27].

4.1 Molecules and Indications

One MEKi, trametinib, has a marketing authorization for melanoma, and others—selumetinib, cobimetinib and binimetinib— are in an advanced stage of development.

4.2 Toxicity Similar to that Induced by EGFR Inhibitors (EGFRi)

Aseptic papulopustular rash on the face and trunk, with an evolution similar to that under EGFRi, is developed early in more than 75 % of patients [23, 25, 26, 38, 39]. It is dose-dependent and rarely severe, with less than 10 % grade 3 or higher. Its incidence decreases to 25 % when the MEKi is associated with a BRAFi [25, 26]. The rash may be erythematous, without pustule. The treatment of papulopustular rash is similar to that used under EGFRi [25, 26]. Despite the absence of data on the prophylactic use of tetracyclines in this indication, it is recommended by some authors, given its frequency. The dose adjustment of MEKi is rarely necessary [25], but dose reduction may be discussed in case of grade 3 toxicity, and treatment discontinuation is recommended for grade 4 toxicity.

Later EGFRi-induced toxicities are also present under MEKi, with progressive occurrence of a xerosis on the extremities and trunk in more than 30 % of patients after several weeks, sometimes associated with fissures and pruritus, followed by the occurrence of paronychia, pyogenic granuloma, change in hair texture, and alopecia after more than 3 months of treatment [25, 26, 38]. Their management is similar to that recommended under EGFRi.

4.3 Toxicity Specifically Induced by MEKi

Facial edemas predominant in the periorbital region, or more diffuse edemas with peripheral involvement, occur in 10–50 % of patients, without specific treatment [25, 27]. More or less extended inflammatory plaques of amicrobial cellulitis have been reported under selumetinib [27]. Reduced pigmentation of hair and skin has also been described under selumetinib [38].

5 Mammalian Target of Rapamycin (mTOR) Inhibitors

Skin toxicity is the most frequent mTOR inhibitor (mTORi)-induced toxicity, affecting 70 % of patients. It is mostly mild to moderate [40], and mainly includes papulopustular rash, stomatitis, nail changes, xerosis, and edemas.

5.1 Molecules and Indications

Two approved molecules target mTOR—everolimus and temsirolimus. Their characteristics and indications are presented in Table 3.

5.2 Papulopustular Rash

Papulopustular rash is the most common skin toxicity. It affects 25–60 % of patients under everolimus, and 50–75 % of patients under temsirolimus [41–43]. Its symptoms are similar to those described under EGFRi but its severity is usually lower, with no or little functional signs associated with mTORi, and more discreet underlying erythema [3, 40, 44]. Pustules may be absent and erythematous papules are frequently the predominant clinical sign of this rash [45]. Some patients present only with erythematous plaques.

Papulopustular rash is treated with emollients, suitable cleansing gels, and avoiding excessive sun exposure and skin irritants [42]. Topical or oral corticosteroids may be used for severe forms.

5.3 Stomatitis

mTORi-associated stomatitis (mIAS) affects 15–50 % of patients under mTORi, and is only rarely grade 3–4 [40, 42, 44, 46]. It corresponds to a mucosal erythema and edema of the oral cavity, inner surface of the lips and tongue which occur within 2 months after treatment initiation [41, 46]. It may be complicated by mouth ulcers, aphthoid lesions, dysgeusia, and burning pain. Signs of herpetic superinfection, including a cluster of very painful post-vesicular ulcers, or fungal superinfection with whitish deposits, a varnished appearance of the tongue, and a mirror effect on the palate, should be investigated.

To prevent mIAS, infectious dental sources should be treated before initiating mTORi. As a curative treatment, good oral hygiene is essential [46]. Local anesthetics may be applied before meals avoiding the posterior zones to reduce the risk of laryngeal penetration. Topical corticosteroids and mouthwashes may also be used. Irritants should be avoided. In case of herpetic or fungal superinfection, a suitable anti-infective therapy should be initiated. Treatment with mTORi should be discontinued then restarted at the same dose in case of intolerable grade 3 toxicity [46]. In case of grade 4 toxicity, treatment should be permanently discontinued.

