

Severe cutaneous adverse reactions induced by targeted anticancer therapies and immunotherapies

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Abstract: With the increasing use of targeted anticancer drugs and immunotherapies, there have been a substantial number of reports concerning life-threatening severe cutaneous adverse reactions (SCARs), including Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms, drug-induced hypersensitivity syndrome, and acute generalized exanthematous pustulosis. Although the potential risks and characteristics for targeted anticancer agent- and immunotherapy-induced SCAR were not well understood, these serious adverse reactions usually result in morbidity and sequela. As a treatment guideline for this devastating condition is still unavailable, prompt withdrawal of causative drugs is believed to be a priority of patient management. In this review, we outline distinct types of SCARs caused by targeted anticancer therapies and immunotherapies. Also, we discuss the clinical course, latency, concomitant medication, tolerability of rechallenge or alternatives, tumor response, and mortality associated with these devastating conditions. Imatinib, vemurafenib, and rituximab were the top three offending medications that most commonly caused SJS/TEN, while EGFR inhibitors were the group of drugs that most frequently induced SJS/TEN. For drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome and acute generalized exanthematous pustulosis, imatinib was also the most common offending drug. Additionally, we delineated 10 SCAR cases related to innovative immunotherapies, including PD1 and CTLA4 inhibitors. There was a wide range of latency periods: 5.5–91 days (median). Only eight of 16 reported patients with SCAR showed clinical responses. Targeted anticancer drugs and immunotherapies can lead to lethal SCAR (14 deceased patients were identified as suffering from SJS/TEN). The mortality rate of TEN was high: up to 52.4%. The information compiled herein will serve as a solid foundation to formulate ideas for early recognition of SCAR and to discontinue offending drugs for better management.

Keywords: acute generalized exanthematous pustulosis, drug rash, eosinophilia, Stevens–Johnson syndrome, toxic epidermal necrolysis, targeted therapy, immunotherapy

Introduction

There has been rapidly increasing use of targeted anticancer therapies and immunotherapies in the clinical oncology field. Although targeted agents used for cancer treatment are generally better tolerated than conventional chemotherapy, cutaneous adverse events following the administration of targeted agents are not sparse. Manifestations of cutaneous adverse reactions induced by targeted agents vary greatly due to distinct molecular and pathological mechanisms, such as rashes, alopecia, hand–foot skin reactions, nail changes, and hair changes.¹ However, it has been reported that an increasing number of targeted agents induce life-threatening severe cutaneous adverse reactions

(SCARs), including Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS)/drug-induced hypersensitivity syndrome (DIHS), and acute generalized exanthematous pustulosis (AGEP).² Unlike mild forms of cutaneous toxicity, these SCARs are idiosyncratic and potentially fatal.³ However, the risk of SCARs caused by targeted anticancer therapies and immunotherapies remains poorly characterized. SJS/TEN typically present as a rapidly developing blistering exanthema of purpuric macules and target-like lesions accompanied by mucosal and skin detachment, in which SJS involves <10% of body surface area skin detachment and TEN >30%.⁴ Although rare, they are potentially fatal, with a mortality rate of 10% for SJS, 30% for SJS–TEN overlapping, and 50% for TEN (Figure 1).^{4–6} SJS/TEN also commonly causes long-term sequelae of the skin and eyes.⁷ In addition, DRESS or DIHS usually mani-

fest with a complex natural course, including fever, cutaneous involvement with typical skin eruptions (eg, generalized maculopapular exanthema, facial edema, infiltration, and purpuric change other than lower extremities), laboratory abnormalities (atypical lymphocytosis and eosinophilia), lymphadenopathy, and systemic organ involvement (eg, liver, kidneys, and lungs; Figure 2).^{8,9} The mortality rate for DRESS is approximately up to 10%.¹⁰ AGEP, another phenotype of SCAR, is characterized by a sudden eruption of mainly small nonfollicular pustules on a background of erythema with systemic involvement associated with fever and neutrophilia.¹¹ The course is relatively benign, but 4% of AGEP cases still develop to life-threatening situations.¹¹ Due to the high morbidity and mortality, early diagnosis of SCAR and prompt medication discontinuation are required for better management. This review article summarizes SCARs induced by distinct targeted anticancer agents and immunotherapies and also delineates the clinical course, duration of anticancer drugs, concomitant medication, tolerability of rechallenge or alternative agents, tumor response with regard to the occurrence of SCAR, and mortality rate associated with these devastating conditions.



Figure 1 Fatal toxic epidermal necrolysis after cetuximab treatment for 8 weeks.
Notes: A 74-year-old man who had moderately differentiated metastatic colon adenocarcinoma presented diffuse erythematous plaques with dusky red centers on trunk and extremities after treatment with cetuximab for 8 weeks. The skin rashes were confluent and formed large blisters or skin detachments involving more than 70% of the body surface area.



Figure 2 Drug rash with eosinophilia and systemic symptoms after erlotinib treatment for 4 weeks.
Notes: A 60-year-old woman with *EGFR*-mutant metastatic lung adenocarcinoma treated with erlotinib for 4 weeks. She developed generalized infiltrative exanthema on trunk and limbs accompanied by fever, acute liver failure, coagulopathy, and leukocytosis with eosinophilia. Further lymphocyte activation testing confirmed a hypersensitivity reaction to erlotinib.

