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

EMILY L. COLEMAN[1], BRIANNA OLAMIJU[1] and JONATHAN S. LEVENTHAL[1,2]

[1]Yale School of Medicine; [2]Department of Dermatology, Yale School of Medicine, New Haven, CT 06510, USA

Received April 20, 2020; Accepted October 21, 2020

DOI: 10.3892/or.2020.7911

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).

Contents

Correspondence to: Dr Jonathan S. Leventhal, Department of Dermatology, Yale School of Medicine, 15 York Street, LMP 5040, New Haven, CT 06510, USA
E-mail: jonathan.leventhal@yale.edu

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 (neratanib, afatanib, 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 eruptic 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 sunitnib (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 erythrodysaesthesia (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), gefitnib (66,67,104), afatinib (68,69,92), erlotinib (70,105), panitimumab (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 panitimumab (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 papuopustular 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 geifitinib (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.

Acknowledgements

Not applicable.

Funding

Ms. Olamiju receives funding from the NIH as part of her Yale School of Medicine research fellowship.

Availability of data and materials

All data were obtained from review of the literature. All information is documented by relevant references.

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.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors state that they have no competing interests.

References

1. National Cancer Institute. Common terminology criteria for adverse events (CTCAE) v5.0, 2017. https://www.meddra.org/. Accessed September 5, 2018.
2. Green MR and Couchman JR: Differences in human skin between the epidermal growth factor receptor distribution detected by EGF binding and monoclonal antibody recognition. J Invest Dermatol 85: 239-245, 1985.
3. Lacouture ME: Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer 6: 803-812, 2006.
4. Rodeck U: Skin toxicity caused by EGFR antagonists-an autoinflammatory condition triggered by deregulated IL-1 signaling? J Cell Physiol 218: 32-34, 2009.
5. Johnston JB, Navaratnam S, Pitz MW, Maniate JM, Wiechec E, Baust H, Gingerich J, Skliris GP, Murphy LC and Los M: Targeting the EGFR pathway for cancer therapy. Curr Med Chem 13: 3483-3492, 2006.
6. Fakih M and Vincent M: Adverse events associated with anti-EGFR therapies for the treatment of metastatic colorectal cancer. Curr Oncol 17 (Suppl 1): S18-S30, 2010.
7. Davies BR, Logie A, McKay JS, Martin P, Steele S, Jenkins R, Cockerill M, Cartlidge S and Smith PD: AZD6244 (ARRY-142886), a potent inhibitor of mitogen-activated protein kinase/extracellular signal-regulated kinase kinase 1/2 kinases: Mechanism of action in vivo, pharmacokinetic/pharmacodynamic relationship, and potential for combination in preclinical. Mol Cancer Ther 6: 2209-2219, 2007.
8. Haass NK, Sproesser K, Nguyen TK, Contractor R, Medina CA, Nathanson KL, Herlyn M and Smalley KS: The mitogen-activated protein/extracellular signal-regulated kinase kinase inhibitor AZD6244 (ARRY-142886) induces growth arrest in melanoma cells and tumor regression when combined with docetaxel. Clin Cancer Res 14: 230-239, 2008.
