

Potentially life-threatening severe cutaneous adverse reactions associated with tyrosine kinase inhibitors (Review)

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Abstract. Tyrosine kinase inhibitors (TKIs) have emerged as a new frontier of cancer therapy. These agents include inhibitors of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), BRAF, mitogen-activated protein kinase kinase (also referred to as MEK), bcr-abl, c-KIT, platelet-derived growth factor (PDGFR), fibroblast growth factor receptor (FGFR), anaplastic lymphoma kinase (ALK) and vascular endothelial growth factor (VEGF). Along with the evolving applications of TKIs, there has been an increased recognition of the breadth of potential cutaneous toxicities to these agents. In this review, we provide an overview of potentially life-threatening severe cutaneous adverse reactions (SCARs) that may occur during therapy with TKIs. These toxicities include Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).

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Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; EM, erythema multiforme; MKIs, multikinase inhibitors; SCAR, severe cutaneous adverse reactions; SJS, Stevens-Johnson Syndrome; TEN, toxic epidermal necrolysis; TKI, tyrosine kinase inhibitor

Key words: life-threatening cutaneous toxicities, severe cutaneous adverse reactions, tyrosine kinase inhibitors, targeted therapy, Stevens-Johnson Syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, acute generalized exanthematous pustulosis

1. Introduction

Tyrosine kinase inhibitors (TKIs) are increasingly utilized in the treatment of various types of cancers. With an increase in the use of these targeted therapies, there has been a concomitant surge in and recognition of a diverse array of cutaneous toxicities associated with these agents. Early diagnosis and proper management of these dermatologic adverse effects is critical to the multidisciplinary care of oncologic patients, as swift treatment may limit the number of patients requiring dose reduction or dose interruption of potentially life-saving therapies.

Cutaneous toxicities are graded on a schema proposed by the National Cancer Institute called 'Common Terminology Criteria for Adverse Events' (CTCAE) (1). According to this schema, grade 1 cutaneous toxicities include those that involve less than 10% body surface area (BSA); grade 2 are those involving 10-30% BSA and typically impact instrumental activities of daily living; grade 3 involve greater than 30% BSA or impact self-care activities of daily living; finally, grade 4 toxicities generally involve ulceration, exfoliation, or full thickness skin sloughing or may result in potentially life-threatening complications (1).

While most dermatologic reactions to targeted anticancer drugs are non-life threatening, severe cutaneous adverse reactions (SCARs) may occur and are of particular concern given their high potential for morbidity and mortality. SCARs include Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS), and acute generalized exanthematous pustulosis (AGEP).

The purpose of this review article is to provide an overview of SCARs associated with TKIs based on a literature review (Table I), and highlight their various morphologies and therapeutic implications, with the goal of aiding oncologists and dermatologists in the recognition and management of these severe toxicities.

2. Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) include inhibitors of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), BRAF, mitogen-activated protein kinase kinase (also referred to as MEK), bcr-abl, c-KIT, vascular endothelial growth factor (VEGF), fibroblast

growth factor receptor (FGFR), anaplastic lymphoma kinase (ALK), and multikinase inhibitors (MKIs).

EGFR, a growth factor found in the epidermis and appendageal units (2), plays a role in epidermal and pilosebaceous homeostasis (3) and inhibits IL-1-dependent inflammation at the level of the hair follicle (4). EGFR inhibitors include monoclonal antibodies to EGFR (panitumumab, cetuximab), small-molecule TKIs (gefitinib, erlotinib), TKIs of EGFR, HER2, and HER4 (dacomitinib), dual kinase inhibitors of EGFR and HER2 (neratinib, afatinib, lapatinib), erbB receptor inhibitors (canertinib), and MKIs (vandetanib). EGFR inhibitors have been approved for use in colorectal, head/neck, breast, and non-small cell lung cancers (NSCLCs) (5). There are numerous cutaneous toxicities associated with EGFR inhibitors, including papulopustular eruption (50-90% of patients), as well as xerosis, paronychia, mucositis, and hair/nail changes (6).

