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Symptom Management and Supportive Care

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, infigratinib, 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. ***The Oncologist*** 2021;26:e316–e326

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

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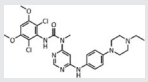
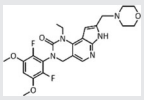
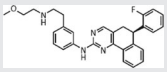
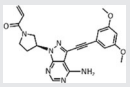
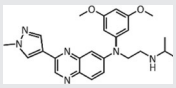
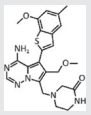
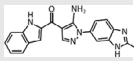
Table 1. Selective FGFR-directed tyrosine kinase inhibitors

Agent	Infigratinib (BGJ398)	Pemigatinib (INCB054828)	Derazantinib (ARQ 087)	Futibatinib (TAS-120)	Erdafitinib (JNJ-42756493)	Rogaratinib (BAY 1163877)	Debio 1347
Chemical structure							
Company	QED	Incyte	ArQule	Taiho	Janssen	Bayer	Debiopharm
Source	[65]	[66]	[67]	[68]	[69]	[70]	[71]
IC_{50}, nM							
FGFR1	0.9	0.4	4.5	1.8	1.2	11.2	9.3
FGFR2	1.4	0.5	1.8	1.4	2.5	<1	7.6
FGFR3	0.9	1.2	4.5	1.6	3	19	22
FGFR4	60	30	34	3.7	5.7	201	—

Abbreviations: FGFR, fibroblast growth factor receptor; IC_{50}, median inhibitory concentration.

binding domain and a tyrosine kinase domain, which are expressed on the cell membrane [3]. FGFR fusions and other alterations have been reported in a wide range of solid tumors, including cholangiocarcinoma [4], bladder cancer [5], lung cancer [6], and glioblastoma [7]. Identification of targetable genomic alterations has resulted in the development of several FGF/FGFR-directed therapies, primarily small-molecule tyrosine kinase inhibitors (TKIs) or multikinase inhibitors, with differing profiles (Table 1). A number of selective FGFR TKIs—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 FGFs 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].

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, 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].

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
Infigratinib (BGJ398)				
NCT03773302	III	Cholangiocarcinoma	Infigratinib vs. gemcitabine/ cisplatin	384
NCT04197986	III	Urothelial cancer	Infigratinib vs. placebo	218
NCT02150967	II	Cholangiocarcinoma	Infigratinib	160
NCT04233567	II	Solid tumors	Infigratinib	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
Erdafitinib (JNJ-42756493)				
NCT03390504	III	Urothelial cancer	Erdafitinib vs. vinflunine or docetaxel or pembrolizumab	631
NCT03210714	II	Solid tumors, non-Hodgkin lymphoma, or histiocytic disorders	Erdafitinib	49 (age >21 years)
NCT04083976	II	Solid tumors	Erdafitinib	280
NCT02699606	II	Urothelial cancer	Erdafitinib	63 (Asian)
NCT03827850 (FIND)	II	NSCLC	Erdafitinib	50
NCT02365597	II	Urothelial cancer	Erdafitinib	217
NCT02952573	II	Multiple myeloma	Erdafitinib	20
NCT03999515	II	Prostate cancer	Erdafitinib + abiraterone acetate or enzalutamide	25
NCT04172675	II	Urothelial cancer	Erdafitinib vs. investigator choice intravesical chemotherapy	280
NCT03473743	I/II	Urothelial cancer	Erdafitinib in combination with cetrelimab and/or platinum	160

Abbreviations: FGFR, fibroblast growth factor receptor; NSCLC, non-small cell lung cancer.

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].

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 infigratinib, pemigatinib, erdafitinib, 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 FGF19, FGF21, and FGF23 [30]. FGF2 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 (onychoschizia). 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 infigratinib [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 infigratinib. Specifically, 26% of patients treated with infigratinib [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 infigratinib [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 infigratinib) [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 receiving infigratinib [35], erdafitinib [42], and futibatinib [43], respectively, and in 12% and 23% of patients with urothelial carcinoma receiving infigratinib [40] and erdafitinib [28], respectively. Among patients with cholangiocarcinoma, grade 3/4 PPES was reported in 5% of patients treated with infigratinib [35] and 4% of those treated with pemigatinib [22], whereas 8% of infigratinib-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-

