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REVIEW ARTICLE

Dermatological Toxicities of Bruton's Tyrosine Kinase Inhibitors

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Abstract

The development of Bruton's tyrosine kinase (BTK) inhibitors represents a major breakthrough in the treatment of chronic lymphocytic leukemia and other B cell malignancies. The first-generation inhibitor ibrutinib works by covalent irreversible binding to BTK, a non-receptor tyrosine kinase of the TEC (transient erythroblastopenia of childhood) family that plays a critical role in the B-cell receptor signaling pathway. It also induces an 'off-target' inhibition of a range of other kinases including (but not limited to) epidermal growth factor receptor (EGFR), SRC, and other kinases of the TEC family (interleukin-2-inducible T-cell kinase [ITK], Tec, BMX). Dermatological toxicities are among the most common toxicities of ibrutinib, but remain of mild to moderate intensity in most cases and are readily manageable. Their incidence is highest during the first year of treatment and declines over time. In addition, it has been postulated that ibrutinib-related dermatologic adverse events are mediated by the direct binding to both BTK and other 'off-target' kinases. Bruising, ecchymoses, and petechiae represent the most characteristic dermatologic adverse events. Nail and hair changes are also common, as skin infections (opportunistic infections including herpes simplex and herpes zoster virus reactivations, and *Staphylococcus aureus* superinfection), folliculitis, and other types of rashes. Panniculitis, aphthous-like ulcerations with stomatitis, neutrophilic dermatosis, peripheral edema, and skin cracking can also occur. Next-generation BTK inhibitors, acalabrutinib and zanubrutinib, have been designed to optimize BTK inhibition and minimize off-target inhibition of alternative kinases (Tec, ITK, EGFR, SRC-family kinases). These drugs have been recently FDA-approved for relapsed or refractory mantle cell lymphoma. Although the overall incidence of their toxicities is expected to be more limited, acalubrutinib and zanubrutinib are associated with a range of dermatologic toxic effects that appear to be similar to those previously described with ibrutinib, including bruising and ecchymoses, panniculitis, human herpesvirus infections, cellulitis, and skin rash. In particular, both drugs induce skin bleeding events in more than 30% of patients treated. However, the available dermatological data are still rather limited and will have to be consolidated prospectively. This review article analyses the wide spectrum of dermatological toxicities that can be encountered with first- and second-generation BTK inhibitors. Finally, recommendations for appropriate treatment as well as a synthesis algorithm for management are also proposed.

1 First-Generation BTK Inhibitor: Ibrutinib

The therapeutic management of chronic lymphocytic leukemia (CLL), the most common form of leukemia in adults, and other B-cell malignancies has been profoundly modified with the development of ibrutinib, a selective first-in-class oral Bruton's tyrosine kinase (BTK) inhibitor.

B-cell receptor (BCR) has emerged as a driving factor for CLL tumorigenesis. BTK, a non-receptor tyrosine kinase of the TEC (transient erythroblastopenia of childhood) family of kinases, is a critical component for the BCR signaling cascade, which has a fundamental role in the proliferation, survival, migration, and homing of B cells and immunoglobulin synthesis.

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Key Points

Dermatological adverse events are among the most frequent toxicities associated with ibrutinib. They are mediated by the direct binding both to Bruton's tyrosine kinase (BTK) and to other off-target kinases.

Bruising and skin ecchymosis are the most representative skin manifestations of ibrutinib. Skin infections, rash, folliculitis, panniculitis, and nail and hair changes are also commonly observed.

Skin toxicities remain in most cases of mild intensity. Proactive management is crucial in order to limit dose intensity modification.

Next-generation irreversible BTK inhibitors (acalabrutinib, zanubrutinib) present a more selective binding to BTK. However, they are also associated with apparently similar dermatological toxicities.

Ibrutinib works by covalent irreversible binding of cysteine residue 481 in the adenosine triphosphate-binding domain of BTK. Whereas ibrutinib was designed to bind and inhibit BTK with high specificity, it also displays varying affinities with a limited number of other kinases that contain a sterically available cysteine in this position including epidermal growth factor receptor (EGFR), SRC kinases, JAK2/3, B-lymphocyte kinase (BLK), and other kinases of the TEC family (including—besides BTK—tyrosine kinase expressed in hepatocellular carcinoma [Tec], bone marrow tyrosine kinase gene in chromosome X [BMX], and interleukin-2-inducible T-cell kinase [ITK]) [1–4].

Ibrutinib is now approved for treatment of adult patients with CLL (as a single agent or in combination in previously untreated CLL, or for those who have received at least one prior therapy), relapsed or refractory mantle cell lymphoma, Waldenström macroglobulinemia (in patients who have received at least one prior therapy or unsuitable for other treatment), and (in the US only) for marginal zone lymphoma and chronic graft-versus-host disease.

Ibrutinib is generally well tolerated and the incidence of the majority of adverse events is expected to be highest during the first year of treatment and decline over time [5]. Diarrhea, upper tract respiratory tract infection, bleeding, fatigue, bruising, nausea, hematologic toxicities, and cardiac adverse events including hypertension and atrial fibrillation represent the most frequent toxicities [5–10]. It is important to note that a range of these adverse events are not characteristic of germline BTK deficiency (i.e., X-linked agammaglobulinemia caused by inactivating Btk mutations) and that the off-target activity of this irreversible BTK inhibitor against other kinases has been postulated to be equally involved in ibrutinib-related toxicities.

Dermatological adverse events associated with single-agent ibrutinib are also common but remain of mild or moderate intensity in most cases (Table 1) [5–10, 13, 16–24], transient in nature, and readily manageable. However, optimized management should be systematically proposed in order to limit the negative impact on patient quality of life and, most importantly, to restrict dose intensity reduction or, what is more, treatment discontinuation, which could promote resistance to therapy.

This review article describes the wide spectrum of dermatological toxicities that can be encountered with ibrutinib monotherapy complemented by our own monocentric specialized experience. Moreover, we propose appropriate management and counseling for the most common cutaneous toxicities.

In the second part, we also address the first available data on dermatological toxicities associated with the more selective second-generation BTK inhibitors, acalabrutinib and zanubrutinib, developed to bind more selectively to BTK and to minimize off-target activity [11–15].