MEK 1 and MEK2 (also known as dual specificity mitogen-activated protein kinase kinase 1 and 2, respectively) are two enzymes involved in the mitogen-activated protein kinase (MAPK) pathway. Three MEK inhibitors, CI-1040, selumetinib and trametinib, have been utilized in colorectal, hepatocellular, melanoma, and NSCLCs (7-9). Toxicities to MEK inhibitors are similar to EGFR inhibitors, and include morbilliform eruption (10), papulopustular eruption (11), nail toxicity, xerosis (12), and alopecia (11). MEK inhibitors have been utilized in conjunction with BRAF inhibitors in the treatment of melanoma to enhance recognition of melanoma cells by immune effector cells (13). Simultaneous inhibition of MEK and BRAF may decrease the severity and frequency of cutaneous toxicities of both MEK and BRAF inhibitors as BRAF inhibition may paradoxically activate the MAPK pathway. As such, downstream inhibition of the MAPK pathway by MEK inhibition may mitigate the toxicity profile of both agents (14).

BRAF is an upstream activator of the MAPK pathway, which is involved in cell proliferation, differentiation, and migration (15). *BRAF* is mutated in 40-60% of melanomas (16). BRAF inhibitors include dabrafenib, vemurafenib, binimetinib, cobimetinib, encorafenib, and trametinib (13,14,17,18). Cutaneous toxicities to BRAF inhibitors include epidermal neoplasms such as verrucal keratosis and invasive squamous cell carcinomas, melanocytic and eruptive nevi, changes in preexistent nevi, keratosis pilaris-like eruption, seborrheic dermatitis-like eruption, hyperkeratotic hand-foot skin reaction, erythema nodosum-like reactions, and photosensitivity (19).

Bcr-abl is a protein resulting from the translocation of chromosomes 9 and 22 (also known as the Philadelphia chromosome) that is active in chronic myeloid leukemia (CML). Stem cell factor receptor (c-Kit) is a receptor that is constitutively active in most gastrointestinal stromal tumors (GISTs). Platelet-derived growth factor (PDGFR) plays a key role in human development and malignancies, including gliomas (20), breast cancers (21), sarcomas (22), and leukemias (23). TKIs of PDGFR, c-kit, and bcr-abl include imatinib, nilotinib, ponatinib, and dasatinib. These agents are approved for use in CML (24), GISTs (25), and Philadelphia chromosome-positive acute lymphocytic leukemia (26). They have also demonstrated clinical efficacy against systemic mastocytosis (27), dermatofibrosarcoma (28), c-KIT-mutated melanoma (29), and AIDS-related Kaposi sarcoma (30).

Fibroblast growth factor receptors (FGFRs) are a subfamily of TKIs comprised of 4 subtypes: FGFR1, FGFR2, FGFR3 and FGFR4. FGFRs contribute to many important physiologic processes such as embryogenesis, tissue repair, and wound healing (31). Erdafitinib, which preferentially targets FGFR2 and FGFR3, was the first FGFR-selective drug approved by the US Food and Drug Administration (FDA) for treating metastatic urothelial carcinoma (32,33). In addition to urothelial carcinoma, *FGFR* mutations are posited to be found in breast cancer, non-small cell lung cancer, kidney cancer, colorectal cancer, and endometrial cancer (34). Hyperphosphatemia is a frequent adverse event in patients prescribed this class of medications and calcinosis cutis is a related cutaneous toxicity that has been reported due to the downstream effect of electrolyte homeostasis dysfunction (35,36).

ALK mutations are most commonly found in NSCLC, with 2 to 7% of cases of NSCLC harboring *ALK* mutations or *ALK* gene fusions (37). Crizotinib was the first ALK TKI to be approved in 2001. Since then, additional drugs within this class have been approved including alectinib, ceritinib, and brigatinib (38). While these agents are rarely associated with severe cutaneous toxicities, they have been linked to erythema multiforme (39) and TEN (40).

MKIs are small-molecule inhibitors of VEGF, PDGF, EGFR, KIT, RET, Flt3, and RAF. These agents, including pazopanib, sunitinib, sorafenib, and vandetanib, are used in a variety of cancers. Cutaneous toxicities to MKIs include alopecia in 44% of patients on sorafenib (41,42), 5-21% of patients on sunitinib (43), and 8-10% of patients on pazopanib (44-46). Other toxicities include hair depigmentation secondary to pazopanib (44,46) and sunitinib (47,48) as well as hyperkeratotic hand-foot skin reaction (49), erythema nodosum (50), and inflammatory eruptions such as morbilliform eruptions (51), SJS/TEN (52-54), chloracne-like eruption (55), DRESS (56), generalized bullous fixed drug eruption (57), and erythema multiforme (EM) (58,59). Cutaneous toxicities to VEGFR inhibitors, such as bevacizumab and ramucirumab, include mucocutaneous hemorrhage (60), exfoliative dermatitis (60), and palmar-plantar erythrodysesthesia (61).