5.4 Nail Changes

Nail changes have been mentioned in 5–46 % of patients in initial development studies [47–50], while, since then, mainly periungual involvements have been reported [40, 44]. The latter, with paronychias and pyogenic granulomas in the lateral periungual folds, are mainly located on the big toes and may cause functional impairment (Fig. 9) [40, 44]. They begin to appear after 3–6 months of treatment and may improve despite treatment continuation [40]. Nail dystrophies with nail fragility, distal onycholysis, and yellowish dyschromia have also been described [51]. Their preventive and curative treatment is similar to that used under EGFRi.

5.5 Xerosis

Xerosis is present in more than 30 % of patients, with an eczema-like appearance in 20 % of patients [40, 44, 52]. Xerosis may be complicated by disabling pruritus impacting the quality of life. Treatment consists of applying emollients, using suitable cleansing gels, and avoiding skin irritants.

5.6 Edemas

Edemas of the upper and lower limbs are reported in 15–35 % of patients [3, 40, 44]. Most are grade 1 or 2 and do not require specific treatment [42, 46].

5.7 Rarer Toxicity

Rare healing delays are described with everolimus, which should thus be discontinued during the perioperative period [42].

6 v-Kit Hardy-Zuckerman 4 Feline Sarcoma Viral Oncogene Homolog (c-KIT), Platelet-Derived Growth Factor Receptor (PDGFR), and Breakpoint Cluster Region-Abelson (BCR-ABL) Inhibitors

Skin toxicity has mainly been described with imatinib, which is the first molecule of this drug class. It is very common, affecting up to 90 % of patients, and

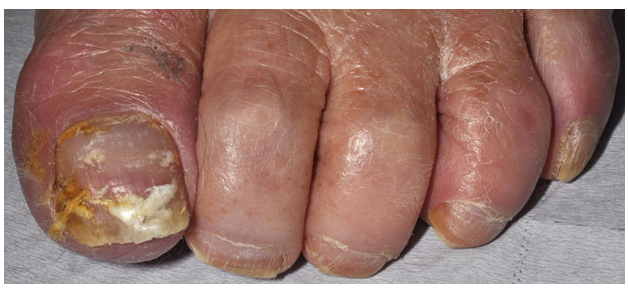

Fig. 9 Paronychia and leukonychia of the big toe associated with diffuse nail dystrophia: yellow fragile nails with longitudinal ridging

corresponding to the second type of toxicity found after digestive disorders [27, 53]. It is dose-dependent and remains generally moderate [53]. The main toxicities reported are edemas, rashes, and pigmentary disorders.

6.1 Molecules and Indications

Five molecules target c-KIT, PDGFR, and BCR-ABL—imatinib, dasatinib, ponatinib, nilotinib, and bosutinib. Their characteristics and indications are presented in Table 3.

6.2 Edemas

Facial edema, most often periorbital, is very common, affecting 60–85 % of patients under imatinib [3, 27]. A more diffuse involvement is possible, affecting the lower limbs or even with occurrence of pleural and peritoneal effusions. On average, edema appears 6 weeks after treatment initiation and is more important at awakening time. It does not usually require a specific treatment, except for severe forms for which diuretic therapy may be introduced.

6.3 Rash

The occurrence of a maculopapular rash is very common, affecting 50 % of patients. It is preferentially located on the trunk and limbs and is sometimes pruriginous [3, 27]. It usually appears within 2 months after treatment initiation. Rash can be psoriasiform, with a more squamous and generally later involvement, and more likely affecting the scalp, palms, and soles (Fig. 10) [54]. It can also have a pityriasis rosea-like aspect with monomorphic, well-delimited plaques. Cutaneous and mucosal lichenoid eruptions have also been published, affecting mainly the trunk and limbs. Rare severe skin reactions with Stevens–Johnson syndrome, acute generalized exanthematous pustulosis (AGEP) or DRESS have been reported [3]. Rashes are treated with emollients, suitable cleansing gels, or even topical corticosteroids, depending on their severity [53]. Dose adjustment of c-KIT inhibitors (c-KITi) is rarely required. Severe skin reactions strictly contraindicate treatment continuation.