1.1 Bleeding Events

1.1.1 Hemorrhage and Bleeding

Ibrutinib is associated with an increased risk of hemorrhage and any grade of bleeding, whether or not there is associated thrombocytopenia [3, 4, 6, 9, 25–27]. Major bleeding,

Table 1 Main dermatologic toxicities reported in phases II/III studies with Bruton's tyrosine kinase inhibitors of first and second generations [5–10, 13, 16–24]

Skin toxicities	Ibrutinib	Acalabrutinib	Zanubrutinib
Rash	13–27% (0–3% grade 3)	15–18%	13–18%
Contusion/petechia/ecchymosis	23–33%	31–39%	43%
Cellulitis/subcutaneous abscesses	6–13%	7%	5%
Peripheral edema	11–29%	21%	5%
Stomatitis/mucositis	11–26%		
Severe bleeding events	1–9%	1–3%	2.5%

mostly spontaneous, occurs in 1–9% of cases (Table 1), especially in the form of subdural hematomas, gastrointestinal hemorrhage or hematuria [3, 5, 9, 25–27]. Combined intracellular inhibition of on-target BTK and off-target Tec kinases by ibrutinib modifies the functioning of signaling pathways downstream of several specific platelet membrane receptors such as GPVI (glycoprotein VI), GP-1b-V-IX (Von Willebrand factor receptor) or CLEC-2 (c-type lectin-like receptor 2) and ultimately the collagen-mediated activation and aggregation of platelets under arterial flow [1, 4, 9, 25–28]. This involves the same mechanisms that are implicated in the occurrence of skin ecchymosis (see Sect. 2.2).

Preventive measures must therefore be recommended before any invasive surgery, with discontinuation of the treatment 3–7 days before and after the procedure [1, 3, 9, 27]. The risk of associated bleeding has also been demonstrated in the case of dermatological surgery [29]. Interruption of treatment for 3 days prior to and after the cutaneous surgery is generally recommended in the event that the surgical procedure is judged essential, especially involving the face. Hemostasis must be carried out meticulously. In the event of a severe hemorrhagic episode, repeated transfusions of platelets may be necessary, even in the absence of thrombocytopenia [1, 3, 28].

The risk of major bleeding is increased in the event of decreased platelet counts or co-medication with antiplatelet agents or direct oral anticoagulants [1, 3, 25]. Vitamin K antagonists (warfarin) and dual antiplatelet therapy should be a priori contraindicated in this context [4, 9]. Finally, the risk of ibrutinib-associated bleeding appears higher during the first 3–12 months of treatment and decreases thereafter [1, 4, 5].

1.1.2 Bruising and Skin Ecchymoses

This is the most common and most characteristic dermatological toxicity of ibrutinib (Table 1). Ibrutinib-associated bruising and ecchymosis is believed to be due to both on-target and off-target inhibition. These are the result of the vital role of BTK and Tec kinases in platelet activation downstream of GPVI and GP-1b-V-IX, leading to dysfunction of collagen-mediated platelet aggregation (see Sect. 2.1).

1.1.2.1 Clinical Features Easy bruising affects almost 30% of patients treated (Table 1). Although not reported in the literature, these ecchymotic lesions are more likely to develop in elderly patients who present with epidermal atrophy, especially where there is associated underlying dermatoporosis [30]. Likewise, the combination of ibrutinib with systemic corticosteroids, which promotes thinning of the epidermis, or with platelet agents and anticoagulants significantly increases the development of these spontaneous hemorrhagic skin lesions, which occur most often without associated thrombocytopenia [31].

The lesions can take on different appearances [9, 31–33]: bruising, skin hematomas, ecchymoses, hemorrhagic crusting or blisters, purpuric nodules/eruption, and/or petechiae (Figs. 1 and 2). These different lesions may occur together, sometimes mimicking a target-like lesion, which is a hallmark of ibrutinib-related bleeding (authors' finding) (Figs. 1 and 2). Central necrosis may be noted. There may be associated epistaxis [4, 9].

As with dermatoporosis, these lesions are very clearly located predominantly on areas subject to repeated microtrauma and/or chronic UV exposure, mainly the dorsal aspect of the hands and the lateral surface of the forearms (Fig. 3). Involvement of the trunk and face is much less common. Finally, there is no evidence to suggest a correlation between bruising/ecchymoses and the occurrence of more severe systemic bleeding events [26, 31].

Management is based on the regular, daily use of emollient creams and limitation of cutaneous traumas. There is no indication to adjust the dose or interrupt the treatment (Fig. 4) [9].

1.1.2.2 Histopathological Features Histopathological findings in ibrutinib-related bruising/ecchymosis are nonspecific. There is the presence of a perivascular lymphohistiocytic infiltrate associated with extravasation of red blood cells. Telangiectasic vessels are noted. However, there is no formal indication to perform a skin biopsy when confronted with this type of hemorrhagic lesion. This may even be associated with significant morbidity with secondary ulceration, especially on the lower limbs (Fig. 2).

1.2 Skin Rash

The development of a pruritic or nonpruritic skin rash was reported in 13–27% in phase I–III studies (Table 1). Lesions typically remain self-limited, with a very low rate of grade 3 or higher [3, 5–8, 17, 18, 26]. It represents in most cases early-onset toxicity, with a progressive decrease over the course of treatment [5]. Although some of these eruptions are now well identified (immune-mediated drug reaction, spongiotic dermatitis, acne-like rash, pityriasis rosea-like rash, see below), there are very few ad-hoc dermatological studies allowing the clinical and histopathological characterization of these rashes. In addition, it cannot be excluded that the occurrence of an inflammatory skin rash has been confused with bruising by some hematological investigators during pivotal studies. Although not specifically evaluated to date, it can also be suggested that some of these rashes, especially those occurring within the first 4 weeks of therapy, may be consistent with the transient hyperlymphocytosis that