3. Severe cutaneous adverse reactions associated with tyrosine kinase inhibitors

Stevens-Johnson Syndrome (SJS)/toxic epidermal necrolysis (TEN) has been associated with EGFR inhibitors (54,62-70), BRAF inhibitors (71-78), bcr-abl/c-KIT/PDGFR inhibitors (79,80), ALK inhibitors (40), and MKIs (52-54). Drug reaction with eosinophilia and systemic symptoms (DRESS) has been associated with BRAF inhibitors (71,81-85), bcr-abl/c-KIT/PDGFR inhibitors (86-91), HER-2 inhibitors (92), and MKIs (56). Finally, acute generalized exanthematous pustulosis (AGEP) has been associated with EGFR inhibitors (93,94), BRAF inhibitors (83), and bcr-abl/c-KIT/PDGFR inhibitors (95-98). To date, severe cutaneous adverse reactions (SCARs) have not been described in association with VEGF or FGFR inhibitors. Thus, this review will focus on the TKIs with reported SCARs.

SJS/TEN: EGFR inhibitors, BRAF inhibitors, bcr-abl/c-KIT/PDGFR inhibitors, ALK inhibitors, MKIs. SJS

Table I. Severe cutaneous adverse reactions to tyrosine kinase inhibitors.

Tyrosine kinase inhibitor	SJS/TEN yes/no (Refs.)	AGEP yes/no (Refs.)	DRESS yes/no (Refs.)
EGFR	Yes (54,62-70,103-105)	Yes (93,94)	No
MEK	No	No	Yes (71)
BRAF	Yes (71-78)	Yes (83)	Yes (71,81-85,108)
bcr-abl/c-Kit/PDGFR	Yes (94-106)	No	Yes (86-91)
MKIs	Yes (52-54)	No	Yes (56)
VEGF	No	No	No
HER2	Yes (68,69,92)	No	No
FGFR	No	No	No
ALK	Yes (40)	No	No

AGEP, acute generalized exanthematous pustulosis; ALK, anaplastic lymphoma kinase; c-Kit, stem cell factor receptor; DRESS, drug reaction with eosinophilia and systemic symptoms; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; HER2, human epidermal growth factor receptor 2; MEK, mitogen-activated protein kinase kinase; PDGFR, platelet-derived growth factor; MKIs, multikinase inhibitors; SJS/TEN, Stevens-Johnson Syndrome/toxic epidermal necrolysis; VEGF, vascular endothelial growth factor.

and TEN are serious mucocutaneous blistering diseases characterized by necrosis and epidermal detachment affecting less than 10% body surface area (BSA) for SJS and greater than 30% BSA for TEN, with SJS/TEN overlap affecting 10-30% BSA (99). SJS/TEN have an estimated incidence rate of 0.4 to 1.9 per million people annually worldwide with SJS more frequently reported than TEN (100). Overall mortality ranges from 1-10% in SJS and 20-40% in TEN (79).

SJS/TEN initially presents with dusky erythematous macules and papules that evolve into tender targetoid erythema distributed over the trunk with mucosal involvement (80). The presentation of cutaneous findings in SJS/TEN is typically preceded by systemic symptoms such as fever and constitutional symptoms (80). Unlike typical SJS/TEN, which is a delayed-type hypersensitivity reaction characterized by release of granulysin by cytotoxic T cells leading to death of keratinocytes, the pathomechanism of EGFR-inhibitor associated SJS/TEN may be related to inhibition of epidermal differentiation and re-epithelialization induced by inhibiting EGFR (80).

The diagnosis of SJS/TEN may be rendered clinically and histopathologically. Biopsy of early lesions typically shows scattered apoptotic keratinocytes in the basal epidermis, whereas more advanced lesions may show full-thickness epidermal necrosis or subepidermal bullae (101). Histopathology may also reveal a perivascular lymphohistiocytic infiltrate with eosinophils in the superficial dermis (101). Direct and indirect immunofluorescence can help exclude immunobullous eruptions, and viral cultures and mycoplasma serologies may help further narrow the diagnosis (80).

Differential diagnosis of SJS/TEN includes EGFR inhibitor-related mucositis, disseminated fixed bullous drug eruption, staphylococcal scalded skin syndrome, and acute generalized exanthematous pustulosis (AGEP) (80,102). EGFR inhibitor-related mucositis may be differentiated from SJS/TEN by lack of constitutional symptoms, fever, or tender erythema in the former (80). Immunobullous disorders, AGEP and SJS/TEN may be differentiated histologically and with direct or indirect immunofluorescence (80).