6.4 Pigmentary Disorders

Fifteen to 40 % of patients experience pigmentation disorders—skin depigmentation or, conversely, hyperpigmentation, or secondary skin or hair repigmentation [3, 27]. Hypopigmentation is homogeneous, localized, or diffuse, and preferentially affects subjects with dark skin. Hypopigmentation is much more frequent than hyperpigmentation. These pigmentation disorders resolve at treatment discontinuation and do not require specific treatment.

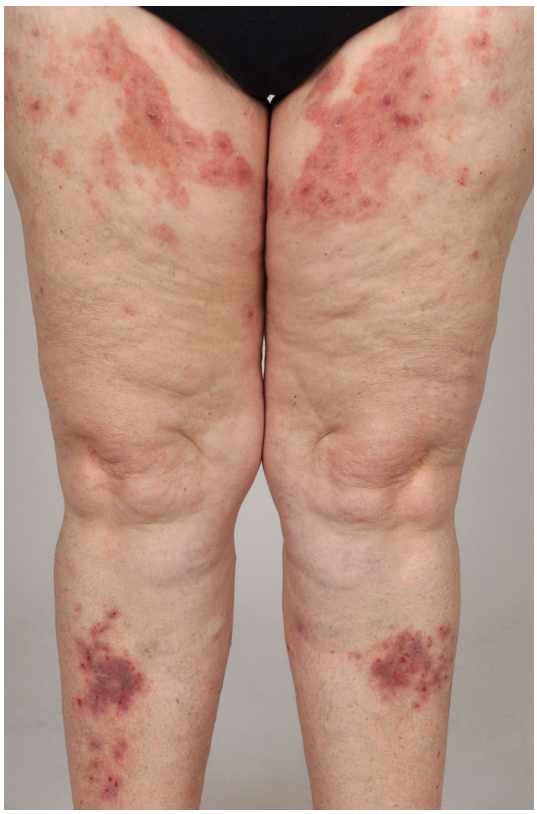

Fig. 10 Atypical maculopapular rash, squamous in some places, occurring under imatinib

6.5 Xerosis

Xerosis, possibly complicated by pruritus, is found in 10–20 % of patients [3]. It is treated with emollients, suitable cleansing gels, and by avoiding skin irritants.

6.6 Rarer Toxicities

Paronychia, alopecia, photosensitivity, and vascular purpura have also been reported [3, 55].

6.7 Specificities Depending on the Molecules

Rashes, xerosis, and pruritus are the most common adverse effects associated with all c-KITi, and have been reported with all molecules. Edemas and alopecia have been reported with imatinib, dasatinib, nilotinib, and ponatinib, panniculitis has been reported with imatinib, dasatinib, and ponatinib, and pigmentation disorders have been reported with imatinib, dasatinib, and nilotinib [3, 56]. Stomatitis

and mucositis have only been reported with dasatinib in 16 % of patients [3]. A few cases of palate pigmentation have been reported with imatinib [57].

7 Anti-Angiogenic Agents

Skin toxicity is very common with anti-angiogenic TKI, affecting 75–90 % of patients [58]. It has mainly been described with sorafenib and sunitinib, and includes hand–foot skin reactions, subungual splinter hemorrhages, rash, mucositis, hair changes, and xerosis. Some toxicities are specific of a single anti-angiogenic agent. Bevacizumab induces different and much rarer skin toxicity.

7.1 Molecules and Indications

Seven molecules target vascular endothelial growth factor receptors (VEGFR)—bevacizumab, sorafenib, sunitinib, pazopanib, regorafenib, vandetanib, and axitinib. Their characteristics and indications are presented in Table 3.

