Dermatologic Adverse Events Associated with Selective Fibroblast Growth Factor Receptor Inhibitors: Overview, Prevention, and Management Guidelines

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Dermatologic • Fibroblast growth factor receptor • Drug-related side effects and adverse events • Guidelines

Abstract

Fibroblast growth factor receptor (FGFR) tyrosine kinases, which are expressed on the cell membrane, are involved in a wide range of biological functions such as cell proliferation, survival, migration, and differentiation. The identification of FGFR fusions and other alterations in a wide range of solid tumors, including cholangiocarcinoma and bladder cancer, has resulted in the development of several selective FGFR inhibitors for use in these indications, for example, infgratinib, erdafitinib, derazantinib, pemigatinib, and futibatinib. In addition to the typical adverse events associated with tyrosine kinases, the FGFR inhibitors appear to give rise to a number of adverse events affecting the skin. Here we describe these skin events, which include the more common nail adverse events (e.g., onycholysis), palmar–plantar erythrodysesthesia syndrome, and stomatitis, as well as less common reactions such as calciphylaxis. This review aims to provide oncologists with an understanding of these dermatologic events and proposes guidelines for the management of treatment-emergent dermatologic adverse events. Awareness of possible adverse events associated with specific drugs should allow physicians to educate patients as to what to expect and implement effective management plans at the earliest possible opportunity, thereby preventing premature discontinuation while maintaining patient quality of life.

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Implications for Practice: Identification of fibroblast growth factor receptor (FGFR) aberrations in cholangiocarcinoma and bladder cancer led to development of selective FGFR inhibitors for these indications, based on clinical benefit and safety profiles. The most frequent adverse events (AEs) include those affecting skin, hair, and nails, a unique class effect of these agents. These are usually mild to moderate in severity. This work reviewed skin AEs reported with FGFR inhibitors and provides management guidelines for physicians, aiming to increase awareness of skin events and provide effective treatment strategies. Early intervention and effective management may improve treatment adherence, optimize outcomes, and improve quality of life.

Introduction

Fibroblast growth factors (FGFs) and their receptors control a wide range of biological functions, regulating cellular proliferation, survival, migration, and differentiation [1]. Twenty-two mammalian FGFs have been identified to date, many of which depend on interaction with FGF receptors (FGFRs) for their biological effects [2]. The human FGFR family comprises five members: FGFR1, FGFR2, FGFR3, FGFR4, and FGFR5. FGFRs 1–4 are receptor tyrosine kinases consisting of an extracellular ligand-bound domain, a transmembrane domain, and an intracellular kinase domain. FGFR5 is a neutral phosphatase and does not have a kinase domain. FGFR aberrations have been identified in a variety of cancers, including cholangiocarcinoma and bladder cancer, leading to the development of selective FGFR inhibitors for these indications. These inhibitors are typically associated with a range of adverse events, including skin events such as nail adverse events, palmar–plantar erythrodysesthesia syndrome, and stomatitis. In addition, less common reactions such as calciphylaxis have been reported. This review aims to provide oncologists with an understanding of these dermatologic events and proposes guidelines for the management of treatment-emergent dermatologic adverse events. Awareness of possible adverse events associated with specific drugs should allow physicians to educate patients as to what to expect and implement effective management plans at the earliest possible opportunity, thereby preventing premature discontinuation while maintaining patient quality of life.

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TKIs can also include those related to vascular endothelial inhibitory targets, adverse events associated with anti-FGFR matologic events [8, 9]. Depending on the breadth of their alopecia, dry mouth/xerostomia, nail changes, and other der- cholangiocarcinoma and urothelial cancers.

Understanding of the dermatologic events associated with as dry eye and retinal pigment epithelium detachment). 

Vomiting and diarrhea, skin reactions, and ocular effects, such as gastrointestinal disorders, such as FGFR signaling has the potential to lead to on-target adverse processes such as tissue regeneration and healing, inhibition of vascular canals of Hering and the main bile duct. These are uncommon cancers, accounting for only 3% of gastrointestinal cancers [10]; however, the mortality rate is high and only 8%–10% of patients are alive at 5 years after diagnosis [11]. 