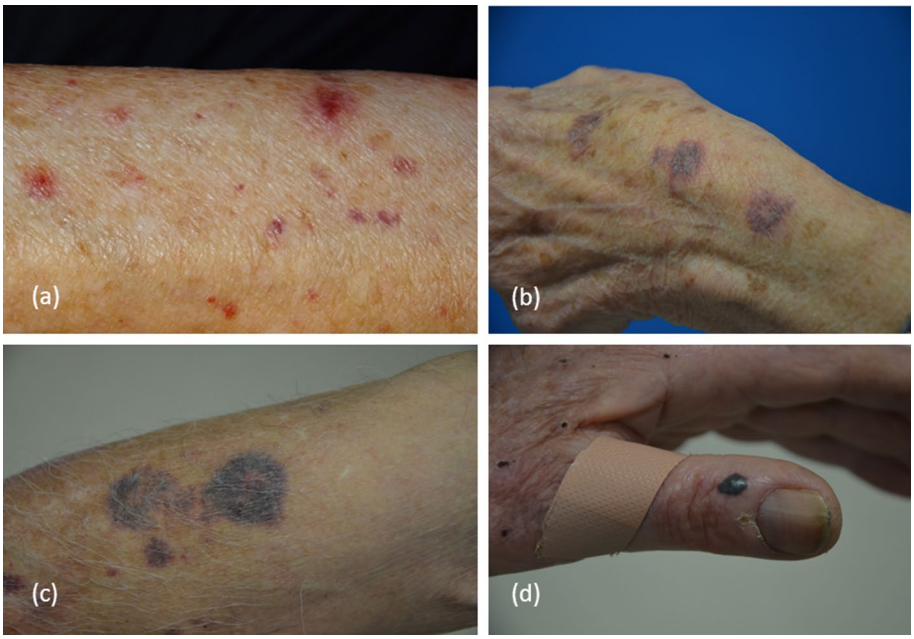

Fig. 1 **a** petechiae; **b** typical lesion with a target-like pattern; **c** ecchymosis; **d** hemorrhagic blister (source V. Sibaud, MD, Toulouse)

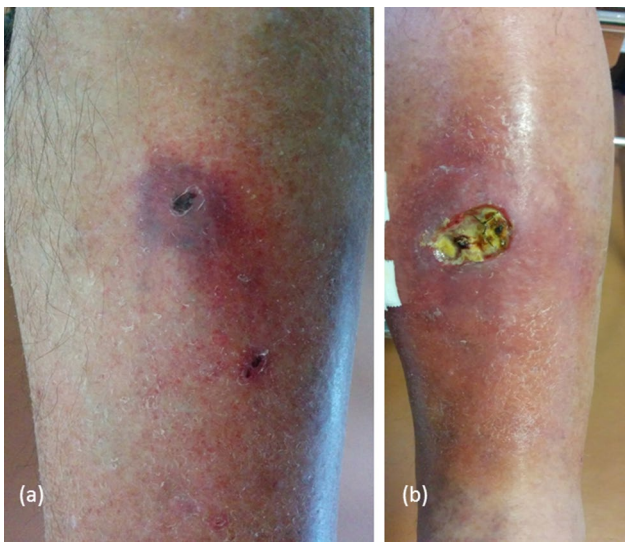

Fig. 2 **a** Cutaneous ecchymosis with central necrosis; **b** severe necrosis following skin biopsy (courtesy of C. Soussain, MD, Paris)

can be associated with ibrutinib (initial egress of CLL cells from lymph nodes and spleen) [9, 33].

Iberri et al. retrospectively reported the largest case series of patients treated with ibrutinib who developed a skin rash [33]. The authors identified two rash variants in a cohort of 14 patients treated with ibrutinib either as monotherapy or in combination with rituximab. The first subtype was a non-palpable petechial rash, akin to the ecchymotic eruptions previously described (see Sect. 2.2) and appearing only after several weeks of treatment. On the other hand, nine patients developed a palpable purpuric rash that occurred quite rapidly after introduction (even if the standard deviation was quite large). Histopathological aspects were rather nonspecific, combining a polymorphic inflammatory dermal infiltrate with extravasation of red blood cells. Patients were treated with topical corticosteroids and oral antihistamines, without permanent discontinuation. A transient interruption and rechallenge at a lower dose were required for two patients presenting a more severe rash.

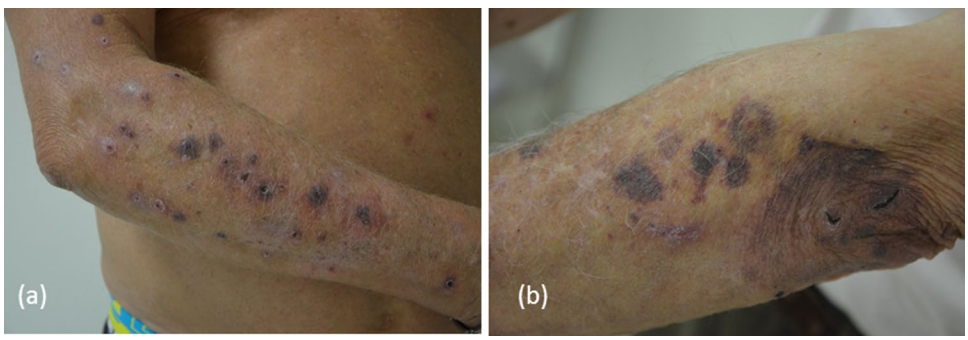

Fig. 3 **a**, **b** : diffuse bruising with apparent ecchymotic lesions and hematomas with associated skin atrophy, mimicking dermatoporosis (source V. Sibaud, MD, Toulouse)

Fig. 4 Proposed algorithm for management of the most frequent skin toxic effects

Although ibrutinib-related rashes usually do not require treatment interruption or dose adjustment [5] and can be managed by topical corticosteroids and antihistamines [1, 3, 9, 26, 33, 34], it appears crucial now to propose prospective dermatological studies to better characterize this dermatological toxicity. Likewise, a skin biopsy and a dermatological assessment should be performed if there are any atypical or severe lesions. Finally, it should be remembered that a viral reactivation with associated exanthem should be systematically discussed in this specific population of patients with potential underlying immunosuppression.

1.2.1 (Potentially) Severe Immune-Mediated Drug Reaction

Like other orally available tyrosine kinase inhibitors, such as sorafenib, vemurafenib, imatinib, dabrafenib, sunitinib or bosutinib, ibrutinib may also induce potentially life-threatening immune-related skin reactions. Although Stevens–Johnson syndromes and lip or tongue swelling have already been reported with ibrutinib [1, 33], the development of very severe dermatological toxicities such as DRESS (drug reaction with eosinophilia and systemic symptoms), toxic epidermal necrolysis and acute generalized exanthematous pustulosis appears to be quite exceptional.