7.2 Hand–Foot Skin Reaction

The most common skin toxicity is the hand–foot skin reaction, affecting 60–85 % of patients under regorafenib, 30–50 % of patients under sorafenib and axitinib, 10–30 % of patients under sunitinib, and less than 10 % of patients under pazopanib [3, 23, 42, 58–64]. Regorafenib also has the highest frequency of grades 3–4 hand–foot skin reactions (20 %). This is the main dermatological cause of treatment discontinuation [65]. Its frequency and severity are dose-dependent, and it occurs within 2–6 weeks after treatment initiation [58]. Localized hand–foot skin reaction should be distinguished from chemotherapy-induced diffuse hand–foot syndrome, also called palmoplantar erythrodysesthesia syndrome—diffuse and painful palmoplantar erythema and edema progressing towards mild homogeneous hyperkeratosis then desquamation (Fig. 11a) [60, 65]. Hand–foot skin reaction with anti-angiogenic agents is characterized by a well-delineated and localized hyperkeratosis, sometimes very thick, which occurs in an inflammatory erythematous context (Fig. 11b). In the most severe forms, tense bullae form on the strongest pressure zones (Fig. 11c), while a superficial skin detachment is common at lesion onset. Prodromes with tingling are common. These lesions are very painful, may interfere with walking, and have a major impact on quality of life [65, 66]. They are bilateral, rather symmetric, occurring on weight-bearing points, usually on the palms and soles, with a higher frequency for soles [58]. Other pressure, friction, repeated microtrauma, or pre-existing hyperkeratotic zones may be involved, such as on the lateral sides of the fingers, elbows, or ears [65].

Preventive management [65, 67–71] is essential, with debridement of the hyperkeratosis by a pedicure before treatment initiation if needed [3, 42, 59]. In case of bad foot positioning, a podiatric examination is needed to adapt to putting the boot on and assessing the benefit of orthopedic insoles [42, 65]. Shoes should be large and comfortable and hands must be protected by gloves for each manipulation of irritants [59, 60]. Hands and feet should be protected from friction and heat. Emollient application is useful. As a curative care, prophylactic actions should be continued or reinforced, except for mechanical debridement, which will tend to sustain the phenomenon. Emollient should be applied 1–2 times daily, possibly under occlusion with gloves or plastic film at night to promote its penetration [3, 25, 65]. The use of topical urea- or salicylic acid-based keratolytic agents may be useful, possibly associated with strong or very strong topical corticosteroids in inflammatory forms. In grade 3 forms, the anti-angiogenic agent should be discontinued [3, 23, 42, 60, 65]. A transient dose reduction may be discussed from grade 2. Pain management, including topical lidocaine use, is mandatory.

7.3 Subungual Splinter Hemorrhages

Subungual hemorrhages are observed in 50–60 % of patients under sorafenib and 25 % of patients under sunitinib from the 2 first months of treatment [23, 65]. They are characterized by asymptomatic red or black lines parallel to the finger axis, affecting predominantly the hands (Fig. 12). They usually affect several fingers and disappear during nail growth, and do not require treatment.

7.4 Rash

Rash affects 20–50 % of patients under sorafenib, 10–25 % of patients under sunitinib and regorafenib, 10–15 % of patients under axitinib, and less than 10 % of patients under pazopanib [3, 63]. It is most often discreet, maculopapular, erythematous, diffuse, and appears within days following treatment initiation [23, 59]. It tends to disappear despite treatment continuation. More severe and persistent forms of rashes have been described, mimicking erythema multiforme [72]. Skin reactions with toxic epidermal necrolysis and DRESS have been reported, supporting the systematic search for severity signs (see Sect. 10). Their treatment is based on the use of emollients, suitable cleansing gels, and avoiding skin irritants and excessive sun exposure. Topical corticosteroids may be proposed in case of severe symptomatic skin inflammation.