The incidence of cholangiocarcinoma varies greatly, with the highest rates seen in Asian countries and lower rates in Western countries [12], although rates of intrahepatic cholangiocarcinoma are increasing in Western countries [13]. In their analysis of SEER data, Saha and colleagues reported an increase in rates of intrahepatic cholangiocarcinoma, from 0.44/100,000 in 1973 to 1.18/100,000 in 2012 [14]. This corresponds to an estimated 8,000 new cases of cholangiocarcinoma per year in the U.S. [15]. 

Treatment options are limited for patients with metastatic cholangiocarcinoma and outcomes are poor. The gemcitabine + cisplatin doublet is the standard of care in the first-line setting, resulting in median overall and progression-free survivals of 11.7 and 8.0 months, respectively [16]. After first-line therapy, there are no established systemic options [17, 18]. However, the practice-changing ABC-06 study demonstrated that treatment with a modified 5-fluorouracil/folinic acid + oxaliplatin regimen and active symptom control was superior to active symptom control alone in patients with cholangiocarcinoma whose disease had progressed during or after treatment with gemcitabine + cisplatin [19]. Despite this, there remains a need for targeted agents with the potential to improve survival in selected patient populations. 

Alterations in genes encoding FGFRs are common in patients with cholangiocarcinoma, the most common being FGFR2 fusions, FGFR19 amplifications, and FGFR2 mutations [20]. FGFR2 fusions are present in 13%–25% of patients with cholangiocarcinoma [20, 21] and therefore represent a promising target for therapy in enriched patient populations. 

Key small-molecule FGFR TKIs currently under clinical development for the treatment of cholangiocarcinoma include multikinase and tyrosine kinase inhibitors such as infigratinib, erdafitinib, derazantinib, pemigatinib, and futibatinib (TAS-120)—are in advanced stages of development in patients with cholangiocarcinoma and urothelial cancer. Ongoing phase II and III trials of these agents are summarized in Table 2.

As FGFRs act with other signaling molecules to orchestrate processes such as tissue regeneration and healing, inhibition of FGFR signaling has the potential to lead to on-target adverse events such as hyperphosphatemia, which is believed to result from inhibition of FGFR signaling in the proximal renal tubule, as well as others associated with off-target effects, including alopecia, dry mouth/xerostomia, nail changes, and other dermatologic events [8, 9]. Depending on the breadth of their inhibitory targets, adverse events associated with anti-FGFR TKIs can also include those related to vascular endothelial growth factor receptor (VEGFR) inhibition (e.g., hypertension, cardiovascular events, and proteinuria), as seen with earlier-generation multikinase inhibitors, and others commonly reported with TKIs (e.g., gastrointestinal disorders, such as vomiting and diarrhea, skin reactions, and ocular effects, such as dry eye and retinal pigment epithelium detachment).

The aim of this review is to provide oncologists with an understanding of the dermatologic events associated with FGFR inhibitors currently in clinical development or approved by regulatory agencies for the treatment of cholangiocarcinoma and urothelial cancers.

**Rationale for Use of FGFR Inhibitors in Cholangiocarcinoma and Other Malignancies**

**Cholangiocarcinoma**

Cholangiocarcinoma is a heterogeneous grouping of malignancies arising from the biliary epithelium between the canals of Hering and the main bile duct. These are uncommon cancers, accounting for only 3% of gastrointestinal cancers [10]; however, the mortality rate is high and only 8%–10% of patients are alive at 5 years after diagnosis [11].

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Key small-molecule FGFR TKIs currently under clinical development for the treatment of cholangiocarcinoma include multikinase and tyrosine kinase inhibitors such as infigratinib, erdafitinib, derazantinib, futibatinib, pazopanib, and Debio 1347. Pemigatinib was approved for use in patients with FGFR2 fusion or rearrangement in April 2020, based on the results of the phase II FIGHT-202 study [22].
Other agents with a broader spectrum of activity, for example, the multikinase inhibitors pazopanib and dovitinib, are also in development for this indication but are not included in this review.

### Urothelial Cancer
An estimated 80,000 new cases of bladder cancer will be diagnosed in the U.S. in 2019, three quarters of which will be in men [23].