Conversely, the occurrence of an early (within the first month of treatment) and potentially severe morbilliform eruption with edematous or purpuric papules is not uncommon in our experience and has also been reported before (Fig. 5) [35]. The screening for associated symptoms suggestive of severity should be systematic in this context, including fever, facial edema, cutaneous detachment with blisters or mucosal erosions, Nikolsky's sign, exfoliative rash, pustules, lymphadenopathy, or laboratory abnormalities (eosinophilia, transaminitis, renal failure, etc.) (Fig. 4). If at least one of these criteria is present, treatment must be permanently discontinued. Otherwise, temporary withholding or treatment continuation with very close monitoring must be discussed in a multidisciplinary approach, on a case-by-case basis. In the first case, a cautious and progressive ibrutinib rechallenge (at a reduced or the same final dose) can be proposed [9, 31], even if there is no rapid drug desensitization protocol available to date with ibrutinib therapy and taking into account the risk of rapid recurrence after reintroduction (Fig. 4) [33, 35]. In the second hypothesis, systemic corticosteroids can be combined during the first month with or without dose reduction, as recently proposed by Ollech et al., with other multikinase inhibitors (Fig. 5) [36].

1.2.2 Eczema-Like Rash/Spongiotic Dermatitis

Eczematous eruptions can also occur with ibrutinib (Fig. 6) [32, 34, 37]. The overall incidence remains unknown. In our experience, they do not occur very early. The lesions often remain self-limited and are well controlled by skin-directed therapy (topical corticosteroids, moisturizers) (Fig. 4). There is no need for temporary discontinuation. Histologically,

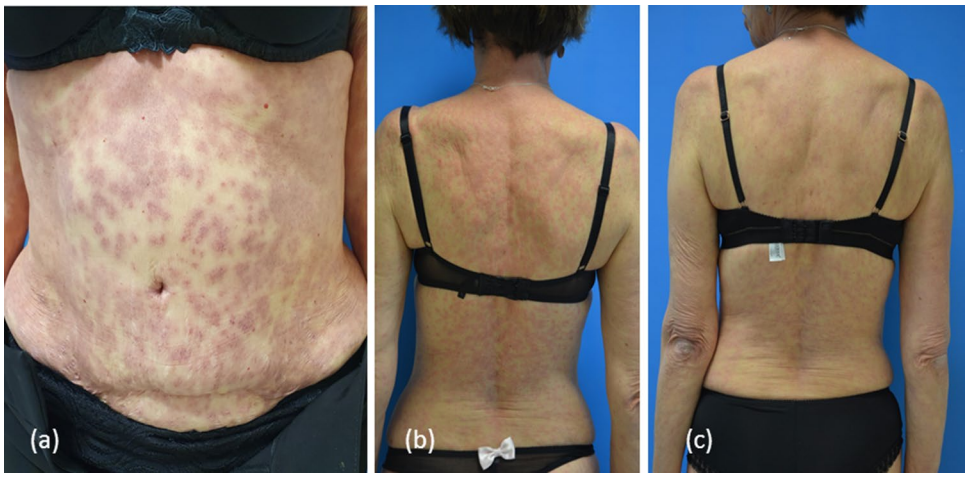

Fig. 5 **a**, **b** diffuse and severe maculopapular rash with purpuric lesions; **c** almost complete regression of the rash after 4 weeks of oral corticosteroids and despite the continuation of ibrutinib (source V. Sibaud, MD, Toulouse)

lesions involve a dermal infiltrate of eosinophils with individualized spongiosis.

1.2.3 Acne-Like Rash (Folliculitis)

Singer et al. reported a short case series of ten patients who developed a papulopustular rash with ibrutinib treatment [32]. The lesions were sited predominantly on the face, although the trunk and extremities were more rarely affected. Papules and pustules appeared mostly from the first weeks of treatment, with a similar presentation to the papulopustular rash reported with pan-HER inhibitors, although with a lower severity grade [32]. These authors considered that the development of this papulopustular rash could represent an off-target effect of ibrutinib on the EGFR signaling pathway. In most of these reported cases there was associated photosensitivity.

In the same way, the occurrence of inflammatory follicular lesions is not uncommon in our experience. The face may be affected but in a non-exclusive manner and lesions of the abdomen, limbs or fingers may also be noted (Fig. 7). Above all, this folliculitis appears to be associated with a *Staphylococcus aureus* superinfection in the vast majority of cases in our patients (Fig. 8), which was not systematically investigated in the Singer et al. case series [32], but has been reported by others [31, 38]. It is not, however, possible at this stage to determine whether this is a primary infection promoted by BTK inhibitor (see Sect. 4) or a secondary infection as previously identified with anti-EGFR therapies [39, 40].

Therapeutic management strategies for these papulopustular rashes require an initial systematic screening for *S. aureus* using a bacterial swab. If this is negative, treatment with tetracyclines and topical corticosteroids may be proposed in accordance with lesion severity. Otherwise, antistaphylococcal treatment must be proposed (Fig. 4).

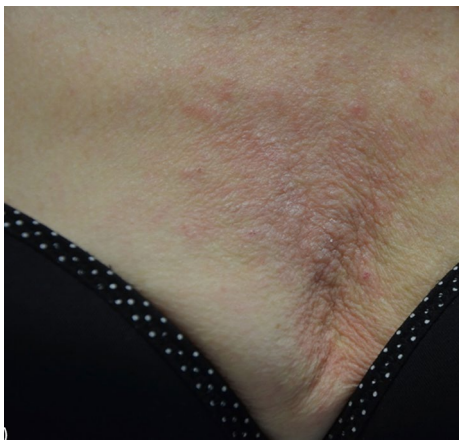

Fig. 6 Pruritic eczematous dermatitis (source V. Sibaud, MD, Toulouse)

1.2.4 Pityriasis Rosea-Like Rash

A rash with a pityriasis rosea-like pattern has also exceptionally been reported with this TKI [32, 41]. Violaceous scaly papules may appear on the trunk, sometimes in a 'Christmas tree' distribution. A perivascular lymphocytic and eosinophilic infiltrate was noted, with spongiotic dermatosis. It seems that treatment with ibrutinib can be continued and the lesions treated with topical corticosteroids. The suggested mechanism is an off-target effect of ibrutinib, potentially on c-KIT [41].