9. Huynh H, Soo KC, Chow PK and Tran E: Targeted inhibition of the extracellular signal-regulated kinase kinase pathway with AZD6244 (ARRY-142886) in the treatment of hepatocellular carcinoma. Mol Cancer Ther 6: 138-146, 2007.
10. Adjei AA, Cohen RB, Franklin W, Morris C, Wilson D, Molina JR, Hanson LJ, Gore L, Chow L, Leong S, *et al*: Phase I pharmacokinetic and pharmacodynamic study of the oral, small-molecule mitogen-activated protein kinase kinase 1/2 inhibitor AZD6244 (ARRY-142886) in patients with advanced cancers. J Clin Oncol 26: 2139-2146, 2008.
11. Flaherty KT, Robert C, Hersey P, Nathan P, Garbe C, Milhem M, Demidov LV, Hassel JC, Rutkowski P, Mohr P, *et al*: Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med 367: 107-114, 2012.
12. Balagula Y, Barth Huston K, Busam KJ, Lacouture ME, Chapman PB and Myskowski PL: Dermatologic side effects associated with the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886). Invest New Drugs 29: 1114-1121, 2011.
13. Kuske M, Westphal D, Wehner R, Schmitz M, Beissert S, Praetorius C and Meier F: Immunomodulatory effects of BRAF and MEK inhibitors: Implications for melanoma therapy. Pharmacol Res 136: 151-159, 2018.
14. Flaherty KT, Infante JR, Daud A, Gonzalez R, Kefford RF, Sosman J, Hamid O, Schuchter L, Cebon J, Ibrahim N, *et al*: Combined BRAF and MEK inhibition in melanoma with BRAF V600 mutations. N Engl J Med 367: 1694-1703, 2012.
15. Sun Y, Liu WZ, Liu T, Feng X, Yang N and Zhou HF: Signaling pathway of MAPK/ERK in cell proliferation, differentiation, migration, senescence and apoptosis. J Recept Signal Transduct Res 35: 600-604, 2015.
16. Curtin JA, Fridlyand J, Kageshita T, Patel HN, Busam KJ, Kutzner H, Cho KH, Aiba S, Bröcker EB, LeBoit PE, *et al* Distinct sets of genetic alterations in melanoma. N Engl J Med 353: 2135-2147, 2005.
17. Hauschild A, Grob JJ, Demidov LV, Jouary T, Gutzmer R, Millward M, Rutkowski P, Blank CU, Miller WH Jr, Kaempgen E, *et al*: Dabrafenib in BRAF-mutated metastatic melanoma: A multicentre, open-label, phase 3 randomised controlled trial. Lancet 380: 358-365, 2012.
18. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, Dummer R, Garbe C, Testori A, Maio M, *et al*: Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 364: 2507-2516, 2011.
19. Macdonald JB, Macdonald B, Golitz LE, LoRusso P and Sekulic A: Cutaneous adverse effects of targeted therapies: Part I: Inhibitors of the cellular membrane. J Am Acad Dermatol 72: 203-218, 2015.
20. Hermanson M, Funa K, Hartman M, Claesson-Welsh L, Heldin CH, Westermark B and Nistér M: Platelet-derived growth factor and its receptors in human glioma tissue: Expression of messenger RNA and protein suggests the presence of autocrine and paracrine loops. Cancer Res 52: 3213-3219, 1992.
21. Seymour L, Dajee D and Bezwoda WR: Tissue platelet derived-growth factor (PDGF) predicts for shortened survival and treatment failure in advanced breast cancer. Breast Cancer Res Treat 26: 247-252, 1993.
22. Smits A, Funa K, Vassbotn FS, Beausang-Linder M, af Ekenstam F, Heldin CH, Westermark B and Nistér M: Expression of platelet-derived growth factor and its receptors in proliferative disorders of fibroblastic origin. Am J Pathol 140: 639-648, 1992.
23. Liu KW, Hu B and Cheng SY: Platelet-derived growth factor signaling in human malignancies. Chin J Cancer 30: 581-584, 2011.
24. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, *et al*: Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 348: 994-1004, 2003.