Search strategy and selection criteria

A literature search was performed for papers from 1950 to September 2017 on Embase, Web of Science, Scopus, and Ovid using the terms Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), drug rash with eosinophilia and systemic symptoms (DRESS), drug-induced hypersensitivity syndrome (DIHS), or acute generalized exanthematous pustulosis (AGEP) combined with targeted therapy drugs and immunotherapies. Primary case reports, case series, reports from clinical trials, and postmarketing surveillance were included. All published peer-reviewed literature from the search was reviewed (reports were limited to the English language only, with inclusion of selected non-English reports with abstracts in English). Histopathologic confirmation for the diagnosis of SCAR was not required for the inclusion criteria. Clinical course, duration of anticancer drugs, concomitant medication, tolerability of rechallenge or alternative agents, tumor response with regard to the occurrence of SCARs, and mortality were analyzed.

Clinical course

Characteristics and demographic data

A search of peer-reviewed literature yielded 73 reports of SCARs: SJS/TEN (n=54), DRESS (n=8), AGEP (n=10), and DRESS–AGEP overlapping (n=1; Table 1). These reported SCAR cases were associated with 17 targeted anticancer agents and immunotherapies, including EGFR inhibitors (afatinib, cetuximab, erlotinib, gefitinib, panitumumab, and vandetanib), multikinase inhibitors (imatinib), antiangiogenic agents (sorafenib), proteasome (bortezomib), anti-CD20 (rituximab), anti-CD30 (brentuximab vedotin), BRAF inhibitors (vemurafenib), recombinant IL2 (aldesleukin), recombinant IL2 and diphtheria toxin (denileukin), anti-PD1 (nivolumab and pembrolizumab), and anti-CTLA4 (ipilimumab). Among 54 cases of SJS–TEN, there were 29 SJS, four SJS–TEN overlapping, and 20 TEN cases. Imatinib (n=12), vemurafenib (n=7), and rituximab (n=5) were identified as the top three offending medications to cause SJS/TEN. EGFR inhibitors (n=12) were the most common group of drugs to induce SJS/TEN, including cetuximab (n=4), afatinib (n=2), gefitinib (n=2), vandetanib (n=2), erlotinib (n=1), and panitumumab (n=1). Imatinib was also the most common offending drug to induce DRESS and AGEP. One infrequent overlapping DRESS–AGEP case was reported in one vemurafenib user.¹² For newly developed immunomodulatory therapeutic antibodies targeting inhibitory receptors expressed by T cell,

such as CTLA4 and PD1, there was one ipilimumab SJS, one ipilimumab TEN, one ipilimumab DRESS, one ipilimumab AGEP, two nivolumab TEN, and four pembrolizumab SJS. In total, latent periods of the anticancer agents were variable in different drug classes, from 5.5 days (aldesleukin) to 91 days (denileukin) (median).

The diagnosis of these SJS/TEN was mainly based on clinical manifestation, with 30 cases (55.6%) confirmed by histopathology. Direct immunofluorescence (DIF) or indirect IF (IIF) to rule out the possibility of other autoimmune diseases was performed in seven cases. For mucosal involvement of SJS/TEN, oral mucosa (35 of 54, 64.8%) was more common than ocular (20 of 54, 37%) or genital mucosa (17 of 54, 31.5%) involvement. Positive Nikolsky signs were mentioned in 17 cases. Laboratory examinations to exclude etiologies other than drug-induced SJS/TEN, such as serology data of mycoplasma, herpes simplex infection, or viral culture were done in six cases, and all showed negative results.

Tolerability

Eighteen patients underwent rechallenge of the same anticancer drugs: one aldesleukin TEN, one denileukin TEN, one erlotinib SJS, one gefitinib AGEP, seven imatinib SJS, two imatinib DRESS, one imatinib AGEP, one ipilimumab AGEP, one sorafenib SJS, one sorafenib AGEP, and one vemurafenib SJS. Among patients with rechallenge, four imatinib SJS/TEN cases tolerated well with slow titration, with systemic corticosteroid used concomitantly in three cases (Table 2). In addition, one vemurafenib SJS showed recurrence with rash and fever after one 50% dose rechallenge, but then tolerated with a program of desensitization with dexamethasone.¹³ However, the other 13 patients had recurrence with different manifestations after rechallenge. Among the eight patients who had received alternative agents with the same class of anticancer drugs, five of eight tolerated well: one gefitinib TEN tolerating icotinib, two imatinib SJS patients tolerating dasatinib, one imatinib DRESS patient tolerated a nilotinib replacement, and one vemurafenib TEN patient was switched successfully to dabrafenib with gradual escalation. However, one afatinib SJS patient suffered liver damage after erlotinib and gefitinib were administered, one cetuximab SJS patient progressed into SJS/TEN after panitumumab treatment, and one imatinib SJS patient had possible cross-reactivity with dasatinib concomitant with sulfamethoxazole–trimethoprim at the same time. One vemurafenib TEN patient who underwent a lymphocyte transformation test (LTT) assay confirmed the

Table 1 Targeted anticancer therapies and immunotherapies-induced severe cutaneous adverse reactions (n=73)