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**Table 2. Current ongoing phase II and III trials with key selective FGFR tyrosine kinase inhibitors**

| Agent and study ID | Phase | Indication | Regimen | No. of patients |
|--------------------|-------|------------|---------|----------------|
| Infgratinib (BGJ398) | NCT03773302 | III Cholangiocarcinoma | Infgratinib vs. gemcitabine/cisplatin | 384 |
|                     | NCT04197986 | III Urothelial cancer | Infgratinib vs. placebo | 218 |
|                     | NCT02150967 | II Cholangiocarcinoma | Infgratinib | 160 |
|                     | NCT04233567 | II Solid tumors | Infgratinib | 50 |
| Pemigatinib (INCB054828) | NCT02872714 (FIGHT-201) | II Urothelial cancer | Pemigatinib | 240 |
|                     | NCT04003610 (FIGHT-205) | II Urothelial cancer | Pemigatinib + pembrolizumab vs. pemigatinib vs. standard of care | 378 |
|                     | NCT03914794 | II Urothelial cancer | Pemigatinib | 43 |
|                     | NCT03822117 (FIGHT-207) | II Solid tumors | Pemigatinib | 170 |
|                     | NCT03011372 (FIGHT-203) | II Myeloproliferative neoplasms | Pemigatinib | 46 |
|                     | NCT02924376 (FIGHT-202) | II Cholangiocarcinoma | Pemigatinib | 140 |
|                     | NCT03656536 (FIGHT-302) | III Cholangiocarcinoma | Pemigatinib vs. gemcitabine/cisplatin | 432 |
|                     | NCT04256980 | II Cholangiocarcinoma | Pemigatinib | 54 |
|                     | NCT04003623 | II Solid tumors | Pemigatinib | 50 |
|                     | NCT02393248 (FIGHT-101) | I/II Solid tumors | Pemigatinib; combination therapy | 325 |
| Derazantinib (ARQ 087) | NCT03230318 | II Cholangiocarcinoma | Derazantinib | 143 |
|                     | NCT04045613 | Ib/II Urothelial cancer | Derazantinib vs. derazantinib + atezolizumab | 303 |
| Futibatinib (TAS-120) | NCT04024436 | II Breast cancer | Futibatinib or futibatinib + fulvestrant | 168 |
|                     | NCT02052778 | I/II Solid tumors | Futibatinib | 371 |
| Erdaftinib (INJ-42756493) | NCT03390504 | III Urothelial cancer | Erdaftinib vs. vinflunine or docetaxel or pembrolizumab | 631 |
|                     | NCT03210714 | II Solid tumors, non-Hodgkin lymphoma, or histiocytic disorders | Erdaftinib | 49 (age >21 years) |
|                     | NCT04083976 | II Solid tumors | Erdaftinib | 280 |
|                     | NCT02699606 | II Urothelial cancer | Erdaftinib | 63 (Asian) |
|                     | NCT03827850 (FIND) | II NSCLC | Erdaftinib | 50 |
|                     | NCT02365597 | II Urothelial cancer | Erdaftinib | 217 |
|                     | NCT02952573 | II Multiple myeloma | Erdaftinib | 20 |
|                     | NCT03999515 | II Prostate cancer | Erdaftinib + abiraterone acetate or enzalutamide | 25 |
|                     | NCT04172675 | II Urothelial cancer | Erdaftinib vs. investigator choice intravesical chemotherapy | 280 |
|                     | NCT03473743 | I/II Urothelial cancer | Erdaftinib in combination with cetrelimab and/or platinum | 160 |

Abbreviations: FGFR, fibroblast growth factor receptor; NSCLC, non-small cell lung cancer.
Approximately 12% of patients have regional or distant metastases at diagnosis [24]. Five-year survival rates are 36% for regional and 5% for distant metastases [24]. Treatment options for locally advanced disease include surgery followed by cisplatin-based chemotherapy if no neoadjuvant treatment has been given [25]. For those with metastatic disease, preferred options include gemcitabine + cisplatin for cisplatin-eligible patients and gemcitabine + carboplatin for those who are not eligible [25]. Targeted therapies currently available for patients whose disease progressed on cisplatin-based therapies include atezolizumab and pembrolizumab, which are approved by the U.S. Food and Drug Administration for use in patients whose tumors express programmed cell death ligand 1 (PD-L1) [26], enfortumab vedotin for patients who have previously received a programmed cell death-1 or PD-L1 inhibitor [27], and erdafitinib for patients with FGFR2- and FGFR3-altered disease, based on the results of the BLC2001 study [28].