Management of SJS and TEN includes supportive care in an intensive care unit, oral or IV corticosteroids, cessation of the suspected drug, and intravenous immunoglobulin when applicable (102).

SJS/TEN has been described in association with EGFR inhibitors, including cetuximab (62-65,103), gefitinib (66,67,104), afatinib (68,69,92), erlotinib (70,105), panitumumab (64), and vandetanib (54). The latency of onset of SJS/TEN from EGFR inhibitors ranges from 5 to 64 days (80). One review found that EGFR inhibitors were the most frequent cause of SJS/TEN among targeted and immunotherapies, with 12 cases of SJS, SJS/TEN or TEN (80). Cetuximab and erlotinib have been associated with fatal cases of SJS/TEN (103,105). Furthermore, according to the FDA, death from complications, such as septic shock, secondary to grade 3 toxicities including 'exfoliation' has also occurred with panitumumab (106). Additionally, grade 3 or 4 'exfoliative skin reactions' have occurred in association with dacomitinib (107).

Eight cases of SJS/TEN have been described in the setting of BRAF inhibitors (71-78). One case of SJS occurred in the setting of vemurafenib and cobimetinib (71). The remaining seven cases occurred in the setting of vemurafenib alone (72-78). The FDA has also reported cases of SJS/TEN in the setting of vemurafenib (108). Interestingly, prior treatment with immune check point inhibitors confers an increased risk of skin toxicity in patients receiving BRAF inhibitor therapies. In these cases, patients previously tolerated anti-PD1 therapy well prior to treatment with BRAF inhibitors, at which point they experienced severe skin toxicity. The proposed pathomechanism of this observed phenomenon is that anti-PD1 therapy 'primes' the immune system such that later on severe reactions may occur (109,110). Therefore, it is important that providers take extra caution when caring for these patients due to their increased predisposition to skin toxicity.

SJS/TEN has been reported in 12 cases in association with imatinib, the TKI of PDGFR, c-kit, and bcr-abl (111-123). Of these, one case occurred in the setting of imatinib and allopurinol (119), and another occurred in the setting of imatinib and lansoprazole (120). Furthermore, an 'exfoliative rash' and

'skin exfoliation' have been reported in association with the TKIs of PDGFR, c-kit, and bcr-abl, nilotinib (124) and dasatinib (125), respectively.

SJS/TEN has also been reported in association with the ALK inhibitor crizotinib in a patient with advanced NSCLC who developed TEN after 56 days of crizotinib (40). MKIs have also been linked to SJS/TEN, including sorafenib in 2 cases (52,53), and vandetanib in one case (54). The FDA has also reported cases of SJS/TEN in association with sorafenib (126) and vandetanib (127).

AGEP: EGFR inhibitors, BRAF inhibitors. Acute generalized exanthematous pustulosis (AGEP), another potentially life-threatening SCAR, is characterized by the acute development of fever and hundreds of nonfollicular pustules on an erythematous base that usually occurs 2 to 3 days after introducing a new medication (128). The pustules in AGEP may be pruritic and tend to favor truncal and intertriginous areas (128). Severe cases may involve the mucous membranes or other organs, such as the kidneys, lungs and liver (128). Overall mortality is less than 5%, and death usually results from disseminated intravascular coagulation or severe organ dysfunction (128).

The diagnosis of AGEP is typically rendered clinically and histopathologically, with biopsy demonstrating dermal papillary edema with exocytosis, neutrophilic and eosinophilic perivascular infiltrate, and intraepithelial and/or subcorneal pustules (80). The differential diagnosis of AGEP includes pustular psoriasis and papulopustular eruption of EGFR inhibitors. In contrast to the nonfollicular pustules of AGEP, pustular psoriasis and papulopustular eruption of EGFR inhibitors can be differentiated from AGEP based on the folliculocentric pustules overlying areas rich in sebaceous glands, such as the trunk, face and scalp (80).

Management of AGEP should focus on removal of the culprit drug, topical or systemic corticosteroids, and close monitoring for secondary infections (80). As they resolve, the lesions of AGEP may desquamate (128).

EGFR inhibitor-associated AGEP has been described in 3 cases, 2 in association with gefitinib (93), and one in association with lapatinib (94). One case of AGEP with features overlapping with DRESS has been reported in the setting of the BRAF inhibitor vemurafenib (83).