Drug class	Agent	Classification	SJS (n=29)	SJS/ TEN (n=4)	TEN (n=21)	DRESS/ DIHS* (n=9)	AGEP* (n=11)	Total (n=73)	Latency, median (range)	Biopsy proved	DIF/ IIF	Mortality	Tumor response	References
EGFR inhibitor	Afatinib	Monoclonal antibody to EGFR	2	0	0	0	0	2	62 (60–64)	2	1	0	PR:1, U:1	30, 110
	Cetuximab	Monoclonal antibody to EGFR	1	1	2	0	0	4	16 (5–45)	1	1	1	R:1, U:3	6, 104, 111, 112
	Erlotinib	TKI specific to EGFR	1	0	0	0	0	1	8 (8)	0	0	0	U:1	26
	Gefitinib	TKI specific to EGFR	0	0	2	0	2	4	8 (7–10)	2	0	1	PR:1, U:3	92, 113, 114
KIT and BCR-ABL inhibitors	Panitumumab	Monoclonal antibody to EGFR	1	0	0	0	0	1	8 (8)	0	0	0	U:1	112
	Vandetanib	Less specific multikinase inhibitors	0	1	1	0	0	2	21 (21)	2	0	0	U:2	115, 116
	Imatinib	KIT, BCR-ABL, PDGFR inhibitors	12	0	0	4	4	20	46 (8–240)	12	2	1	CR:1, PD:1, Rev:2, U:16	40–44, 88–91, 117–126
	Sorafenib	Nonselective antitumor angiogenesis multikinase agents	2	0	1	0	3	6	17 (2–30)	4	0	0	U:6	51, 55, 127–130
Proteasome	Bortezomib	—	1	0	1	1	0	3	49 (42–56)	1	0	1	CR:1, PR:1, U:1	131–133
CD20	Rituximab	Monoclonal antibody to CD20	2	2	1	0	0	5	14 (14–56)	2	1	2	PD:1, U:4	63, 134–136
CD30	Brentuximab vedotin	CD30	1	0	1	0	0	2	7 (7)	1	0	1	U:2	137, 138
RAF inhibitors	Vemurafenib	BRAF (V600E) inhibitors	1	0	6	3*	1*	10	23 (8–42)	9	1	3	CR:1, PR:1, PD:1, U:7	12, 14, 68, 70, 139–144
Immunomodulators	Aldesleukin	Recombinant IL2	0	0	2	0	0	2	5.5 (4–7)	1	0	1	U:2	76, 77
	Denileukin	Recombinant IL2 and diphtheria toxin	0	0	1	0	0	1	91 (91)	1	0	1	U:1	75
	Ipilimumab	CTLA4 inhibitors	1	0	1	1	1	4	22.8 (14–35)	3	0	0	PR:1, U:3	82–84, 145
	Nivolumab	PDI inhibitors	0	0	2	0	0	2	64.5 (39–90)	2	2	2	U:2	16, 79
	Pembrolizumab	PDI inhibitors	4	0	0	0	0	4	83.5 (7–140)	2	0	0	U:2, SD:1, PD:1	80, 81, 85

Note: *One patient presented as DRESS and AGEF overlapping.

Abbreviations: AGEF, acute generalized exanthematous pustulosis; CR, complete remission; DIF, direct immunofluorescence; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug rash with eosinophilia and systemic symptoms; IIF, indirect immunofluorescence; IL-2, interleukin-2; PD, progressive disease; PR, partial remission; R, recurrence; Rev, reversion to second chronic-phase chronic myelogenous leukemia; SCAR, severe cutaneous adverse reaction; SD, stable disease; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; U, unknown.

Table 2 Tolerability follow-up for rechallenge or alternatives in patients with targeted anticancer therapies and immunotherapy-induced severe cutaneous adverse reactions (n=25)

Agent	Phenotype	Rechallenge	Tolerability to other drugs	Reference
Afatinib	SJS	Not reported	Erlotinib (liver damage); gefitinib (liver damage)	30
Aldesleukin	TEN	Recurrent with diffuse erythema and punctuated lesions over left forearm		76
Cetuximab	SJS	Not reported	Panitumumab (SJS/TEN)	112
Denileukin	TEN	Recurrent with extensive erythema and edema with flaccid bulla, and denudation was apparent on flanks, thighs, and arms		75
Erlotinib	SJS	Recurrent with continued erythematous and congested eruption on the face		26
Gefitinib	TEN	Not reported	Icotinib (tolerance)	114
Gefitinib	AGEP	Recurrent with few pustules on previous skin lesion, but tolerated with continuation		92
Imatinib	SJS	Not reported	Dasatinib (possible cross-reactivity, but taking sulfamethoxazole–trimethoprim at the same time); nilotinib (tolerance)	117
Imatinib	SJS	Recurrent with lesions flared up at lower doses	Dasatinib (tolerance)	118
Imatinib	SJS	Recurrent with perioral pruritic eruption after reinitiation at a lower dose of 200 mg/day, but then tolerated with slow titration (100–300 mg/day) with 100 mg together with prednisolone (1 mg/kg)	Not reported	40
Imatinib	SJS	Tolerance with slow titration from 100 mg/day gradually escalated to 400 mg/day	Not reported	41
Imatinib	SJS	Tolerance with slow titration from 100 mg/day and prednisolone 30–400 mg/day, with continuation of prednisolone at 10 mg/day	Not reported	42
Imatinib	SJS	Recurrent with pruritic eruption at a lower dose of 300 mg/day, then tolerated after adding prednisolone at 30 mg/day with gradual tapering		43
Imatinib	SJS	Recurrent with multiple pruritic vesicles and bullae suddenly appeared after single-dose 600 mg/day	Not reported	89
Imatinib	SJS	Recurrent with palpebral and labial edema with generalized body rash after 1-day rechallenge	Not reported	123
Imatinib	DRESS	Recurrent erythematous skin rashes developed in 12 hours		124
Imatinib	DRESS	Recurrent with periorbital edema, itching over face, and eosinophilia after taking 50% dose (200 mg); however, tolerated with combination of low-dose imatinib and oral steroid		44
Imatinib	DRESS		Nilotinib (tolerance)	88
Imatinib	AGEP	Recurrent with urticaria		90
Ipilimumab	AGEP	Skin rashes got worse after second infusion		83
Sorafenib	SJS	Recurrent with pruritic erythematous eruptions and high fever	Not reported	127
Sorafenib	AGEP	Recurrent grouped pustules over the site close to previous skin lesion		129
Vemurafenib	SJS	Recurrent with rash and fever after taking 50% dose (480 mg) once, but tolerated with a program of desensitization with dexamethasone	Not reported	13
Vemurafenib	TEN	Not reported	Lymphocyte transformation test positive for vemurafenib with cross-reactivity to dabrafenib and sulfamethoxazole, but negative for trametinib	14
Vemurafenib	TEN	Not reported	Dabrafenib (tolerance) with gradual escalation	70