Selective small-molecule FGFR TKIs currently in development for use in patients with urothelial carcinoma include infgratinib, pemigatinib, erdaftinib, and rogaratinib.

Dermatologic Events in Patients Treated with FGFR TKIs: Skin, Hair, Nails, and Oral Mucosa

Dermatologic adverse events, including hair loss/alopecia, hand–foot skin reaction or palmar–plantar erythrodysesthesia syndrome (PPES), stomatitis (oral mucositis), and nail changes, have been reported in phase II studies in patients with cholangiocarcinoma and urothelial carcinoma treated with FGFR inhibitors (Fig. 1; Tables 3, 4). The pathophysiological mechanisms behind these adverse events are not yet fully elucidated. Several possible mechanisms have been proposed, including inhibition of FGFR in keratinocytes, inducing dysregulation of hair-follicle homeostasis and epidermal proliferation and/or differentiation with downregulation of tight junction gene expression, as demonstrated in FGFR-deficient mice [29] and by inhibiting hormonal (nonpathological) FGF signaling by FGFR19, FGFR21, and FGFR23 [30]. FGFR2 expression has been shown to be upregulated in the nail epithelium after digit amputation in the mouse, suggesting a role for FGF signaling in digit regeneration [31].

Nail Changes

Nail changes are common in patients undergoing treatment with FGFR TKIs [32]. Patients can develop significant adverse events, the most important of which is onycholysis [33], and dose adjustment may be required as a result of this adverse event. Other less common nail events include paronychia, Beau’s lines/onychomadesis, and brittle nails (onychoshizia). Paronychia was reported in 24% and 17% of patients with cholangiocarcinoma and urothelial carcinoma, respectively, treated with erdafitinib [28, 34]; furthermore, onycholysis and nail dystrophy were observed in 18% and 16%, respectively, of patients with urothelial carcinoma [28]. Paronychia and onychomadesis were reported in 7% and 18%, respectively, of patients with cholangiocarcinoma who received infgratinib [35].

Nail adverse events, which typically develop within 1–2 months of treatment initiation, can be prolonged and debilitating [32, 36], and in severe cases can cause pain and discomfort, which can lead to treatment discontinuation [37].

Alopecia

Alopecia is a psychosocially impactful consequence of cytotoxic chemotherapy and treatment with kinase inhibitors [38]. Alopecia, which includes the textural changes, thinning, or patchy hair categorized as grade 1 alopecia, and the complete hair loss categorized as grade 2 alopecia, has been reported in patients with cholangiocarcinoma treated with infgratinib. Specifically, 26% of patients treated with infgratinib [35], 46% of those treated with pemigatinib [22], and 24% of patients treated with derazantinib [39] experienced grade 1 or 2 alopecia. In patients with urothelial carcinoma, grade 1 or 2 alopecia occurred in 31%, 39%, and 29% of patients treated with infgratinib [40], pemigatinib [41], and erdafitinib [34].

Other body hair can also be adversely affected in patients undergoing treatment with FGFR inhibitors (e.g., eyelash trichomegaly has been reported with infgratinib) [33].

Palmar–Plantar Erythrodysesthesia Syndrome (Hand–Foot Skin Reaction; Hand–Foot Syndrome)