1.3 Skin Infections

The increased risk of severe infections with ibrutinib is clearly established, promoted in particular by a B-cell dysfunction (after BCR inhibition), hypogammaglobulinemia associated with an initial decrease in IgA levels, induced neutropenia, reduction in macrophagic phagocytosis

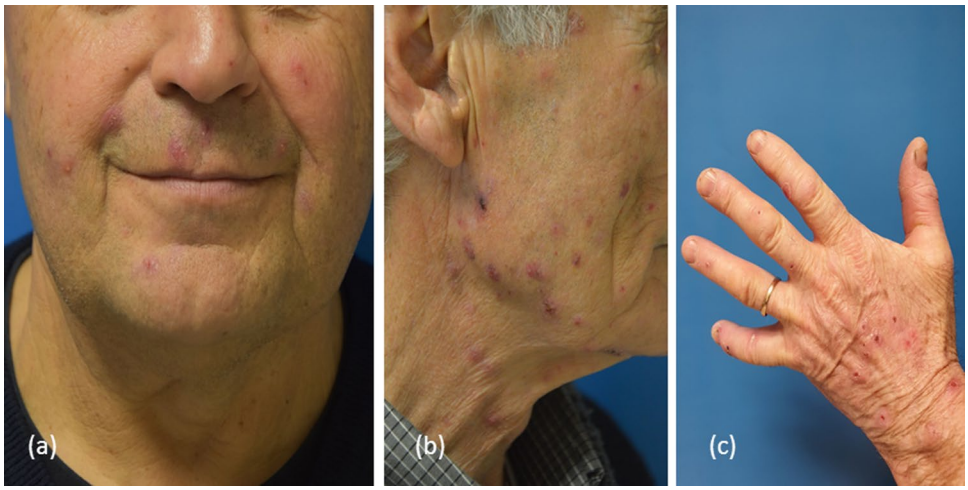

Fig. 7 **a**, **b** papulopustular rash of the face; **c** similar lesions of the dorsal aspect of the hand associated with *Staphylococcus aureus* superinfection (source V. Sibaud, MD, Toulouse)

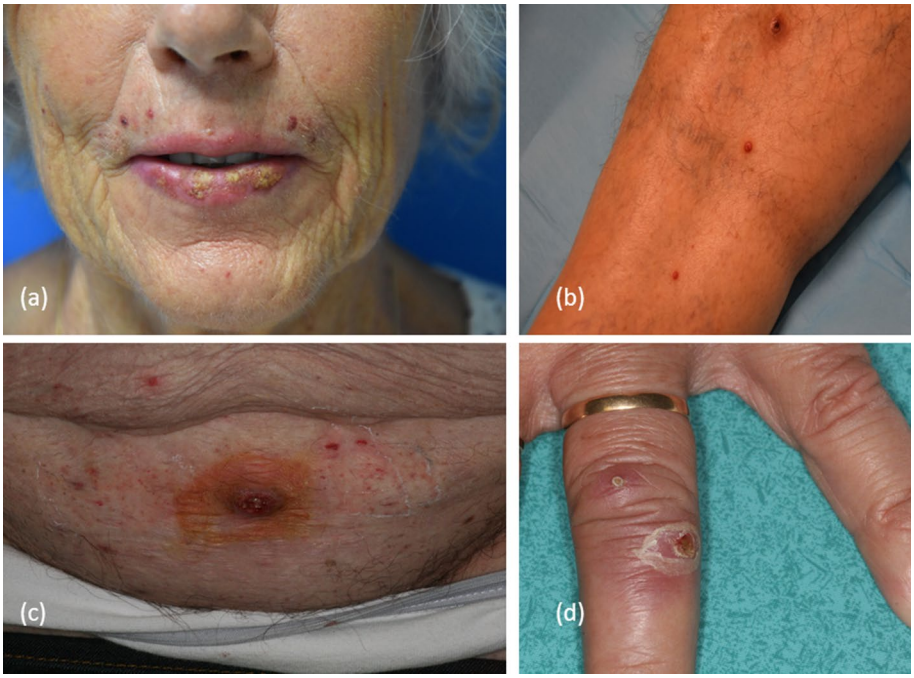

Fig. 8 **a** perioral herpes simplex reaction; **b** progressive development of molluscum contagiosum (poxvirus); **c**, **d** necrotizing folliculitis with S*taphylococcus aureus* superinfection (source V. Sibaud, MD, Toulouse)

mechanisms, decrease in T-regulatory cells or by off-target inhibition of other kinases such as ITK (IL-2-inducible T-cell kinase) with a decreased Th-1-mediated response (particularly in T-helper cells) against intracellular pathogens, especially fungal microorganisms [1, 3, 9, 27, 31, 42, 43]. This risk is greater during the first year of treatment [5, 31] with gradual secondary restoration of cellular and humoral immunity [3]. It also appears increased in the case of associated immunosuppressive treatments or prior chemotherapy (particularly with fludarabin, bendamustine and/or rituximab) [1, 44] or in the case of relapsed/refractory CLL. Pneumonia, sinusitis, and infections of the upper respiratory and urinary tracts are the most frequent [7, 9, 20]. Evidence is growing rapidly that opportunistic infections may also occur, particularly invasive fungal infections (mainly aspergillus and pneumocystosis, cryptococcosis, mucormycosis). These may be severe and may arise at an early stage [1, 3, 9, 27, 43].

Increased skin infection rates are also reported in patients treated with ibrutinib [8, 31, 32, 38], particularly *Staphylococcus aureus* infections (Fig. 8) [32, 38]. In our experience, it manifests most often as moderate folliculitis (see Sect. 3.3), associated or not with focal necrosis (Fig. 8). Much more severe forms of the type SSS syndrome (*staphylococcal scalded skin syndrome,* caused by the systemic spread of exfoliative toxins) with extensive blistering of skin have, however, also been exceptionally described [45]. It is therefore imperative to perform a bacterial swab

with detection of gram + cocci (or toxins) in all suggestive lesional or perilesional areas. Cellulitis and subcutaneous abscess can also occur (Table 1).

The occurrence of opportunistic skin infections has also been reported with ibrutinib, particularly nontuberculous mycobacteria or mucormycosis [42, 46]. A systematic investigation must be proposed when confronted with any atypical or severe rash. The risk of Herpes viruses infection, sometimes of severe intensity, also appears increased [7, 8, 10, 17, 27, 31, 38]. Of note, herpes zoster virus infections and oral herpes reactivation represent the most frequent opportunistic infections reported with ibrutinib [5]. Prophylactic treatment with valaciclovir may be proposed [3], notably in patients with more than two flares per year (authors recommendation).

1.4 Panniculitis

As may be observed with exclusive BRAF inhibitors (vemurafenib, dabrafenib, encorafenib), ibrutinib can also induce panniculitis [32, 47–49]. The incidence remains to be determined but the presence of panniculitis was reported, in a retrospective case series, in more than 20% of patients presenting with cutaneous toxicity [32]. This does not, however, correspond with our own experience, where these lesions remain uncommon.