Abbreviations: AGEP, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

causality of vemurafenib and also showed positive cross-reactivity for dabrafenib, but was negative for trametinib. This patient did not take dabrafenib or trametinib further.¹⁴

Mortality

A total of 14 patients died after SCAR episodes (Table 3): two SJS, one SJS/TEN, and 11 TEN. In total, the mortality of SJS/TEN was 26.9% (14 of 52) and higher in TEN cases (11 of 21, 52.4%). Seven patients died due to TEN reactions: six with progression of malignancies and one secondary to acute graft-versus-host disease of the gut. No mortality was seen in DRESS or AGEP cases. These cases were mostly treated with supportive care or immunosuppressants, including corticosteroids, cyclosporine, intravenous immunoglobulin, and TNF α inhibitors (etanercept and infliximab). One rituximab TEN case showed a good outcome after etanercept treatment.¹⁵ One nivolumab TEN case died 6 days after the onset of TEN due

to septic shock and multisystem organ failure, despite treatment with infliximab, high-dose corticosteroids, intravenous immunoglobulin, and systemic antibiotics.¹⁶

Malignancy was an independently poor prognostic factor for patients with SJS/TEN.^{17–19} Several factors may contribute to poor prognosis in SJS/TEN patients with malignancies, including specific cancer types (hepatocellular carcinoma, colorectal cancer), chemotherapy, and malnutrition.¹⁹ The mortality rate from the reviewed TEN cases, 52.4%, was higher than the average.^{4,5}

Prognosis and response to anticancer drugs after SCAR

Interestingly, the occurrence of some adverse cutaneous reactions was found to have a positive correlation with the patient's response to treatment and overall survival (eg, EGFR inhibitors for patients with non-small-cell lung

Table 3 Mortality in severe cutaneous adverse reactions related to targeted anticancer therapies and immunotherapies (n=14)

Agent	Phenotype	Age/sex	Underlying disease	Cause of death	Latency	Reference
Cetuximab	TEN	74/male	Adenocarcinoma of the sigmoid colon with hepatic metastasis	Pneumonia with renal/respiratory failure	14 days	6
Gefitinib	TEN	U/U	Non-small-cell lung cancer with leptomeningeal metastases	Systemic lung cancer progression	21 days	113
Imatinib	SJS	52/male	Chronic myeloid leukemia	Acute graft-versus-host disease of the gut	2 months	121
Bortezomib	TEN	61/male	IgG multiple myeloma	Multiorgan failure	4 days	131
Brentuximab vedotin	TEN	22/male	Anaplastic large-cell lymphoma, stage IIIA	Disease progression of lymphoma	20 days	138
Rituximab	SJS	36/male	Follicular non-Hodgkin's lymphoma	Disease progression of lymphoma with inferior vena cava obstruction	5 months	134
Rituximab	SJS/TEN	78/male	Diffuse large B-cell lymphoma with bone marrow involvement	Died secondary to complications of SJS/TEN	U	63
Vemurafenib	TEN	69/male	Melanoma with axillary lymph nodes and pulmonary metastasis	Sepsis	4 days	139
Vemurafenib	TEN	63/female	Melanoma with cervical lymph-node, scalp, lung, and liver metastases	Disease progression of melanoma	3 months	68
Vemurafenib	TEN	73/female	Melanoma with inguinal lymph node metastasis	Multiple-organ failure after ventilator-acquired pneumonia and melena	35 days	142
Aldesleukin	TEN	67/female	Renal cell carcinoma with lung metastasis	Septic shock and hypovolemia secondary to pancytopenia and TEN	10 days	77
Denileukin	TEN	45/male	Follicular large-cell lymphoma with widespread lymphadenopathy, splenomegaly, and bone marrow involvement	Multisystem organ failure with massive TEN and disease progression of lymphoma	18 days	75
Nivolumab	TEN	64/female	Melanoma with pulmonary and liver metastases	Disease progression of melanoma and sepsis	4 months	79
Nivolumab	TEN	50/female	Metastatic malignant melanoma	Septic shock and multisystem organ failure	6 days	81

Abbreviations: SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; U, unknown.

cancer, and nivolumab or pembrolizumab for patients with melanoma).^{20–22} However, the possible connection between treatment response to anticancer therapies and SCAR reactions remains not fully defined. Only eight of 16 reported cases (50%) showed positive clinical responses to causative anticancer drugs, including three with complete remission and five with partial response (Table 1). Most patients discontinued causative agents for SCAR reactions to prevent possible recurrence of this deadly condition. This limited the assessment for the prognostic significance of SCAR related to anticancer agents.