PPES has been reported with chemotherapy and TKI treatment. It is characterized by hyperkeratosis and focal calluses, which result in diffuse xerosis and erythema combined with fissures, mostly localized to digits. This skin reaction was reported in 21%, 29%, and 18% of patients with cholangiocarcinoma and urothelial carcinoma receiving infgratinib [35], erdafitinib [42], and futibatinib [43], respectively, and in 12% and 23% of patients with urothelial carcinoma receiving infgratinib [40] and erdafitinib [28], respectively. Among patients with cholangiocarcinoma, grade 3/4 PPES was reported in 5% of patients treated with infgratinib [35] and 4% of those treated with pemigatinib [22], whereas 8% of infgratinib-treated [40] and 5% of erdafitinib-treated patients with urothelial cancer [28] reported this event. Of note, this adverse event differs from that seen with traditional chemotherapeutic agents. PPES with cytotoxic agents such as capecitabine and doxorubicin is characterized by diffuse erythema, edema, and pain of the entire surface of the palms and soles [44]. With VEGFR/platelet-derived growth factor receptor multikinase inhibitors, painful blisters located in areas of friction or pressure in the palms and soles are observed [44, 45]. Conversely, with FGFR inhibitors, the ventral aspect of the distal digits and lateral aspects of the palms and soles are affected by erythema and pain, accompanied by onycholysis and secondary paronychia, reminiscent of changes observed with microtubule inhibitors (i.e., taxanes). PPES often presents as a mild to moderate cutaneous edema, erythema, and hyperkeratosis with FGFR inhibitors; this evolves into painful digits that can impact patients’ quality of life [46, 47] and can ultimately limit daily functioning and lead to a reduction of the duration and intensity of treatment or its discontinuation [48].

Stomatitis

Stomatitis is one of the most commonly observed adverse events in patients treated with FGFR inhibitors, with lesions appearing rapidly after treatment initiation. In contrast to radiation- or cytotoxic therapy-induced oral mucositis, stomatitis is characterized by painful, well-
defined lesions. The incidence of stomatitis among patients with cholangiocarcinoma ranged from 7% with derazantinib [39] to 65% with erdafitinib [42]; furthermore, 18% of patients treated with erdafitinib experienced grade ≥ 3 stomatitis [42]. Among patients with urothelial carcinoma, the incidence of stomatitis ranged from 12% with rogaratinib [49] to 58% with erdafitinib [28]. Although usually self-limiting, stomatitis can be very painful and can significantly impact patients’ quality of life.

Dry Skin (Xerosis)
Xerosis is a common side effect of treatment with FGFR inhibitors, reported in 18% of patients in a systematic review of 58 targeted agents [50]. Xerosis may manifest as pruritus, fine scaling, and fissures. It may also progress to xerotic dermatitis and can lead to bacterial or viral superinfection with *Staphylococcus aureus*, herpes simplex, or other bacterial and viral agents. Although severe or life-threatening complications are uncommon, low-grade xerosis can result in dose delays or discontinuations, potentially impacting the overall efficacy of treatment.

The incidence of dry skin in patients with cholangiocarcinoma treated with the FGFR inhibitors ranged from 10% in derazantinib-treated patients [39] to 35% in erdafitinib-treated patients [42], whereas for those with urothelial cancer, dry skin was reported in 12% of infgratinib-treated patients [40] and...
32% of erdafitinib-treated patients [34]. The dry skin associated with FGFR inhibition was generally mild to moderate (grade 1 or 2) in nature.

**Dry Mouth/Xerostomia**

Dry mouth, or xerostomia, is a subjective complaint that can be very severe and represents a significant burden for patients if speech, chewing, swallowing, and general wellbeing are affected [51]. Dry mouth can be associated with dysgeusia, which can occasionally be very severe [36]. FGFs and FGFRs play a central role in salivary gland branching morphogenesis and disruption of these factors or their receptors has been shown to have implications for salivary gland function [52]. Dry mouth, generally grade 1 or 2, was common in patients treated with FGFR inhibitors, occurring in 23%–59% of patients with cholangiocarcinoma and 31%–46% of patients with urothelial cancers (Tables 3, 4).

**Calcinosis Cutis/Calciphylaxis**

A rare skin/soft tissue reaction that has been observed in patients undergoing treatment with FGFR inhibitors is calcinosis cutis, a condition in which calcium salts are deposited in the skin and subcutaneous tissues. This has been reported in one patient treated with inifgratinib [53] and another treated with pemigatinib [54]. Of further interest is the risk of nonuremic calciphylaxis, or intimal vascular calcifications, resulting in vascular thrombosis and extensive skin necrosis resulting in grade 3 and 4 cutaneous ulcerations. These conditions may be related to changes in underlying serum phosphatase known to be associated with these agents [55], or to the role of FGF/FGFR signaling in skeletal development [56]. Expression of FGF2 and its coreceptor syndecan-4 is increased at sites of calcification in human atherosclerotic plaques, suggesting a role for FGFR inhibition in vascular calcification, a major cause of morbidity and mortality [57].