25. Das D, Ganguly S, Deb AR and Aich RK: Neoodjuvant imatinib mesylate for advanced primary and metastactic/recurrent gastro-intestinal stromal tumour (GIST). J Indian Med Assoc 111: 21-23, 2013.
26. Liu-Dumlao T, Kantarjian H, Thomas DA, O'Brien S and Ravandi F: Philadelphia-positive acute lymphoblastic leukemia: Current treatment options. Curr Oncol Rep 14: 387-394, 2012.
27. Pardanani A: Systemic mastocytosis in adults: 2015 update on diagnosis, risk stratification, and management. Am J Hematol 90: 250-262, 2015.
28. Ugurel S, Mentzel T, Utikal J, Helmbold P, Mohr P, Pföhler C, Schiller M, Hauschild A, Hein R, Kämpgen E, *et al*: Neoadjuvant imatinib in advanced primary or locally recurrent dermatofibrosarcoma protuberans: A multicenter phase II DeCOG trial with long-term follow-up. Clin Cancer Res 20: 499-510, 2014.
29. Hodi FS, Corless CL, Giobbie-Hurder A, Fletcher JA, Zhu M, Marino-Enriquez A, Friedlander P, Gonzalez R, Weber JS, Gajewski TF, *et al*: Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol 31: 3182-3190, 2013.
30. Koon HB, Krown SE, Lee JY, Honda K, Rapisuwon S, Wang Z, Aboulafia D, Reid EG, Rudek MA, Dezube BJ and Noy A: Phase II trial of imatinib in AIDS-associated Kaposi's sarcoma: AIDS malignancy consortium protocol 042. J Clin Oncol 32: 402-408, 2014.
31. Liu FT, Li NG, Zhang YM, Xie WC, Yang SP, Lu T and Shi ZH: Recent advance in the development of novel, selective and potent FGFR inhibitors. Eur J Med Chem 186: 111884, 2020.
32. de Almeida Carvalho LM, de Oliveira Sapori Avelar S, Haslam A, Gill J and Prasad V: Estimation of percentage of patients with fibroblast growth factor receptor alterations eligible for off-label use of erdafitinib. JAMA Netw Open 2: e1916091, 2019.
33. Katoh M: FGFR inhibitors: Effects on cancer cells, tumor microenvironment and whole-body homeostasis (Review). Int J Mol Med 38: 3-15, 2016.
34. Helsten T, Elkin S, Arthur E, Tomson BN, Carter J and Kurzrock R: The FGFR landscape in cancer: Analysis of 4,853 tumors by next-generation sequencing. Clin Cancer Res 22: 259-267, 2016.
35. Arudra K, Patel R, Tetzlaff MT, Hymes S, Subbiah V, Meric-Bernstam F, Torres-Cabala C, Aung PP, Nagarajan P, Diab A, *et al*: Calcinosis cutis dermatologic toxicity associated with fibroblast growth factor receptor inhibitor for the treatment of Wilms tumor. J Cutan Pathol 45: 786-790, 2018.
36. Carr DR, Pootrakul L, Chen HZ and Chung CG: Metastatic calcinosis cutis associated with a selective FGFR inhibitor. JAMA Dermatol 155: 122-123, 2019.
37. Miyanaga A, Shimizu K, Noro R, Seike M, Kitamura K, Kosaihira S, Minegishi Y, Shukuya T, Yoshimura A, Kawamoto M, *et al*: Activity of EGFR-tyrosine kinase and ALK inhibitors for EML4-ALK-rearranged non-small-cell lung cancer harbored coexisting EGFR mutation. BMC Cancer 13: 262, 2013.