Stevens-Johnson syndrome/toxic epidermal necrolysis

EGFR inhibitors

EGFRs are a large family of receptor tyrosine kinases expressed in several types of cancers, including non-small-cell lung, colorectal, breast, pancreatic, head-and-neck, and esophageal cancers.^{23,24} Clinical use of EGFR-targeted therapies has been approved for treating various cancers.^{23,24} Despite the benefits, EGFR inhibitors cause enormous cutaneous adverse drug reactions (ADRs) with incidence up to 80%.²⁵ EGFR inhibitor-induced cutaneous ADRs are present in a broad spectrum, including papulopustular eruptions, mucositis, photosensitivity, xerosis, and paronychia.¹ In addition, EGFR inhibitors can induce fatal SCARs, initially mimicking mucositis or papulopustular eruptions, including SJS/TEN, DRESS, and AGEP.^{26,27} From the literature search, five SJS, two SJS/TEN, and five TEN cases induced by EGFR inhibitors were reported in total. In spite of being rare, SJS/TEN should be distinguished from EGFR inhibitor-related mucositis if mucosal lesions are accompanied by fever, constitutional symptoms, and severe painful erythema or blisters noted over mucosa and skin as well. Skin eruptions with SJS/TEN usually present as erythematous spots progressing into painful targetoid erythema with truncal distribution, which is different from the papulopustular eruption induced by EGFR inhibitors.^{25,28} Three patients have been found to have cross-reactivity to alternative EGFR inhibitors, although one report showed successful treatment with gefitinib in an afatinib SJS patient with adenocarcinoma of the lung.²⁹ The pathomechanism underlying EGFR inhibitor-induced SJS/TEN could be due to interference of epidermal differentiation and re-epithelialization by the irreversible inhibition of EGFR, ultimately resulting in extensive erosions. This is different from typical SJS/TEN, which is a delay-type hypersensitivity reaction where cytotoxic T cells generate and release granulysin, a cytotoxic protein responsible for

disseminated keratinocyte death.^{30,31} In one reported case of afatinib SJS, the patient had no sign of fever, no ocular and genital mucosae affected, and no obvious epidermal necrosis detected histopathologically, which is inconsistent with typical SJS.³⁰ As such, the diagnosis and pathophysiology of EGFR inhibitor-induced SJS/TEN need further elucidation.

KIT and BCR-ABL inhibitors

KIT and BCR-ABL inhibitors, such as imatinib, nilotinib, and dasatinib, are tyrosine kinase inhibitors used for the treatment of Philadelphia chromosome-positive chronic myeloid leukemia and gastrointestinal stromal tumors.^{32–34} Their utilization has extended to different tumors and accomplished a first-line position in cancers like Philadelphia chromosome-positive acute lymphoblastic leukemia, advanced dermatofibrosarcoma protuberans, hypereosinophilic syndrome, and systemic mastocytosis.³⁵ Among these agents, imatinib is the major targeted anticancer drug to induce SCARs, including twelve SJS/TEN, four DRESS, and four AGEP. Cutaneous adverse effects of imatinib are common and have been well described. Of these, maculopapular rashes and facial edema occur most commonly, with incidence of 66.7% and 65.0%, respectively.³⁶ Maculopapular rashes usually develop on average about 9 weeks after initiation. The incidence of cutaneous reactions with imatinib has been reported to increase with escalating doses of the drug, indicating that these conditions may be related to the pharmacologic effects of the drug, rather than to hypersensitivity.³⁷ Besides, in one multivariate analysis, female sex and daily dose of imatinib were independent risk factors for the development of rashes.³⁶ These cutaneous events with dose-dependent manifestations may need temporary discontinuation or dose reduction.¹ Moreover, the pathomechanism of SJS and DRESS is immunorelated, and further rechallenge with a dose reduction is not usually suggested.^{38,39} However, several cases have been tolerated well under slow titration with or without prednisolone use.^{40–44}

Multikinase inhibitors

Multikinase inhibitors are small-molecule inhibitors of VEGF tyrosine kinase and also inhibit other tyrosine kinases (PDGFR, EGFR, KIT, Ret, FLT3, CSF1R, and Raf).⁴⁵ This class of agents, including sorafenib, sunitinib, pazopanib, regorafenib, and vandetanib, has been approved for the treatment of patients with renal cell cancer, gastrointestinal stromal tumors, hepatocellular cancer, and colorectal cancer.⁴⁶ These drugs often cause notorious hand–foot skin reactions and other skin eruptions, such as maculopapular eruptions, stomatitis, and genital erosions.^{47–49} Among these medica-