With the exception of calciphylaxis, the dermatologic adverse events described above are predominantly grade 1 and 2 in severity, but these adverse events have the potential to disrupt treatment, as reflected by the extent of dose modification shown in Tables 3 and 4. The time to onset of dermatologic adverse events associated with pan-FGFR inhibition is summarized in Figure 2. Awareness and anticipation of these adverse events is critical in order to ensure patient adherence to FGFR-targeted therapies.

| **Table 3. Dermatologic AEs associated with selective FGFR tyrosine kinase inhibitors in cholangiocarcinoma** |
| **Agent** | **Infgratinib (BGJ398)** | **Pemigatinib (INCB054828)** | **Erdafitinib (INJ-42756493)** | **Derazantinib (ARQ 087)** | **Futibatinib (TAS-120)** | **Debio 1347** |
| **Reference** | [35] | [22] | [42] | [39] | [43] | [72] |
| **No. of patients** | 61 | 146 | 17 | 29 | 67 | 8 |
| **AE, all grade/grade ≥ 3, %** | | | | | | |
| Stomatitis | 30/7 | 32/5 | 65/18 | 7/3 | 16/3 | 38 |
| Alopecia | 26/0 | 46/0 | — | 24/0 | 30/0 | — |
| Dry skin | 18/0 | 16/1 | 35/6 | 10/0 | 27/0 | — |
| PPES | 21/5 | 15/4 | 29/0 | — | 18/1 | — |
| Dry mouth | 23/0 | 29/0 | 59/6 | 45/0 | 33/0 | 50 |
| Nail discoloration | 8/0 | 8/1 | 18/6 | — | — | — |
| Nail-bed disorder | 7/0 | — | — | — | — | — |
| Nail ridging | 8/0 | — | — | — | — | — |
| Paronychia | 7/0 | 6/1 | 24/6 | — | — | — |
| Onychomadesis | 18/0 | — | — | — | — | — |
| Nail disorder/changes | — | 3/1 | 29/6 | — | 16/0 | 63 |
| Mucosal dryness | 7/0 | — | — | — | — | — |
| Conjunctivitis | — | — | — | 14/0 | — | — |
| Pruritus | — | — | — | 10/0 | — | — |
| Rash | 7/0 | — | — | — | 10/0 | — |
| Rash maculopapular | 7/2 | — | — | — | — | — |
| Dermatitis | — | — | — | 7/0 | — | — |
| **AEs leading to, %** | | | | | | |
| Interruptions | 70 | 42 | 94 | — | 55 | — |
| Dose reductions | 38 | 14 | 47 | — | 51 | — |
| Discontinuations | 8 | 9 | — | 14 | 1 | — |

**Abbreviations:** —, not reported; AE, adverse event; FGFR, fibroblast growth factor receptor; PPES, palmar–plantar erythrodysesthesia syndrome.
FGFR inhibitors; however, data specific to preventive therapies for use with FGFR-targeted therapy are scarce. When preventive measures are unsuccessful and adverse events emerge, effective management strategies can ensure continuation of treatment, particularly if used at the earliest appearance of grade 1 symptoms. Management approaches are shown in Figure 3 and summarized below. Notably, although treatment for skin toxicities will be initiated by the oncologic team, referral to a dermatologist for consultation is recommended for patients with grade 3/intolerable grade 2 events, or grade 2 events that have not responded to ≥4 weeks of therapy.

**Nail Changes**
Counseling and education on the potential for nail changes are essential before initiation of treatment with FGFR inhibitors. Preventive strategies include avoidance of prolonged contact with water, repeated trauma, friction, and pressure on nails and nail beds. The use of protective gloves and limiting use of nail polish removers and nail hardeners is also helpful. Patients are also advised to avoid biting nails or cutting nails too short and to use topical emollients and loose-fitting socks and footwear. Preventive correction of nail curvature may be considered.