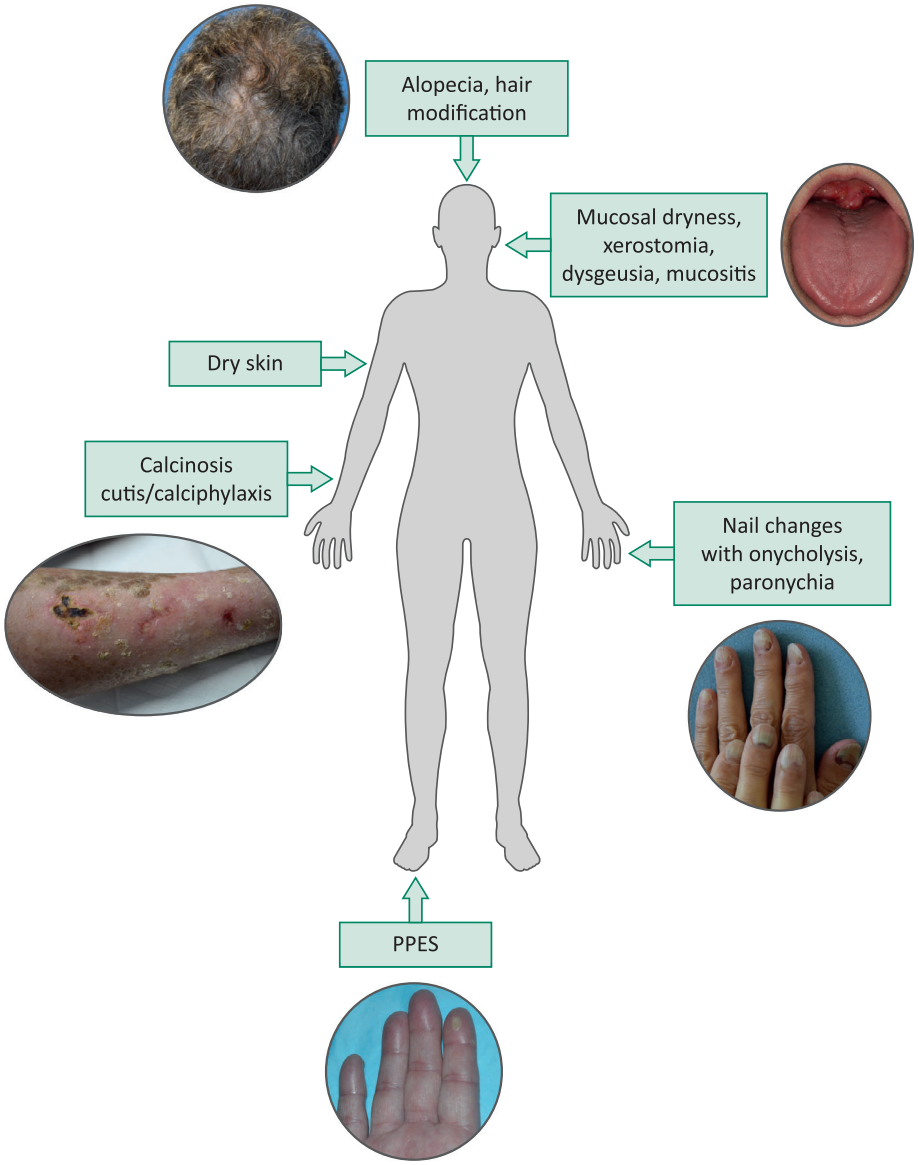


Figure 1. Schematic representation of dermatologic adverse events associated with fibroblast growth factor receptor inhibition. Suggested dose modifications for dermatologic adverse events: Grade 1/2: continue drug at standard dose. Grade 3, first occurrence: hold drug until resolved to grade ≤ 1 or baseline and reduce drug to the next dose level; second occurrence: interrupt drug until grade ≤ 1 or baseline. Once recovered, reduce drug to the next dose level; third occurrence: interrupt drug until grade ≤ 1 or baseline. Once recovered, reduce drug to the next dose level, if available as dose level –2. If already at dose level –2 at time of occurrence, permanently discontinue drug; fourth occurrence: permanently discontinue drug. Package insert to be consulted in the event of emergence of dermatologic adverse events and doses modified as recommended.
Abbreviation: PPES, palmar–plantar erythrodysesthesia syndrome.