tions, higher frequency of cutaneous toxicity has been found in patients using sorafenib.¹ Hand–foot skin reactions are severe, painful edematous erythema lesions on the palms and soles, and even progression with blistering or hyperkeratotic plaques.⁴⁹ Skin eruptions with variable morphology have been reported, particularly morbilliform eruptions in the early weeks after initiation.¹ The infrequent genital or perineal involvement with erosion is also characteristic of multikinase inhibitor-related ADRs, and this manifestation should be distinguished from SJS or fixed drug eruptions.^{1,48,50} Based on the literature search, three sorafenib SJS/TEN and three sorafenib AGEF cases have been reported. One patient who restarted sorafenib treatment for 2 weeks after administration of sorafenib for 1.5 years and then a temporal discontinuation for 1 month suffered from TEN.⁵¹ Considering that SJS/TEN is a delayed-type hypersensitivity, sensitization of 1.5 years could be too long. Further, the authors proposed that the concomitant oral tosufloxacin may have contributed to the development of the skin manifestation by inhibiting sorafenib metabolism, since both drugs are metabolized by cytochrome P450 family enzymes in the liver.⁵¹ The pathogenesis involved in the cutaneous toxicity due to multikinase inhibitors is believed to be related to direct VEGF inhibition, vessel regression, and negative effects on vascular repair capacities.⁵² Furthermore, our previous study has revealed that keratinocyte death in sunitinib-induced hand–foot skin reaction was mediated via Fas/FasL.⁵³ Recently, Zimmerman et al demonstrated a pathway by which sorafenib enters keratinocytes through OAT6 (an uptake carrier of sorafenib) and then causes keratinocyte cytotoxicity driven by inhibition of MAP3K7 (Tak1).⁵⁴ These predisposing factors can promote skin toxicity once severe epidermal necrolysis occurs in patients who used this class of medications and delay wound healing. Moreover, the incidence of sorafenib-induced erythema multiforme is much higher in Japanese patients than in white populations.⁵⁵ It could be reasonable to speculate that genetic background in different ethnicities may play a role in the pathogenesis of this ADR.

Monoclonal antibodies to CD20

Rituximab is a chimeric (mouse–human) monoclonal antibody to target CD20⁺ blood cells for treating non-Hodgkin lymphoma, chronic lymphocytic leukemia, and some autoimmune diseases, such as pemphigus, bullous pemphigoid, and rheumatoid arthritis.^{56–58} There were two SJS, two SJS-TEN, and one TEN caused by rituximab in several case reports. The diagnosis of SJS from one previously published case report might have been erroneously associated with rituximab, since

the clinical presentation, histopathology, and nature course in the case report were mimicking paraneoplastic pemphigus (PNP).⁵⁹ PNP is a fatal mucocutaneous blistering disorder associated with hematologic malignancies.⁶⁰ PNP shares overlapping clinical features with SJS, including severe mucositis, flaccid sloughing bullae, keratinocyte necrosis histopathologically, and possible pulmonary involvement with features of bronchiolitis obliterans.⁶¹ Nevertheless, refractory chronic mucositis with polymorphous PNP skin lesions is different from an acute, rapidly progressing course with targetoid lesions of SJS/TEN. Typical histopathological features with suprabasal acantholysis, lichenoid interface dermatitis, positive DIF/IIF, and immunoblotting recognition of envoplakin and/or periplakin can support a diagnosis of PNP.^{61,62} In cases of suspicious rituximab SJS/TEN, DIF or IIF has been suggested to exclude PNP.⁵⁹ Moreover, rituximab is usually prescribed with concomitant bendamustine or allopurinol, which adds a difficulty to assessing causality. In five rituximab SJS/TEN, three cases were independent from the use of bendamustine or allopurinol. Also, seven rituximab TEN cases have been reported without concomitant allopurinol, bendamustine, or nonbendamustine chemotherapy based on the US Food and Drug Administration adverse event reporting system.⁶³

BRAF inhibitors

BRAF inhibitors, including vemurafenib and dabrafenib, have emerged as a remarkable anticancer therapy and improved the survival of melanoma patients carrying *BRAF*^{V600E/K}.⁶⁴ Cutaneous adverse events induced by BRAF inhibitors vary from skin eruptions with photosensitivity, folliculocentric morbilliform eruptions, hyperkeratotic hand–foot skin reactions, and panniculitis to secondary epidermal neoplasms (verruca keratoses, squamous-cell carcinoma, and keratoacanthoma).^{65–67} In our survey, vemurafenib was the most notorious drug to cause TEN among the anticancer-targeted drugs. Of note, one case with vemurafenib-induced TEN was reported after nivolumab failure and another with vemurafenib SJS after initiation of ipilimumab.^{13,68} Development of grade 3 rash was found to be significantly higher with vemurafenib treatment after administration of ipilimumab.⁶⁹ The reduction in immuncheckpoint inhibition may predispose patients to skin hypersensitivity reactions caused by vemurafenib.⁶⁹ This phenomenon might be explained by immuncheckpoint inhibitor strongly provoking activation of CD8⁺ cytotoxic T cells, which are also the key cellular mediators in SJS/TEN. In addition, biopsy of skin metastases during nivolumab

treatment has also shown evidence of CD8⁺ T-cell infiltrations.⁶⁸ A successful switch from vemurafenib to dabrafenib has been reported in one vemurafenib TEN patient.⁷⁰ Dabrafenib may thus be considered a relatively newer and safer alternative treatment option for vemurafenib. However, another vemurafenib TEN patient who underwent an LTT assay confirmed the causality of vemurafenib and positive cross-reactivity for dabrafenib.¹⁴ Besides, cross-reactivity has also been found between vemurafenib and the sulfonamide antibiotic sulfamethoxazole, but not seen in trametinib.¹⁴ Based on the cross-reactivity reaction due to structural similarity between the drug with sulfonamide compounds, such as sulfamethoxazole and vemurafenib or dabrafenib, the use of sulfonamide compounds in patients with vemurafenib S CAR was not suggested.