**Paronychia**
Recommended treatments for grade 1 paronychia include topical povidone iodine 2%–10% applied twice daily [58] or daily nail soaking in 1:1 vinegar:water for 15 minutes a day. Patients with grade 2 or 3 paronychia should be treated with a 14-day course of oral antibiotics in addition to daily nail soaking in 1:1 vinegar:water; bacterial cultures should be obtained to confirm sensitivity to antimicrobial agents. Dermatology consultation is recommended for grade ≥2 paronychia, given the potential chronicity of this event.

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**Table 4. Dermatologic AEs associated with selective FGFR tyrosine kinase inhibitors in urothelial carcinoma**

| Agent | Infigratinib (BGJ398) | Pemigatinib (INC8054828) | Erdafitinib (JNJ-42756493) | Rogaratinib (BAY 1163877) |
|-------|------------------------|--------------------------|---------------------------|--------------------------|
| Reference | [40] | [41] | [28] | [49] |
| No. of patients | 67 | 108 | 99 | 86 |
| AE, all grade/grade ≥ 3, % | | | | |
| Stomatitis | 25/3 | 34/7 | 58/10 | 12/1 |
| Alopecia | 31/0 | 40/1 | 29/0 | 22/0 |
| Dry skin | 12/0 | — | 32/0 | — |
| PPES | 12/8 | — | 23/5 | — |
| Dry mouth | 31/2 | 32/1 | 46/0 | — |
| Nail disorder | 21/0 | — | 8/3 | — |
| Paronychia | — | — | 17/3 | — |
| Onycholysis | — | — | 18/2 | — |
| Nail dystrophy | — | — | 16/6 | — |
| Mucositis | — | — | — | — |

| AEs leading to, % | | | | |
| Interruptions | — | 37 | — | — |
| Dose reductions | 46 | 14 | 56 | — |
| Discontinuations | 15 | 6 | 13 | 16 |

Abbreviations: —, not reported; AE, adverse event; FGFR, fibroblast growth factor receptor; PPES, palmar–plantar erythrodysesthesia syndrome.

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**Figure 2.** Onset over time of dermatologic adverse events associated with fibroblast growth factor receptor tyrosine kinase inhibitors. Abbreviation: PPES, palmar–plantar erythrodysesthesia syndrome.
### Onycholysis

**Recommended management options for onycholysis consist of:**
- Trimming the raised distal nails
- Clipping of the nails
- Application of topical povidone iodine 2%–10% b.i.d. solution around and under the nails
- Soaking for 15 minutes daily in white vinegar in tap water
- Topical antibiotics/corticosteroids
- If infected, begin oral antibiotics with anti-S. aureus and gram-positive coverage
- Reassess after 2 weeks; if reactions worsen or do not improve, proceed to next step

**Oral antibiotics should be started if infection is suspected (bacterial cultures and sensitivities should be obtained prior to initiating antibiotics), and nail avulsion may be needed if the patient has painful hematoma or subungual abscess.**

### Alopecia

**Preventive measures normally considered for patients undergoing traditional chemotherapy regimens, for example, scalp compression, scalp cooling, and medications, are not applicable to patients receiving FGFR inhibitors, and the health care provider’s attention should be focused on early identification and management of symptoms.**

**Management of alopecia consists of:**
- Prophylactic or reactive topical minoxidil 5% applied once daily to the scalp
- Moisturizing creams/ointments without fragrances/irritants, containing urea (≥10%), colloidal oatmeal, salicylic acid (3%)
- Gustatory and masticatory stimulants (eg, acidic candy, salivary-stimulating lozenges)
- Nutritional supplements containing carboxymethylcellulose or hydroxypropylmethyl cellulose

### Figure 3. Management of fibroblast growth factor receptor-related adverse events.

**A:** Nail changes.
- Grade 1: Clindamycin 1% solution or other topical antibiotic around and under nails t.i.d. or mupirocin ointment
- Grade 2: Cefadroxil 500 mg B.I.D. or TMP/SMX DS B.I.D. for 14 days
- Grade ≥3: Cefadroxil 500 mg B.I.D. or TMP/SMX DS B.I.D. for 14 days