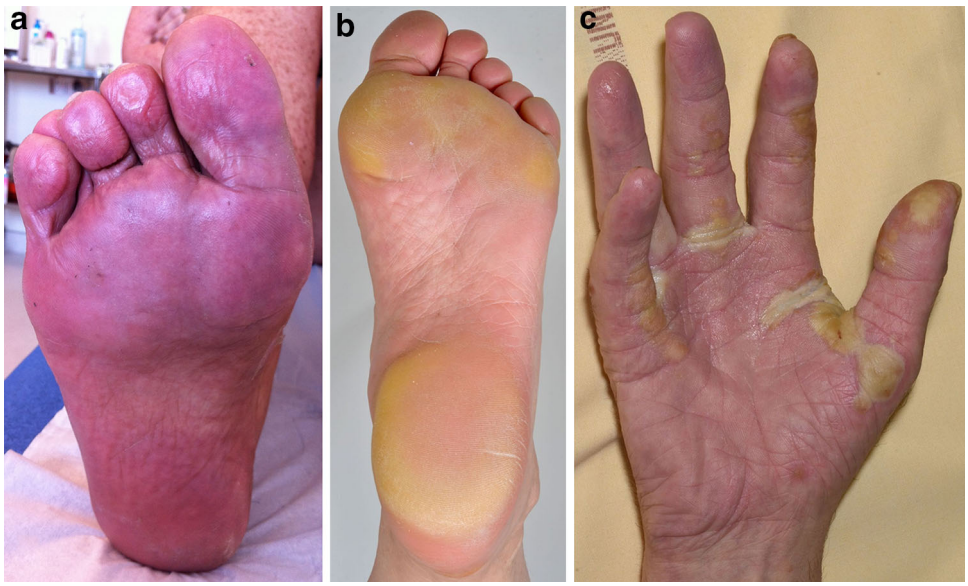

Fig. 11 Hand–foot syndrome under chemotherapy [liposomal doxorubicin] (**a**). Hand–foot skin reaction under sorafenib with hyperkeratosis on weight-bearing points in a mild form (**b**), complicated with tense bullae in a severe form (**c**)

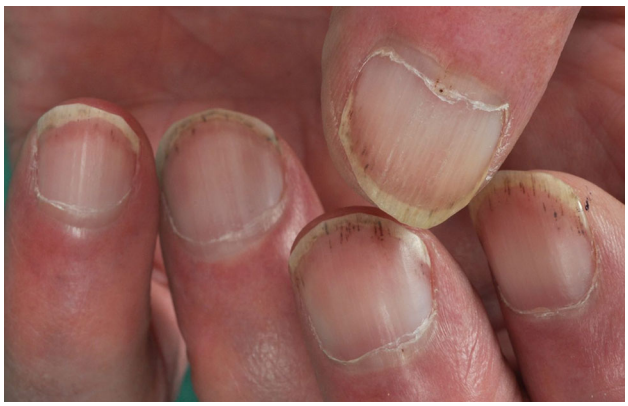

Fig. 12 Subungual splinter hemorrhages under anti-angiogenic therapy

7.5 Mucositis

Mucositis occurs in 20–45 % of patients, usually from the first month of treatment [58, 59, 73]. It is more common under sunitinib than under sorafenib. Oral hygiene, mouthwashes, or local xylocaine may then be prescribed. This toxicity may require a dose reduction or treatment discontinuation. Geographic tongue, usually associated with dysgeusia, has also been reported in a few patients under sorafenib, sunitinib, and also bevacizumab [74].

7.6 Hair Changes

A change in hair texture affects more than half of the patients after 3 months of treatment [3, 23]. It seems more common under sorafenib than under sunitinib. The hair becomes thin, curly, difficult to manage and grows slowly. Progressive alopecia may be associated in a quarter of the patients [58, 65]. Hair usually regrows afterward despite treatment continuation.

7.7 Xerosis

Cutaneous xerosis affects 10–20 % of patients and increases throughout treatment duration [23, 59]. Its treatment is based on the use of emollients, suitable cleansing gels, and avoiding skin irritants.