Immuno-oncology therapies

Immunotherapies are developing innovative therapeutics with significant advances in treatment for melanoma, non-small-cell lung cancer, and renal cell carcinoma, etc.^{71–73} Therapeutic monoclonal antibodies targeting the coinhibitory immunocheckpoints have been associated with vitiligo, pruritus, morbilliform eruptions, lichenoid dermatitis, delayed type hypersensitivity, and autoimmune bullous disease.⁷⁴ Although uncommon, SJS/TEN related to anti-PD1 (nivolumab and pembrolizumab) and anti-CTLA4 (ipilimumab) has also been reported. In total, three SJS/TEN cases associated with conventional immunotherapies (recombinant IL2) – aldesleukin (n=2) and denileukin (n=1) – were described.^{75–77} For newly developed immunotherapies, there have been nivolumab TEN, four pembrolizumab SJS, one ipilimumab SJS, and one ipilimumab TEN case.^{78–84} These patients were diagnosed with advanced metastatic melanoma, metastatic nasopharyngeal carcinoma, and metastatic sarcomatoid renal cell carcinoma. The drug latency to induce SJS/TEN varied from 7 days to 140 days. Two melanoma patients suffered from morbilliform eruption and progressed to TEN over 39 days to 3 months after receiving nivolumab treatment.^{16,78} Initial biopsy of these two nivolumab TEN cases showed interface dermatitis that further progressed into full-thickness epidermal necrosis.¹⁶ By immunohistochemistry staining, increased expression of PDL1 was evident on skin-infiltrating T cells and keratinocytes at foci of lymphocytic epidermal infiltration in the epidermis.^{16,79} PDL1 is not usually detectable in skin, but the use of anti-PD1 therapy could increase the expression of PDL1 in keratinocytes and permit the activated CD8⁺ cytotoxic T cells to target keratinocytes, leading to keratinocyte apoptosis.⁷⁹ Notably, the gene expression profile of anti-PD1-induced adverse cutane-

ous eruption was similar to that of SJS/TEN, but different from that of acute cutaneous graft-versus-host disease or maculopapular rashes.⁷⁹ Anti-PD1-treated patients and SJS/TEN patients shared similar gene expression profiles, with upregulation of major inflammatory chemokines, including CXCL9, CXCL10, and CXCL11, cytotoxic mediators, such as PRF1 and GZMB, and the proapoptotic molecule FASLG.⁷⁹ Bullous pemphigoid, an autoimmune bullous mucocutaneous disease, induced after initiation of immunotherapy has also been reported.⁸⁵ To clarify further, a diagnosis of SJS/TEN, DIF or IIF can help eliminate the possibility of autoimmune bullous diseases.

Drug rash with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome

Although relatively rare, nine cases of DRESS/DIHS caused by imatinib (n=4), vemurafenib (n=3), bortezomib (n=1), and ipilimumab (n=1) have been reported. Many targeted anticancer drugs, including KIT, BCR-ABL inhibitors, multikinase inhibitors, BRAF inhibitors, MEK inhibitors, CTLA4 inhibitors, and PL1 inhibitors, can result in aspecific maculopapular eruptions.^{1,86} Distinguishing maculopapular rashes from DRESS is important, mainly because there are prognostic differences. Concomitant generalized maculopapular rashes with facial edema could overlap characteristics of DRESS, but the lack of systemic involvement with fever, eosinophilia, atypical lymphocytosis, and hepatic or renal function impairment can help distinguish from DRESS.^{9,87} Typically, the cutaneous manifestation of DRESS progresses from maculopapular exanthema into infiltrative erythema and purpuric changes beyond lower extremities.

Acute generalized exanthematous pustulosis

In our search, 11 cases of AGEPS caused by imatinib (n=4), sorafenib (n=3), gefitinib (n=2), vemurafenib (n=1), and ipilimumab (n=1) were identified.^{88–91} AGEPS usually presents as pinhead-sized “nonfollicular” pustules on an erythematous base, starting mainly on the fold area (axillary, inguinal, and submammary) and spreading quickly to the trunk and limbs with further characteristic large-sheet collaret desquamation.⁹² AGEPS should be differentiated from the common acneiform papulopustular eruptions caused by EGFR inhibitors. It is characteristic of a “folliculocentric” erythematous papule or pustule with dominant distribution in sebaceous gland-rich areas, such as the scalp, face, upper trunk.⁹³ Although the acneiform eruption caused by EGFR inhibitors may involve

the lower trunk, buttocks, and extremities, histopathology can help to distinguish between these two entities. The major histopathologic findings of acneiform eruption are superficial suppurative folliculitis with neutrophilic infiltrate with ectatic follicular infundibula and rupture of the epithelial lining.⁹⁴ In contrast, AGEF typically shows subcorneal and/or intraepithelial pustules, an edematous papillary dermis with exocytosis, and perivascular infiltrates of neutrophils and eosinophils.^{95,96} Occasionally, dyskeratosis or necrosis of keratinocytes can be seen in AGEF.⁹⁷ In addition, systemic manifestation with fever and neutrophilia require attention to be paid to AGEF, and further short-term topical and corticosteroid treatment may be considered.⁹⁸