38. Hou H, Sun D, Liu K, Jiang M, Liu D, Zhu J, Zhou N, Cong J and Zhang X: The safety and serious adverse events of approved ALK inhibitors in malignancies: A meta-analysis. Cancer Manag Res 11: 4109-4118, 2019.
39. Sawamura S, Kajihara I, Ichihara A, Fukushima S, Jinnin M, Yamaguchi E, Kohrogi H and Ihn H: Crizotinib-associated erythema multiforme in a lung cancer patient. Drug Discov Ther 9: 142-143, 2015.
40. Yang S, Wu L, Li X, Huang J, Zhong J and Chen X: Crizotinib-associated toxic epidermal necrolysis in an ALK-positive advanced NSCLC patient. Mol Clin Oncol 8: 457-459, 2018.
41. Autier J, Escudier B, Wechsler J, Spatz A and Robert C: Prospective study of the cutaneous adverse effects of sorafenib, a novel multikinase inhibitor. Arch Dermatol 144: 886-892, 2008.
42. Kong HH and Turner ML: Array of cutaneous adverse effects associated with sorafenib. J Am Acad Dermatol 61: 360-361, 2009.
43. Robert C, Sibaud V, Mateus C and Cherpelis BS: Advances in the management of cutaneous toxicities of targeted therapies. Semin Oncol 39: 227-240, 2012.
44. Hurwitz HI, Dowlati A, Saini S, Savage S, Suttle AB, Gibson DM, Hodge JP, Merkle EM and Pandite L: Phase I trial of pazopanib in patients with advanced cancer. Clin Cancer Res 15: 4220-4227, 2009.
45. Hutson TE, Davis ID, Machiels JP, De Souza PL, Rottey S, Hong BF, Epstein RJ, Baker KL, McCann L, Crofts T, *et al*: Efficacy and safety of pazopanib in patients with metastatic renal cell carcinoma. J Clin Oncol 28: 475-480, 2010.
46. Sternberg CN, Davis ID, Mardiak J, Szczylik C, Lee E, Wagstaff J, Barrios CH, Salman P, Gladkov OA, Kavina A, *et al*: Pazopanib in locally advanced or metastatic renal cell carcinoma: Results of a randomized phase III trial. J Clin Oncol 28: 1061-1068, 2010.
47. Hartmann JT and Kanz L: Sunitinib and periodic hair depigmentation due to temporary c-KIT inhibition. Arch Dermatol 144: 1525-1526, 2008.
48. Robert C, Spatz A, Faivre S, Armand JP and Raymond E: Tyrosine kinase inhibition and grey hair. Lancet 361: 1056, 2003.
49. Cheng AL, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, *et al*: Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol 10: 25-34, 2009.
50. Coleman EL, Cowper SE, Stein SM and Leventhal JS: Erythema nodosum-like Eruption in the setting of sorafenib therapy. JAMA Dermatol 154: 369-370, 2018.
51. Ollech A, Stemmer SM, Merims S, Lotem M, Popovtzer A, Hendler D, Hodak E, Didkovsky E and Amitay-Laish I: Widespread morbilliform rash due to sorafenib or vemurafenib treatment for advanced cancer; experience of a tertiary dermato-oncology clinic. Int J Dermatol 55: 473-478, 2016.
52. Choi MK, Woo HY, Heo J, Cho M, Kim GH, Song GA and Kim MB: Toxic epidermal necrolysis associated with sorafenib and tosufloxacin in a patient with hepatocellular carcinoma. Ann Dermatol 23 (Suppl 3): S404-S407, 2011.