7.8 Toxicity Similar to that Induced by c-KIT Inhibitors

Sunitinib and pazopanib, like imatinib, strongly inhibit cKIT, unlike sorafenib and the other anti-angiogenic agents, which explains the occurrence of pigmentation disorders and facial edemas with close symptoms.

Hair pigmentation disorders occur in two-thirds of patients under sunitinib from the first weeks of treatment and resolve spontaneously at treatment discontinuation [62, 65]. The hair may grow white under treatment and repigment during washout periods, resulting in an alternation of white and black bands during sequential treatments [3, 65]. Rarer, early vitiligoid facial hypopigmentation, occurring within 1 month, has also been reported under sunitinib and pazopanib [23, 58]. These hair and skin pigmentation disorders are also observed in 27–44 % of patients under pazopanib [3].

Mild facial edemas predominant at the eyelids are described in a quarter of patients under sunitinib and more rarely under pazopanib [58, 65, 75]. They usually occur after the first month of treatment.

7.9 Toxicity Similar to that Induced by BRAFi

Homogeneous, monomorphic eruptive nevi of a few millimeters in size have been reported in a few patients under sorafenib [65, 76]. Unlike BRAFi, no progression towards melanoma has been published but their evolution should be routinely monitored.

As under BRAFi, a keratinocyte hyperproliferation may be observed under sorafenib, causing various lesions ranging from simple microcysts on the face, back, or limbs, epidermal cysts or atypical proliferations with KA up to cSCC [3, 65]. They are less common than under vemurafenib, affecting less than 10 % of patients. Keratinocyte proliferation has also been reported under regorafenib. Atypical lesions may be multiple and appear after several weeks or months of treatment. Their treatment is based on surgical removal. In case of multiple KAs, a simple close clinical monitoring may be discussed. Keratosis pilaris located on the trunk and limbs or more diffuse may also be observed after prolonged treatment, affecting up to 20 % of patients [3, 65].

7.10 Toxicity Similar to that Induced by EGFRi

Papulopustular rash of the same type as that induced by EGFRi and paronychias have been observed under vandetanib, which inhibits the EGFR [77].

7.11 Specificities Depending on the Molecules

Two-thirds of patients under sorafenib experience facial erythema after 1–2 weeks of treatment, sparing periorbital areas, sometimes associated with nasolabial folds superficial desquamation [23, 65]. This erythema resolves spontaneously within a few weeks. The use of emollients is rarely necessary. Scalp dysesthesias associated with an erythema may be observed early, with spontaneous resolution within a few weeks [65]. They are characterized by the appearance of burns, bites, or pain when passing a comb through [78]. They do not require a particular treatment.

A yellowish skin coloration is possible after prolonged exposure to sunitinib because of the color of the drug itself [23, 58].

Inflammatory and painful genital lesions would affect more than 10 % of patients under sunitinib, and have also been described under vandetanib, sorafenib, and pazopanib [3, 58, 79]. They are characterized in men by eczema-like or psoriasis-like lesions on the scrotum, sometimes extending to the groin, and in women by similar lesions on the vulva or perineum. Perianal involvement is possible in both sexes. Patients may only have isolated genital pruritus. This toxicity is dose-dependent and rarely requires dose reduction.

Healing delays have been described under bevacizumab and pazopanib [59].

Vandetanib causes photosensitivity reactions, sometimes very severe, with maculopapular or lichenoid rash between 7 days and 2 months after treatment initiation in one-third of patients [77]. Blue spots may also appear on the zones previously affected by papulopustular rash.

8 Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA4) Inhibitors

Skin toxicity is drug class-specific and related to autoimmunity phenomena induced by the mechanism of action of the drug. It belongs to the 'immune-related adverse events' (irAEs) category, and is dose-dependent. It is the most common toxicity, affecting almost half of the patients, but it is rarely severe [26, 80]. It is characterized by rash and vitiligo.

8.1 Molecules and Indications

This class contains a single approved molecule, ipilimumab (Yervoy®). Its characteristics and indications are presented in Table 3.