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 infigratinib-treated patients [40] and

Table 3. Dermatologic AEs associated with selective FGFR tyrosine kinase inhibitors in cholangiocarcinoma

Agent	Infigratinib (BGJ398)	Pemigatinib (INCB054828)	Erdafitinib (JNJ-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.

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 infigratinib [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.

Management and Supportive Care for Dermatologic Adverse Events: Proposed Guidelines

Prevention and early treatment of dermatologic adverse events are key to maximizing adherence to therapy and optimizing outcomes in patients undergoing treatment with

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

Agent	Infigratinib (BGJ398)	Pemigatinib (INCB054828)	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.

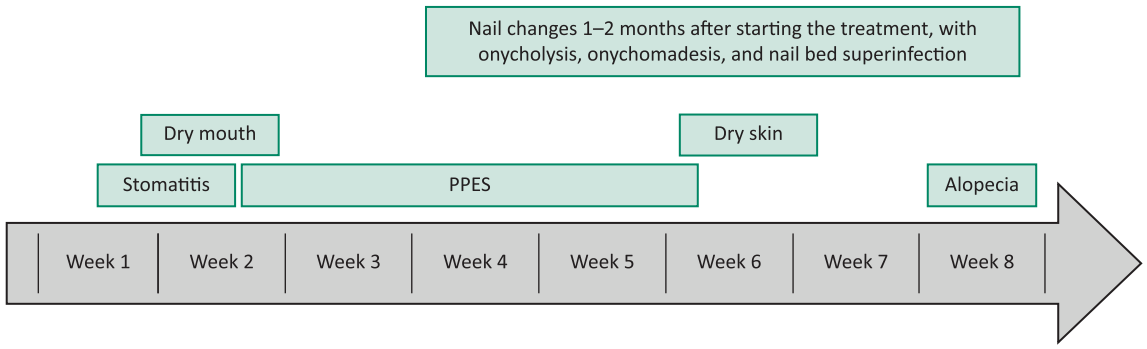


Figure 2. Onset over time of dermatologic adverse events associated with fibroblast growth factor receptor tyrosine kinase inhibitors. Abbreviation: PPES, palmar–plantar erythrodysesthesia syndrome.

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.

A

	Paronychia	Onycholysis
Grade 1	• Clindamycin 1% solution (or other topical antibiotic) around and under nails t.i.d. OR mupirocin ointment • Consider gentamicin if gram-negative infection is suspected • Soak for 15 minutes daily in white vinegar in tap water (1:1) • Topical povidone iodine 2%; topical antibiotics/corticosteroids	• If infected, begin oral antibiotics with anti-*Staphylococcus aureus* and gram-positive coverage • Reassess after 2 weeks; if reactions worsen or do not improve, proceed to next step
Grade 2	• Cefadroxil 500 mg b.i.d. or TMP/SMX DS b.i.d. for 14 days • Soak for 15 minutes daily in white vinegar in tap water (1:1) • Obtain bacterial cultures to confirm sensitivity to antimicrobial agents • Dermatology consultation*	• If infected, begin oral antibiotics with anti-*S. aureus* and gram-positive coverage • If painful hematoma or subungual abscess is suspected, partial or total nail avulsion is required • Reassess after 2 weeks; interrupt treatment until severity decreases to grade 0/1
Grade ≥3	• Cefadroxil 500 mg b.i.d. or TMP/SMX DS b.i.d. for 14 days • Obtain bacterial cultures to confirm sensitivity to antimicrobial agents • Consider partial nail avulsion • Dermatology consultation*	• If infected, begin oral antibiotics with anti-*S. aureus* and gram-positive coverage • If painful hematoma or subungual abscess is suspected, partial or total nail avulsion is required • Reassess after 2 weeks; if reactions worsen or do not improve, discontinuation per protocol may be discussed