53. Ikeda M, Fujita T, Amoh Y, Mii S, Matsumoto K and Iwamura M: Stevens-Johnson syndrome induced by sorafenib for metastatic renal cell carcinoma. Urol Int 91: 482-483, 2013.
54. Yoon J, Oh CW and Kim CY: Stevens-johnson syndrome induced by vandetanib. Ann Dermatol 23 (Suppl 3): S343-S345, 2011.
55. Pickert A, Hughes M and Wells M: Chloracne-like drug eruption associated with sorafenib. J Drugs Dermatol 10: 1331-1334, 2011.
56. Kim DK, Lee SW, Nam HS, Jeon DS, Park NR, Nam YH, Lee SK, Baek YH, Han SY and Lee SW: A case of sorafenib-induced DRESS syndrome in hepatocelluar carcinoma. Korean J Gastroenterol 67: 337-340, 2016.
57. Epskamp C, Snels DGCTM, Yo GL, Zuetenhorst HJ and Hamberg P: Bullous fixed drug eruption in a patient with metastatic renal cell carcinoma induced by iodinated contrast during pazopanib treatment. Eur J Dermatol 26: 207-208, 2016.
58. MacGregor JL, Silvers DN, Grossman ME and Sherman WH: Sorafenib-induced erythema multiforme. J Am Acad Dermatol 56: 527-528, 2007.
59. Caro-Gutiérrez D, Floristán Muruzábal MU, Gómez de la Fuente E, Franco AP and López Estebaranz JL: Photo-induced erythema multiforme associated with vandetanib administration. J Am Acad Dermatol 71: e142-e144, 2014.
60. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: Plan B (levonorgestrel). https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125085s0169lbl.pdf. Accessed August 31, 2018.
61. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: CYRAMZA. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125477s002lbl.pdf. Accessed December 23, 2019.
62. Lin WL, Lin WC, Yang JY, Chang YC, Ho HC, Yang LC, Yang CH, Hung SI and Chung WH: Fatal toxic epidermal necrolysis associated with cetuximab in a patient with colon cancer. J Clin Oncol 26: 2779-2780, 2008.
63. Urosevic-Maiwald M, Harr T, French LE and Dummer R: Stevens-Johnson syndrome and toxic epidermal necrolysis overlap in a patient receiving cetuximab and radiotherapy for head and neck cancer. Int J Dermatol 51: 864-867, 2012.
64. Pantano F, Silletta M, Iovieno A, Vincenzi B, Santini D, Galluzzo S, Bonini S and Tonini G: Stevens-Johnson syndrome associated with reduced tear production complicating the use of cetuximab and panitunumab. Int J Colorectal Dis 24: 1247-1248, 2009.
65. Lee SS and Chu PY: Toxic epidermal necrolysis caused by cetuximab plus minocycline in head and neck cancer. Am J Otolaryngol 31: 288-290, 2010.
66. Jackman DM, Cioffredi LA, Jacobs L, Sharmeen F, Morse LK, Lucca J, Plotkin SR, Marcoux PJ, Rabin MS, Lynch TJ, *et al*: A phase I trial of high dose gefitinib for patients with leptomeningeal metastases from non-small cell lung cancer. Oncotarget 6: 4527-4536, 2015.