The lesions generally start during the first weeks of treatment and are located predominantly on the lower limbs [47]. These subcutaneous well defined erythematous nodules are sensitive, even painful, and may take on an ecchymotic appearance. Histopathology shows a septal and/or lobular panniculitis, with a superficial and perivascular mixed inflammatory infiltrate, adipocyte necrosis, and prominent leukocytoclasis [47, 48]. A localized T-cell driven adaptive immune response against ibrutinib-conjugated peptides has been suggested [47]. Later onset panniculitis has also been described [49].

Treatment with ibrutinib can generally be maintained, sometimes with a transient dose reduction. These lesions respond to systemic corticosteroid therapy at low doses or to non-steroidal anti-inflammatory drugs [32], which must, however, sometimes be maintained to avoid relapses [47]. Spontaneous resolution despite continuation of the causative treatment also appears possible [48]. Finally, a deep cutaneous infection must systematically be excluded, with tissue culture if necessary [31, 48, 49].

1.5 Nail and Hair Changes

1.5.1 Nail Toxicities

Nail changes appear progressively with ibrutinib, which may affect almost two-thirds of patients treated [50]. They develop gradually, only become visible after several months of treatment, and are located predominantly on the fingers [50, 51]. Nail brittleness represents the most common manifestation. Nail plates grow more slowly and become more friable and fragile, which can lead to onycholysis, onychorrhexis, onychoschizia, koilonychia or trachyonychia (Fig. 9). Nail lesions in most cases remain of low to moderate severity but can significantly impact patient quality of life [19, 32, 50, 51].

It has been suggested that these nail plate abnormalities are secondary to the covalent binding of ibrutinib to cysteine 481, a cysteine residue present both on BTK and keratin. This is thought to modify the disulfide bonds between cysteine residues that are fundamental to the integrity of keratin [50, 52]. A similar mechanism has also been put forward for hair changes under ibrutinib treatment (see Sect. 6.2) [50].

Periungual tissue may also be affected, with the appearance of inflammatory paronychia involving proximal or lateral nail folds, associated (or not) with a pyogenic granuloma (Fig. 9) [10, 37, 51, 52]. This damage is probably secondary to nail plate changes with progressive onychocryptosis, mimicking an ingrown nail. An interaction with inhibition of the NF-κB signaling pathway by ibrutinib has also been suggested, as a possible off-target effect of ibrutinib on the EGFR signaling pathway [37, 52].

Finally, subungual splinter hemorrhages can also occur (Fig. 9) [51].

Nail changes do not represent a dose-limiting toxicity but supportive measures must be proposed which, by analogy, appear similar to those proposed for patients under chemotherapy or treated with EGFR or MEK inhibitors [53, 54]. In particular, it is important to preventively educate patients in order to avoid repeated trauma and excessive pressure on nails, to trim nails regularly, to wear comfortable wide-fitting footwear, and to apply topical emollients daily.

1.5.2 Hair Toxicities

Changes to hair texture are also possible, which may affect a quarter of patients evaluated prospectively [19, 50]. After several months of treatment, the hair follicle changes from curly to straight, although the reverse is also possible [32, 50]. The same pathophysiological mechanisms as those presented in the previous section (Sect. 6.1) may similarly be evoked.

In our experience, the progressive development of grade 1 alopecia with hair thinning is not exceptional (Fig. 10), although it has only rarely been reported in pivotal studies [7, 19]. Topical treatment with minoxidil may be proposed.

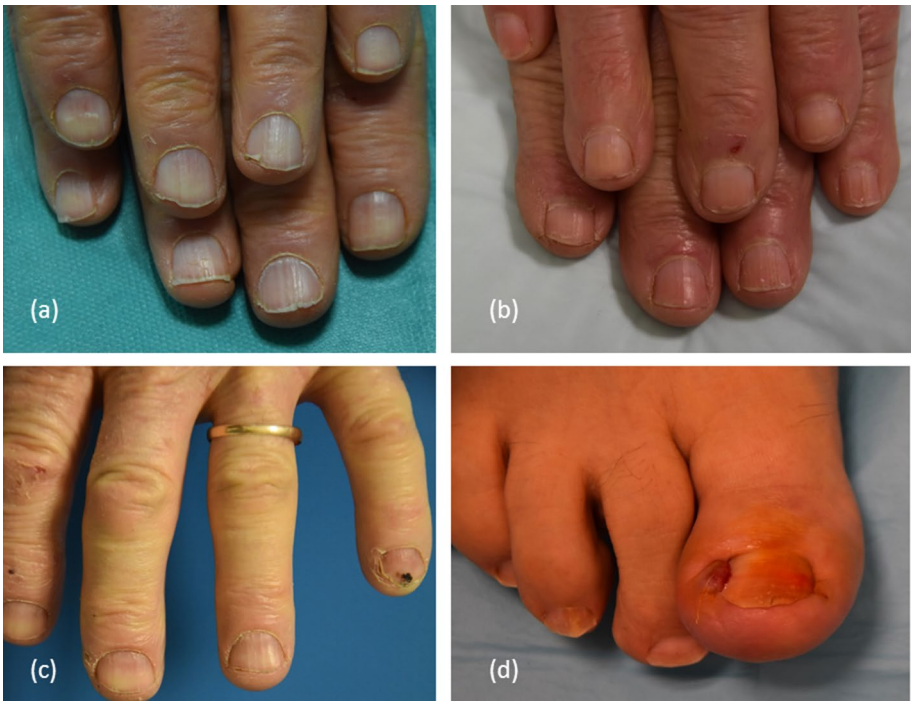

Fig. 9 **a**, **b** progressive nail changes combining brittle nails, mild onycholysis, early onychorrhexis, and onychoschizia; **c** nail brittleness with apparent subungual hematoma; **d** paronychia involving the big toe with the formation of pyogenic granuloma in the lateral fold (source V. Sibaud, MD, Toulouse)