8.2 Rash

Rash is observed in 20–30 % of patients, of whom 3 % experience a grade of 3–4 [26, 27, 80, 81]. They occur 2–3 weeks after treatment initiation, and are maculopapular, diffuse, and often pruriginous (Fig. 13). Their severity relies on the rare possibility of an evolution towards Stevens–Johnson syndrome or toxic epidermal necrolysis, which are potentially lethal [81]. Treatment is mainly symptomatic [26, 81]—use of urea-based emollients and suitable cleansing gels. In case of failure of the first-line treatment or occurrence of ulcers, necrosis, bullae, or hemorrhagic manifestations, treatment with ipilimumab should be discontinued and systemic corticosteroids should be initiated. Ipilimumab may be restarted in the absence of potentially lethal skin adverse reactions.

8.3 Vitiligo

Vitiligo occurs in 5–10 % of patients, sometimes located around melanoma cutaneous metastases [26, 27, 80, 81]. Its onset could be associated with a better outcome [80].

8.4 Rarer Toxicities

Prurigo, acneiform rash, lichenoid exanthema, photosensitivity reaction, pyoderma gangrenosum-like ulcerations, skin toxicity in irradiated area, Sweets syndrome, Stevens–Johnson syndrome/toxic epidermal necrolysis, and DRESS have also been reported under ipilimumab [80].

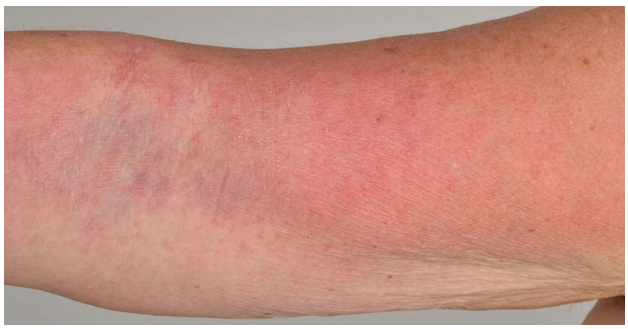

Fig. 13 Eczema-like rash under ipilimumab

9 Smoothened Inhibitors

Skin toxicity affects approximately half of the patients treated with SMO inhibitors, including mainly alopecia.

9.1 Molecules and Indications

This class contains a single approved molecule, vismodegib (Erivedge®). Its characteristics and indications are presented in Table 3.

9.2 Alopecia

Diffuse alopecia concerns 40–60 % of patients [27, 82, 83]. It can be partial or complete and can also affect eyebrows, eyelashes, and hair of the body.

9.3 Other toxicities

Pruritus grade 1 and erythema grades 1–2 have also been reported in around 10 % of patients without further information [84].

10 Classic Skin Adverse Reactions

Targeted therapies may cause classic skin reactions or hypersensitivity reactions [85]. The signs suggestive of a severe form should always be searched before diagnosing a specific toxicity of the molecule: occurrence of transient and migratory pruriginous papules within a few minutes to a few hours after taking the drug suggests urticaria; swelling of oral or pharyngeal mucosa or dyspnea suggests angioedema; occurrence of an important facial edema associated with fever, organ failure, and hypereosinophilia suggests DRESS; occurrence of mucosal ulcer and Nikolsky sign (skin detachment during a gentle friction) suggests Stevens–Johnson syndrome or toxic epidermal necrolysis. When these signs occur, ongoing treatments should always be discontinued as an emergency, and a dermatological opinion is needed.

11 Conclusions

Targeted therapy-induced skin toxicity is common and can significantly impact patient quality of life. It can sometimes question the benefit-risk ratio of the treatment, especially when targeted therapy is indicated as long-term palliative care for cancer. Their variable clinical presentations and specific treatments should be known by dermatologists to optimize patient management and this, in conjunction with the clinician in charge of the cancer treatment (oncologist or specialist). A multidisciplinary approach including the oncologist, dermatologist, and nurse is often necessary.

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