B

	Alopecia	PPES	Stomatitis	Dry skin	Dry mouth
Grade 1	• Minoxidil 5% (OTC) solution or foam once daily to scalp • Hair concealers	•Topical urea ≥10% t.i.d to palms and soles	• Dexamethasone elixir 0.5 mg/mL swish and spit 5 mL t.i.d • Mouthwash for oral hygiene • Augmented betamethasone dip 0.05% gel applied on gauze, held to affected cheek for 15 minutes b.i.d.	• Moisturizing creams/lotions without fragrances/irritants, containing urea (≥10%), colloidal oatmeal, salicylic acid (3%)	• Gustatory and masticatory stimulants (eg acidic candy; salivary-stimulating lozenges) • Mucosal lubricants/saliva substitutes containing carboxymethylcellulose or hydroxypropylmethyl cellulose
Grade 2	• Minoxidil 5% (OTC) solution or foam b.i.d. to scalp • High-potency corticosteroid, eg fluocinonide 0.05% solution, daily to scalp • Hair concealers • Wigs, hats, turbans	•Topical urea ≥10% t.i.d to palms and soles (consider increasing to 40%) • High-potency corticosteroid, eg fluocinonide 0.05%, to palms and soles	• Dexamethasone elixir 0.5 mg/mL swish and spit 5 mL t.i.d. AND • Doxepin 10 mg/mL solution OR "magic mouthwash" swish and spit 5 mL PRN for pain • Consider intralesional triamcinolone acetonide 10 mg/mL to area if localized	• Moisturizing creams/lotions without fragrances/irritants, containing urea (≥10%), colloidal oatmeal, salicylic acid (3%)	• Gustatory/masticatory stimulants and mucosal lubricants as per grade 1 • High percent fluoride toothpaste • Sialogogues eg pilocarpine 5 mg po t.i.d or cevimeline 30 mg po t.i.d
Grade ≥3		•Topical urea ≥10% t.i.d to palms and soles • High-potency corticosteroid, eg fluocinonide 0.05%, to palms and soles	• Dexamethasone elixir 0.5 mg/mL swish and spit 5 mL t.i.d. AND • Doxepin 10 mg/mL solution OR magic mouthwash swish and spit 5 mL PRN for pain • Clotrimazole 10 mg lozenges q.i.d.	• Medium-potency topical steroid, eg triamcinolone acetonide 0.1%, b.i.d. PLUS • Moisturizing creams/lotions without fragrances/irritants, containing urea (≥10%), colloidal oatmeal, salicylic acid (3%)	• Gustatory/masticatory stimulants and mucosal lubricants as per grade 1 • Sialogogues, eg pilocarpine 5 mg po t.i.d. or cevimeline 30 mg po t.i.d

Figure 3. Management of fibroblast growth factor receptor-related adverse events. **(A):** Nail changes. **(B):** Other dermatologic events. *Referral to a dermatologist for consultation is recommended for grade 3 and intolerable grade 2 events, or grade 2 events that have not responded to 4 weeks of therapy.
Abbreviations: OTC, over the counter; PPES, palmar–plantar erythrodysesthesia syndrome; PRN, as needed; TMP/SMX DS, trimethoprim/sulfamethoxazole double strength.

Onycholysis

Recommended management options for onycholysis consist of trimming the raised distal nails, clipping of the nails, and application of topical povidone iodine 2%–10% b.i.d. solution [58] around and under the nails. 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

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 and held against the affected surface may also assist in alleviating symptoms.

Dry Skin

Patients should be advised to moisturize skin to minimize the risk of skin adverse events and to avoid excessive exposure to detergents and soaps containing fragrances. Urea preparations have been shown to prevent transepidermal water loss, and salicylic acid preparations are helpful for their keratolytic, bacteriostatic, and fungicidal effects [50]. Exfoliation of scaly areas of xerosis is recommended. For more severe grade 3 xerosis, which results in asteatotic dermatitis, treatment can be initiated with low-potency topical steroids such as hydrocortisone 2.5% cream/ointment or triamcinolone 0.1% cream.

Dry Mouth/Xerostomia

Patient education is an important component of dry mouth prevention. The importance of good oral hygiene, regular dentist visits, and other strategies for preventing oral disease should be stressed.

Treatment may include systemic and topical salivary stimulants, such as cevimeline and pilocarpine, and intraoral topical agents, such as chewing gums and saliva stimulants and substitutes [59]. High-fluoride toothpaste is also recommended to prevent cavities.

Calcinosis Cutis/Calciphylaxis

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 intralesional 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 intralesional 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.

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.

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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