DRESS: BRAF inhibitors, bcr-abl/c-kit/PDGFR inhibitors, and MKIs. Drug reaction with eosinophilia and systemic symptoms (DRESS) is a severe reaction to a culprit medication that is characterized by fever, rash, lymphadenopathy, eosinophilia, atypical leukocytosis, and abnormal liver function tests (80,129). The cutaneous presentation of DRESS is variable, and includes maculopapular eruption (classically with facial edema), urticaria, vesicles, pustules, purpura, targetoid lesions, cheilitis, and erythroderma (129). Accompanying pneumonitis, pericarditis, myocarditis, nephritis, colitis, or hepatitis represent the main sources of morbidity and mortality (129). Overall mortality from DRESS ranges from 5 to 10% (130,131). DRESS typically presents within two to eight weeks of initiating the culprit drug (129).

Diagnosis of DRESS is based on the RegiSCAR criteria, in which three of the following criteria are required:

Lymphadenopathy in at least two sites, fever greater than 38°C, involvement of at least one organ, and abnormal blood counts (129). Histopathology may demonstrate features of several inflammatory conditions such as interface dermatitis, erythema multiforme, eczema, or AGEP (132).

The differential diagnosis of DRESS includes maculopapular eruption, hypereosinophilic syndrome, acute viral infections, pseudolymphoma and lymphoma. Maculopapular eruptions will lack fevers, and multiorgan involvement can distinguish DRESS from other differential diagnoses (80).

Management of DRESS includes withdrawal of the culprit drug, and consideration of systemic corticosteroids tapered over weeks to months (133).

DRESS has been reported in the setting of the BRAF inhibitor vemurafenib and the MEK inhibitor cobimetinib in 14 cases and in the setting of the BRAF inhibitor dabrafenib and the MEK inhibitor trametinib in one case (71,85). DRESS has also been reported in the setting of the vemurafenib alone (81-84). Interestingly, in one of these cases, the patient was subsequently successfully treated with the BRAF-inhibitor dabrafenib after experiencing DRESS secondary to vemurafenib (84). Furthermore, the FDA has reported cases of DRESS with vemurafenib (108).

DRESS has also been described in association with bcr-abl/c-kit/PDGFR inhibitor imatinib in 6 cases (86-91). In one of these cases, imatinib was reintroduced according to a desensitization protocol in which imatinib was restarted at a low dose and gradually increased to the target dose without recurrence of DRESS (90). Imatinib was discontinued in 2 of the cases (87,88). In 2 other cases, imatinib was switched to dasatinib and nilotinib without recurrence of DRESS (89,91). Lastly, imatinib was reintroduced in one case with recurrence of DRESS within 12 h of reinitiation (86). Although more data are required, these data suggest that DRESS may be related to the specific drug rather than a class effect. Thus, switching agents rather than switching classes of drugs may be an effective management strategy for patients with DRESS.

MKI-associated DRESS has been described in one case with sorafenib (56). In this case, sorafenib was discontinued and the patient eventually returned to baseline with supportive care (56).

Limitations. One limitation of our literature review is that these toxicities are rare and based on case reports, case series, and FDA reports. Therefore, the incidence and frequency with which these toxicities occur are not well classified. Future clinical studies prospectively investigating the rate of these toxicities among all patients receiving TKI therapy would be useful in better elucidating their frequency.

4. Conclusion

Life-threatening SCARs may rarely develop in patients on TKIs, and include SJS/TEN, DRESS, and AGEP. These severe dermatologic toxicities may cause substantial morbidity and mortality in cancer patients. According to our literature review, these dermatologic toxicities may necessitate dose reduction, interruption, and commonly cessation of potentially life-saving or life-prolonging anticancer therapies. While dermatologists and oncologists should be cognizant of the typical reaction patterns of these dermatologic toxicities, the development of

SCARs must be considered in the differential diagnosis of severe presentations or recalcitrant eruptions. Treatment of SCARs often necessitates the use of systemic corticosteroids, and cessation of the causative agent. While mortality has been reported in several cases, there are many documented cases of complete response and resolution of the SCAR. As such, awareness of the diverse array of life-threatening cutaneous toxicities is essential for the prompt recognition and treatment of these adverse events by both dermatologists and medical oncologists.

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Authors' contributions

ELC organized and wrote the majority of the first draft of this article and helped with edits and revisions. BO wrote portions of the first draft and helped with edits and revisions. JSL conceived the study idea and helped guide content revisions.

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Not applicable.

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Not applicable.

Competing interests

The authors state that they have no competing interests.

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