**B:** Other dermatologic events.
- Grade 1: Minoxidil 5% (OTC) solution or foam once daily to scalp
- Grade 2: Minoxidil 5% (OTC) solution or foam B.I.D. to scalp
- Grade ≥3: Minoxidil 5% (OTC) solution or foam B.I.D. to scalp

**Abbreviations:** OTC, over the counter; PPES, palmar–plantar erythrodysesthesia syndrome; PRN, as needed; TMP/SMX DS, trimethoprim/sulfamethoxazole double strength.
to encourage hair regrowth, and a high-potency topical corticosteroid (e.g., fluocinonide 0.05% solution). In addition, hair camouflaging methods, which create the appearance of naturally thicker, fuller hair, may be considered. Alopecia typically reverses when treatment is discontinued.

**PPES**

Prevention strategies for PPES include prophylactic removal of hyperkeratotic areas, application of moisturizing cream containing urea ≥10%, pedicures, and cushioning of callused areas using soft or padded shoes [48]. Other preventive tactics include avoidance of activities that cause force or rubbing on the hands and feet during the first 6 weeks of treatment and limiting contact with harsh chemicals and sources of heat, such as sitting in saunas or the sun.

Management of PPES consists of keratolytic agents such as urea ≥10% for grade ≥1 PPES, with addition of high-potency topical steroids such as fluocinonide 0.05% for grade ≥2 symptoms.

**Stomatitis**

Preventive strategies include undertaking dental work aimed at eliminating existing tooth and gum disease before the start of treatment and education regarding the importance of thorough and frequent cleaning of the oral cavity. Avoidance of salty, spicy, or citrus-based foods, as well as hot beverages, may help prevent stomatitis.

Upon emergence of grade 1 or 2 stomatitis, dexamethasone 0.5 mg/5 mL elixir is recommended; an augmented betamethasone dipropionate 0.05% gel applied to gauze to encourage hair regrowth, and a high-potency topical corticosteroid (e.g., fluocinonide 0.05% solution). In addition, hair camouflaging methods, which create the appearance of naturally thicker, fuller hair, may be considered. Alopecia typically reverses when treatment is discontinued.

**Dose Modifications**

Dose modification in the event of dermatologic adverse events should be performed as recommended in the relevant package insert.

Unless otherwise recommended, treatment should be continued in cases of grade 1 and 2 adverse events and interrupted for grade 3 adverse events. When dermatologic events improve to grade ≤1, a rechallenge at a reduced dose is recommended.

**Calcino sis Cutis/Calci phylaxis**

Owing to the potential for ulcerations to develop and expand rapidly, as well as an extremely poor 1-year mortality rate [60], drug discontinuation should be recommended for patients with calcinosis cutis. Treatment with oral or topical calcium channel blockers, intravenous immunoglobulin, and compounded or intraleosomal sodium thiosulfate may be initiated. For calciphylaxis, treatments generally include three-times-a-week dosing at 3- to 4-week intervals with intravenous sodium thiosulfate or intraleosomal sodium thiosulfate diluted 1:1 with 1% lidocaine to minimize the pain [60–62]. Patients should be screened for additional hypercoagulation disorders [63]. In addition, monitoring calcium and phosphate levels with phosphate binders, consideration for anticoagulation, and use of bisphosphonates may be considered. Dermatologic or endocrine consultations are warranted upon occurrence of grade 3 events and for patients who do not respond to therapy.

**Conclusion**

The FGFR inhibitors have a distinctive adverse-event profile that includes a range of dermatologic adverse events, the incidences of which vary between agents. The events are seldom severe or life threatening but can nonetheless limit the delivery of treatment through dose holds and may lead to premature drug discontinuation. In order to optimize patient outcomes, physicians should be mindful of possible untoward events associated with the drug being used, educate their patients, and be ready to implement effective management plans in a timely fashion. Prescribing information for erdafitinib should be consulted if appropriate [64]. Intervention and treatment at the earliest possible opportunity may prevent premature discontinuation while maintaining patients’ quality of life.

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