67. Huang JJ, Ma SX, Hou X, Wang Z, Zeng YD, Qin T, Dinglin XX and Chen LK: Toxic epidermal necrolysis related to AP (pemetrexed plus cisplatin) and gefitinib combination therapy in a patient with metastatic non-small cell lung cancer. Chin J Cancer 34: 94-98, 2015.
68. Honda Y, Hattori Y, Katsura S, Terashima T, Manabe T, Otsuka A and Miyachi Y: Stevens-Johnson syndrome-like erosive dermatitis possibly related to afatinib. Eur J Dermatol 26: 413-414, 2016.
69. Doesch J, Debus D, Meyer C, Papadopoulos T, Schultz ES, Ficker JH and Brueckl WM: Afatinib-associated Stevens-Johnson syndrome in an EGFR-mutated lung cancer patient. Lung Cancer 95: 35-38, 2016.
70. Wnorowski AM, de Souza A, Chachoua A and Cohen DE: The management of EGFR inhibitor adverse events: A case series and treatment paradigm. Int J Dermatol 51: 223-232, 2012.
71. Lamiaux M, Scalbert C, Lepesant P, Desmedt E, Templier C, Dziwniel V, Staumont-Sallé D and Mortier L: Severe skin toxicity with organ damage under the combination of targeted therapy following immunotherapy in metastatic melanoma. Melanoma Res 28: 451-457, 2018.
72. Bellón T, Lerma V, González-Valle O, González Herrada C and de Abajo FJ: Vemurafenib-induced toxic epidermal necrolysis: Possible cross-reactivity with other sulfonamide compounds. Br J Dermatol 174: 621-624, 2016.
73. Minor DR, Rodvien R and Kashani-Sabet M: Successful desensitization in a case of Stevens-Johnson syndrome due to vemurafenib. Melanoma Res 22: 410-411, 2012.
74. Arenbergerova M, Mrazova I, Horazdovsky J, Sticova E, Fialova A and Arenberger P: Toxic epidermal necrolysis induced by vemurafenib after nivolumab failure. J Eur Acad Dermatol Venereol 31: e253-e254, 2017.
75. Jeudy G, Dalac-Rat S, Bonniaud B, Hervieu A, Petrella T, Collet E and Vabres P: Successful switch to dabrafenib after vemurafenib-induced toxic epidermal necrolysis. Br J Dermatol 172: 1454-1455, 2015.
76. Lapresta A, Dotor A and González-Herrada C: Toxic epidermal necrolysis induced by vemurafenib. Actas Dermosifiliogr 106: 682-683, 2015 (In English, Spanish).
77. Wantz M, Spanoudi-Kitrimi I, Lasek A, Lebas D, Quinchon JF and Modiano P: Vemurafenib-induced toxic epidermal necrolysis. Ann Dermatol Venereol 141: 215-218, 2014.
78. Sinha R, Lecamwasam K, Purshouse K, Reed J, Middleton MR and Fearfield L: Toxic epidermal necrolysis in a patient receiving vemurafenib for treatment of metastatic malignant melanoma. Br J Dermatol 170: 997-999, 2014.
79. Rosen AC, Balagula Y, Raisch DW, Garg V, Nardone B, Larsen N, Sorrell J, West DP, Anadkat MJ and Lacouture ME: Life-threatening dermatologic adverse events in oncology. Anticancer Drugs 25: 225-234, 2014.
80. Chen CB, Wu MY, Ng CY, Lu CW, Wu J, Kao PH, Yang CK, Peng MT, Huang CY, Chang WC, *et al*: Severe cutaneous adverse reactions induced by targeted anticancer therapies and immunotherapies. Cancer Manag Res 10: 1259-1273, 2018.
81. Wenk KS, Pichard DC, Nasabzadeh T, Jang S and Venna SS: Vemurafenib-Induced DRESS. JAMA Dermatology 149: 1242, 2013.
82. Munch M, Peuvrel L, Brocard A, Saint Jean M, Khammari A, Dreno B and Quereux G: Early-onset vemurafenib-induced DRESS syndrome. Dermatology 232: 126-128, 2016.
83. Gey A, Milpied B, Dutriaux C, Mateus C, Robert C, Perro G, Taieb A, Ezzedine K and Jouary T: Severe cutaneous adverse reaction associated with vemurafenib: DRESS, AGEP or overlap reaction? J Eur Acad Dermatology Venereol 30: 178-179, 2016.
84. Pinard C, Mignard C, Samain A, Duval-Modeste AB and Joly P: Successful use of dabrafenib after the occurrence of drug rash with eosinophilia and systemic symptoms (DRESS) induced by vemurafenib. JAAD Case Reports 3: 532-533, 2017.
85. Brégeon B, Bernier C, Josselin N, Peuvrel L, Moigne ML, Saint-Jean M and Quéreux G: Drug reaction with eosinophilia and systemic symptoms syndrome induced by combination of vemurafenib and cobimetinib in melanoma: A series of 11 cases. J Am Acad Dermatol 80: 558-562, 2019.
86. Goldman J, Duval-Modeste AB, Lambert A, Contentin N, Courville P, Musette P and Joly P: Imatinib-induced DRESS: Ann Dermatol Venereol 135: 393-396, 2008 (In French).