1.6 Oral Mucosal Toxicities

Mucositis occurs in more than 10% of patients treated (Table 1). In the vast majority of cases this is of moderate severity, with less than 3% grade 3 or higher [16–20]. We have, however, personally observed several cases of severe stomatitis requiring the temporary discontinuation of ibrutinib and the introduction of symptomatic measures, particularly with topical and/or systemic corticosteroids. Reintroduction at a lower dose was not associated with recurrence of the lesions, suggesting a dose-dependent mechanism [55]. This involved clearly defined, necrotic aphthous-like ulcers (Fig. 11) that were very painful and developed early (within 4 weeks) or conversely in a delayed manner (16 months) after the introduction of treatment [55]. Unlike the aphthous-like lesions classically described with other tyrosine kinase inhibitors, particularly mTOR and anti-HER inhibitors, which are located exclusively on non-keratinized mucosa (buccal mucosa, soft palate, floor of the mouth, ventral surface of the tongue), those induced by ibrutinib seem to be able to also affect the keratinized mucosa (hard palate, gums, dorsal aspect of the tongue) [56]. In all cases, herpes simplex virus reactivation or fungal infection must be ruled out (Fig. 11), particularly before introduction of corticosteroid therapy [5]. Likewise, a concomitant severe neutropenia must also be sought [55, 56].

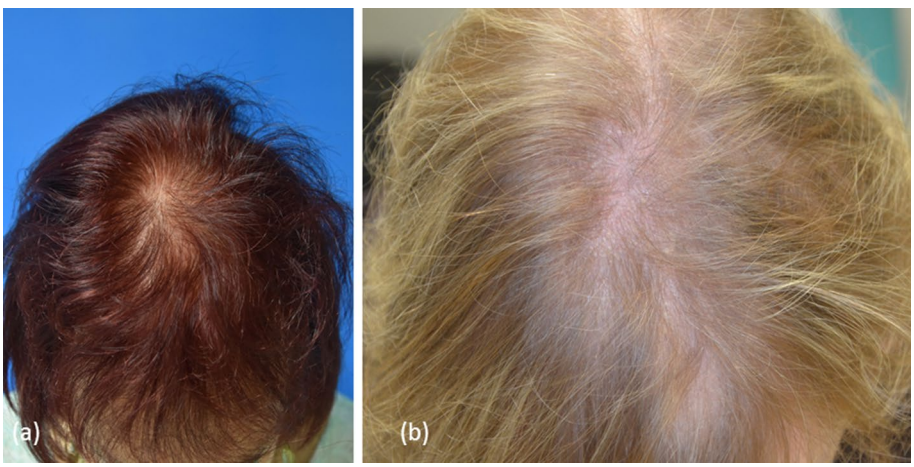

Fig. 10 **a**, **b**: grade 1 alopecia after several months of treatment (source V. Sibaud, MD, Toulouse)

Finally, the patients treated may also report xerostomia [16], mucosal bleeding or the recurrent formation of hemorrhagic bullae (Fig. 11).

1.7 Other Skin Toxicities

1.7.1 Neutrophilic Dermatosis

Some observations of neutrophilic dermatoses, consistent with the diagnosis of pyoderma gangrenosum or Sweet syndrome, have recently been described [57, 58]. The lesions, which may be multiple, appear dose-dependent and may require a dose reduction and/or the maintenance of daily low-dose oral corticosteroids. It has been suggested that ibrutinib could promote Th1 polarization by blocking ITK [59].

In our experience, we have observed very mutilating forms of pyoderma gangrenosum or, conversely, limited lesions of neutrophilic dermatosis of the dorsal hands (Fig. 12).

1.7.2 Skin Carcinomas

Squamous cell carcinomas and basal carcinomas have been reported with ibrutinib in pivotal studies [5, 18, 20]. Given the well established increase in the incidence of these skin cancers in patients with B-cell malignancies, it remains speculative to evaluate causality of ibrutinib as an inducing or triggering factor [60].

1.7.3 Auto-Immune Skin Disorders

Ibrutinib can be associated with reactivation of an underlying autoimmune disease such as cytopenia or autoimmune hemolytic anemia, particularly during the first weeks of treatment [1, 9, 27]. The development of bullous pemphigoid has exceptionally been reported [37]. The causality is still to be established.

1.7.4 Xerosis

Cutaneous xerosis is frequently noted [10, 19]. It is sometimes severe [32], and may be associated with pruritus [8, 17, 19]. Palmoplantar or digital fissures, which tend to be painful, may develop secondarily (Fig. 13). It could be related to an off-target activity of ibrutinib on the EGF receptor [61].

1.7.5 Peripheral Edema

Peripheral edema, of variable severity, is common and in the order of 20% (Table 1). Some authors [3] have also reported the development of a significant thickening of the skin of the lower limbs, known as 'tree trunk legs,' which we also seldom observed (< 1% of our patient cohort), with complete recovery after drug discontinuation.

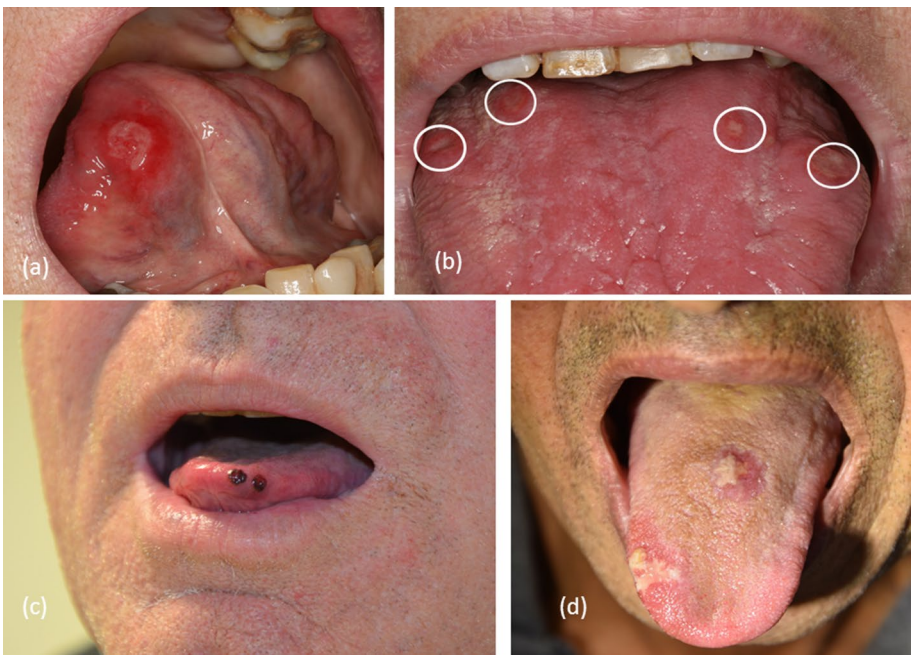

Fig. 11 **a**, **b** painful aphthous-like ulcerations involving both nonkeratinized and keratinized mucosae; **c** hemorrhagic blisters developing on the tongue; **d** HSV-1 superinfection (source V. Sibaud, MD, Toulouse)