87. Le Nouail P, Viseux V, Chaby G, Billet A, Denoeux JP and Lok C: Drug reaction with eosinophilia and systemic symptoms (DRESS) following imatinib therapy. Ann Dermatol Venereol 133: 686-688, 2006 (In French).
88. Kumar M, Mandal PK, Dolai TK and Bhattacharrya M: Imatinib causing drug rash with eosinophilia and systemic symptoms: A rare cutaneous reaction. Indian Dermatol Online J 5 (Suppl 2): S120-S122, 2014.
89. Saidi W, Lahouel I, Laarif M and Aounallah A: A new case of imatinib-induced drug reaction with eosinophilia and systemic symptoms. Indian J Dermatol Venereol Leprol 83: 224, 2017.
90. Ben-Ami E, Castells MC, Connell NT, Rutherford AE and Thornton KA: Imatinib-induced drug reaction with eosinophilia and systemic symptoms in solid tumors: A patient with dermatofibrosarcoma protuberans and successful desensitization management. Anticancer Drugs 29: 919-923, 2018.
91. Vatel O, Aumont C, Mathy V, Petit M, Feriel J, Sloma I, Bennaceur-Griscelli A and Turhan AG: Drug reaction with eosinophilia and systemic symptoms (DRESS) induced by imatinib in chronic myeloid leukemia. Leuk Lymphoma 58: 473-474, 2017.
92. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: Gilotrif. www.fda.gov/medwatch. Accessed November 13, 2019.
93. Shih HC, Hsiao YP, Wu MF and Yang JH: Gefitinib-induced acute generalized exanthematous pustulosis in two patients with advanced non-small-cell lung cancer. Br J Dermatol 155: 1101-1102, 2006.
94. Lakshmi C, Pillai S and Srinivas CR: Lapatinib-induced acute generalized exanthematous pustulosis. Indian Dermatol Online J 1: 14-17, 2010.
95. Brouard MC, Prins C, Mach-Pascual S and Saurat JH: Acute generalized exanthematous pustulosis associated with STI571 in a patient with chronic myeloid leukemia. Dermatology 203: 57-59, 2001.
96. Scott AD, Lee M, Kubba F and Chu A: Acute generalized exanthematous pustulosis (AGEP) secondary to imatinib in a patient with chronic myeloid leukaemia. Clin Exp Dermatol 40: 926-927, 2015.
97. Schwarz M, Kreuzer KA, Baskaynak G, Dörken B and le Coutre P: Imatinib-induced acute generalized exanthematous pustulosis (AGEP) in two patients with chronic myeloid leukemia. Eur J Haematol 69: 254-256, 2002.
98. Gambillara E, Laffitte E, Widmer N, Decosterd LA, Duchosal MA, Kovacsovics T and Panizzon RG: Severe pustular eruption associated with imatinib and voriconazole in a patient with chronic myeloid leukemia. Dermatology 211: 363-365, 2005.
99. Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L and Roujeau JC: Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. Arch Dermatol 129: 92-96, 1993.
100. Schwartz RA, McDonough PH and Lee BW: Toxic epidermal necrolysis: Part I. Introduction, history, classification, clinical features, systemic manifestations, etiology, and immunopathogenesis. J Am Acad Dermatol 69: 173.e1-e13, 185-186, 2013.
101. Rzany B, Hering O, Mockenhaupt M, Schröder W, Goerttler E, Ring J and Schöpf E: Histopathological and epidemiological characteristics of patients with erythema exudativum multiforme major, Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol 135: 6-11, 1996.
102. Harr T and French LE: Stevens-Johnson syndrome and toxic epidermal necrolysis. Chem Immunol Allergy 97: 149-166, 2012.
103. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: Erbitux. http://www.fda.gov/medicaldevices/productsandmedicalprocedures/invitrodiagnostics/ucm301431.htm. Accessed November 13, 2019.
104. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: Iressa. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/206995s003lbl.pdf. Accessed November 13, 2019.
105. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: Tarceva. https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021743s14s16lbl.pdf. Accessed November 13, 2019.
106. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: Vectibix® (panitumumab). https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/125147s080lbl.pdf. Accessed November 13, 2019.

107. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: Vizimpro. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/211288s000lbl.pdf. Accessed November 13, 2019.
108. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: ZELBORAF (Vemurafenib) Tablet for Oral Use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/202429s012lbl.pdf. Accessed November 13, 2019.
109. Johnson DB, Wallender EK, Cohen DN, Likhari SS, Zwerner JP, Powers JG, Shinn L, Kelley MC, Joseph RW and Sosman JA: Severe cutaneous and neurologic toxicity in melanoma patients during vemurafenib administration following anti-PD-1 therapy. Cancer Immunol Res 1: 373-377, 2013.
110. Harding JJ, Pulitzer M and Chapman PB: Vemurafenib sensitivity skin reaction after ipilimumab. N Engl J Med 366: 866-868, 2012.
111. Mahapatra M, Mishra P and Kumar R: Imatinib-induced Stevens-Johnson syndrome: Recurrence after re-challenge with a lower dose. Ann Hematol 86: 537-538, 2007.
112. Pavithran K and Thomas M: Imatinib induced Stevens-Johnson syndrome: Lack of recurrence following re-challenge with a lower dose. Indian J Dermatol Venereol Leprol 71: 288-289, 2005.
113. Bois E, Holle LM and Farooq U: Late onset imatinib-induced Stevens-Johnson syndrome. J Oncol Pharm Pract 20: 476-478, 2014.
114. Sanchez-Gonzalez B, Pascual-Ramirez JC, Fernandez-Abellan P, Belinchon-Romero I, Rivas C and Vegara-Aguilera G: Severe skin reaction to imatinib in a case of Philadelphia-positive acute lymphoblastic leukemia. Blood 101: 2446, 2003.
115. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: GLEEVEC (Imatinib Mesylate) Tablets Label. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/021588s047lbl.pdf. Accessed November 13, 2019.
116. Hsiao LT, Chung HM, Lin JT, Chiou TJ, Liu JH, Fan FS, Wang WS, Yen CC and Chen PM: Stevens-Johnson syndrome after treatment with STI571: A case report. Br J Haematol 117: 620-622, 2002.
117. Rule SA, O'Brien SG and Crossman LC: Managing cutaneous reactions to imatinib therapy. Blood 100: 3434-3435, 2002.
118. Jha P, Himanshu D, Jain N and Singh AK: Imatinib-induced Stevens-Johnsons syndrome. BMJ Case Rep 2013: bcr2012007926, 2013.
119. Nakamoto K, Nagahara H, Noda E, Inoue T, Maeda K, Ohira G, Amano R, Kubo N, Tanaka H, Muguruma K, *et al*: Three cases of giant rectal gastrointestinal stromal tumor. Gan To Kagaku Ryoho 38: 1984-1986, 2011 (In Japanese).
120. Vidal D, Puig L, Sureda A and Alomar A: Sti571-induced Stevens-Johnson syndrome. Br J Haematol 119: 274-275, 2002.
121. Schaich M, Schäkel K, Illmer T, Ehninger G and Bornhäuser M: Severe epidermal necrolysis after treatment with imatinib and consecutive allogeneic hematopoietic stem cell transplantation. Ann Hematol 82: 303-304, 2003.
122. Hsieh HJ, Chan ALF and Lin SJ: Stevens-Johnson syndrome induced by combination of imatinib and allopurinol. Chemotherapy 55: 197-199, 2009.
123. Severino G, Chillotti C, De Lisa R, Del Zompo M and Ardau R: Adverse reactions during imatinib and lansoprazole treatment in gastrointestinal stromal tumors. Ann Pharmacother 39: 162-164, 2005.
124. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: Tasigna (Nilotinib). https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/022068lbl.pdf. Accessed November 13, 2019.
125. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: Sprycel (Dasatinib). https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021986s7s8lbl.pdf. Accessed November 13, 2019.
126. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: NEXAVAR (Sorafenib) Tablets, for Oral Use. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021923s020lbl.pdf. Accessed November 13, 2019.
127. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Highlights of prescribing information: Caprelsa (Vandetanib). https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/022405s007lbl.pdf. Accessed November 13, 2019.
128. Szatkowski J and Schwartz RA: Acute generalized exanthematous pustulosis (AGEP): A review and update. J Am Acad Dermatol 73: 843-848, 2015.
129. Choudhary S, McLeod M, Torchia D and Romanelli P: Drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome. J Clin Aesthet Dermatol 6: 31-37, 2013.
130. Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L and Roujeau JC: The DRESS syndrome: A literature review. Am J Med 124: 588-597, 2011.
131. Kardaun SH, Sekula P, Valeyrie-Allanore L, Liss Y, Chu CY, Creamer D, Sidoroff A, Naldi L, Mockenhaupt M and Roujeau JC; RegiSCAR study group: Drug reaction with eosinophilia and systemic symptoms (DRESS): An original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. Br J Dermatol 169: 1071-1080, 2013.
132. Ortonne N, Valeyrie-Allanore L, Bastuji-Garin S, Wechsler J, de Feraudy S, Duong TA, Delfau-Larue MH, Chosidow O, Wolkenstein P and Roujeau JC: Histopathology of drug rash with eosinophilia and systemic symptoms syndrome: A morphological and phenotypical study. Br J Dermatol 173: 50-58, 2015.
133. Funck-Brentano E, Duong TA, Bouvresse S, Bagot M, Wolkenstein P, Roujeau JC, Chosidow O and Valeyrie-Allanore L: Therapeutic management of DRESS: A retrospective study of 38 cases. J Am Acad Dermatol 72: 246-252, 2015.