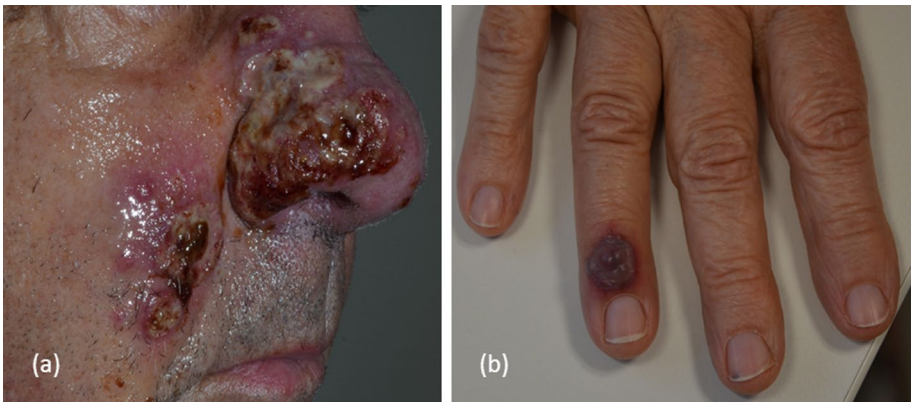

Fig. 12 **a** severe pyoderma gangrenosum involving the face; **b** early phase of neutrophilic dermatosis of the dorsal hands (source V. Sibaud, MD, Toulouse)

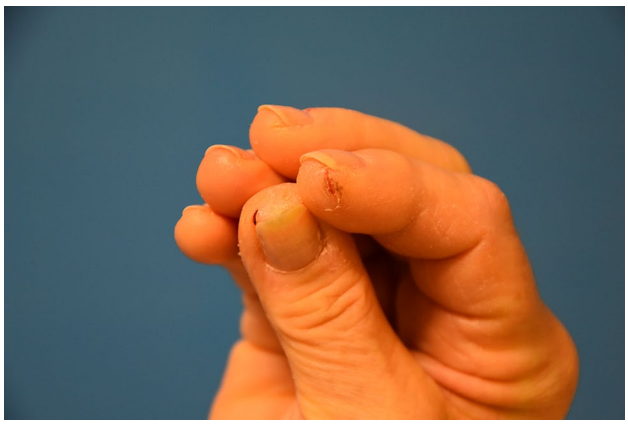

Fig. 13 Skin cracking associated with digital xerosis (source V. Sibaud, MD, Toulouse)

1.7.6 Eosinophilic Dermatosis of Hematologic Malignancy (EDHM)

B-cell lymphoproliferative diseases, especially CLL, are frequently associated with the development of pruritic insect-bite–like reactions or EDHM [62]. However, ibrutinib does not seem to modify EDHM outcome, whether in terms of improvement or worsening.

2 Next-Generation BTK Inhibitors: Acalabrutinib and Zanubrutinib

Acalabrutinib and zanubrutinib are next-generation irreversible BTK inhibitors designed to maximize BTK inhibition and minimize off-target inhibition of interleukin-2 inducible T-cell kinase, or TEC- and EGFR-family kinases. Acalabrutinib and zanubrutinib also bind covalently to Cys481 located at the ATP-binding site of BTK, showing a favorable pharmacokinetics profile with a better bioavailability in comparison with ibrutinib [11–15]. Acalabrutinib and zanubrutinib recently received accelerated FDA approval for treatment of patients with relapsed or refractory mantle cell lymphoma.

The global incidence of toxicities associated with these two new drugs is expected to be limited, considering the greater relative selectivity over ibrutinib for BTK and minimal off-target activity. Overall, these new oral BTK inhibitors are considered relatively safe [11, 12, 15], both in naïve patients and in patients previously intolerant to ibrutinib [23]. In the ASPEN phase III study comparing zanubrutinib with ibrutinib in a population of patients with Waldenström macroglobulinemia (ClinicalTrials.gov identifier NCT03053440; unpublished, open-label, randomized study), the incidence of adverse events of special interest including diarrhea, atrial fibrillation and severe hemorrhages was lower in the zanubrutinib group.

Although the clinical data available is currently still fairly limited (especially with zanubrutinib) and in the vast majority of cases obtained in a non-comparative way, the spectrum of dermatological toxic effects appears roughly comparable to that described with ibrutinib (rash, ecchymoses and petechiae, panniculitis, HSV or VZV infections, cellulitis, risk of hemorrhage, etc.) [13, 14, 21–24, 63] with an incidence that is probably lower [31]. It has also been reported that some toxicities that have occurred under ibrutinib treatment, including dermatological toxicities (panniculitis, contusion, ecchymoses, peripheral edema, skin rash) may recur in the same form in patients treated with acalabrutinib prescribed as second-line treatment [23].

2.1 Bleeding Events

Acalabrutinib and zanubrutinib also induce petechiae and skin contusions or potentially severe hemorrhages, at a rate appearing to be equivalent to that reported in ibrutinib-treated patients (Table 1). Conversely, acalabrutinib and zanubrutinib do not block aggregation of platelets from healthy donors or mice but induce very similar effects to ibrutinib in donors with CLL. It has also been established ex vivo that acalabrutinib delayed collagen-induced platelet

aggregation in CLL patients [64]. Finally, zanubrutinib does not seem to interact with the GPIb-IX-V signaling pathway, unlike ibrutinib [65].

In summary, the risk of hemorrhage for these newly approved BTK inhibitors is yet to be evaluated with greater precision.

3 Conclusion

A large majority of patients treated with ibrutinib develop dermatological toxic effects. These, however, remain most often of moderate severity and do not require treatment discontinuation. Some of these toxicities are now well identified, such as bruising, skin infections, acne-like rashes and nail or hair changes. It appears necessary, however, to initiate prospective studies in patients treated with ibrutinib or with next-generation BTK inhibitors, particularly in order to allow better clinical and/or histological characterization of the skin rashes that have been described in almost one-third of patients during pivotal studies.

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Compliance with Ethical Standards

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