Simultaneous predisposing factors

About one-third of reported cases have been exposed to multiple medications during the same period of anti-cancer-targeted therapies (Table 4). Among these medications, there were some notorious drugs to cause SCARs, including allopurinol, phenytoin, and sulfamethoxazole. Multiple concomitant medications increase complexities

and difficulties in identifying the offending medication. The Naranjo score and algorithm of drug causality in epidermal necrolysis are considered the standard assessment tools to evaluate the causality of ADRs and SJS/TEN, respectively.^{99,100} Few cases reported in the literature were evaluated by these scoring algorithms. In addition, the use of multiple medications increased the risk of ADRs and also for pharmacokinetic and pharmacodynamic drug interactions.^{101,102} Moreover, several predisposing factors were discussed in this review. One patient developed erlotinib SJS after herpes zoster superinfection.²⁶ Exposure to radiation was a common factor seen in cancer patients with SJS/TEN.² There was one cetuximab SJS/TEN overlapping with radiotherapy for squamous cell carcinoma of the hypopharynx and larynx and two pembrolizumab SJS patients received radiotherapy before skin eruption (one with whole-brain radiotherapy and concomitant phenytoin use and the other with radiotherapy for bone metastases).^{80,84,103} Moreover, the initiation of immuncheckpoint inhibitors may also predispose patients to skin hypersensitivity reactions and SJS/TEN.^{13,68,69,104}

Table 4 Targeted anticancer therapies and immunotherapy-induced severe cutaneous adverse reaction cases with multiple concomitant medication (n=24)

Agent	Coadministered medication	Phenotype	Reference
Afatinib	Carboplatin, pemetrexed, esomeprazole, and sulfamethoxazole	SJS	30
Brentuximab vedotin	Naproxen	SJS	137
Brentuximab vedotin	Piperacillin–tazobactam, omeprazole, morphine, granisetron, pregabalin, and amisulpride	TEN	138
Cetuximab	Minocycline	TEN	111
Cetuximab	Camptothecin-II	SJS	112
Gefitinib	Pemetrexed and cisplatin	TEN	114
Imatinib	Ibuprofen	SJS	117
Imatinib	Mercaptopurine	SJS	42
Imatinib	Allopurinol and sulfamethoxazole–trimethoprim	SJS	89
Imatinib	Fludarabine, busulfan	SJS	121
Imatinib	Allopurinol	SJS	122
Imatinib	Lansoprazole	SJS	123
Imatinib	Allopurinol	DRESS	124
Pembrolizumab	Phenprocoumon, spironolactone, acetylsalicylic acid, bisoprolol, metamizole, rabeprazole, mirtazapine, lorazepam, torasemide, ramipril, oxycodone, and dalteparin	SJS	80
Pembrolizumab	Phenytoin (with whole-brain radiotherapy)	SJS	81
Rituximab	Bendamustine	SJS/TEN	135
Rituximab	Allopurinol and bendamustine	SJS/TEN	63
Sorafenib	Tosufloxacin	TEN	51
Sorafenib	Furosemide, spironolactone, and lansoprazole	AGEP	129
Vemurafenib	Ipilimumab	SJS	13
Vemurafenib	Valproate	TEN	142
Vemurafenib	Levothyroxine sodium	TEN	68
Vemurafenib	Metoprolol and hydrochlorothiazide	DRESS	144
Vandetanib	Temozolomide	TEN	116

Abbreviations: AGEF, acute generalized exanthematous pustulosis; DRESS, drug rash with eosinophilia and systemic symptoms; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

Causative drug validation

To confirm a potential offending drug, drug provocation is a gold standard. However, rechallenge is generally avoided, because of the potentially fatal consequences. Clinically, the drug notoriety scoring systems, including Naranjo score and algorithm of drug causality in epidermal necrolysis (for SJS/TEN only), have been implemented to assess the causality of ADRs.^{99,100} In vitro, a positive LTT is helpful for identifying causality and cross-reactivity.¹⁰⁵ The LTT is a reproducible test that measures enhanced proliferative response of peripheral blood mononuclear cells after sensitization of T cells to a drug.¹⁰⁵ Its relevance in DRESS/DIHS and AGEP is relatively higher than in SJS/TEN.¹⁰⁶ To avoid cross-reactivity in patients with a history of severe hypersensitivity reactions to medications with similar structures, an LTT may be considered before prescription. It is worth mentioning that sensitivity varies with diverse drugs and different timing among studies, and a negative result does not rule out the possibility of reactivity or cross-reactivity.^{106,107} After an LTT, no evidence for a drug-specific immunoresponse to concomitant medication was revealed in one pembrolizumab SJS case.⁷⁹ Moreover, in vivo patch tests may also provide a low-risk method to validate delayed hypersensitivity with suspected offending drugs or alternative drugs.¹⁰⁸

Conclusion

SCARs are potentially life-threatening cutaneous adverse events in patients treated with targeted anticancer drugs and immunotherapies. Patients with malignancies usually have additional comorbidities, multisystemic involvement, and multiple concomitant medications and treatment modalities, all of which may increase the complexities and difficulties in managing SCARs in cancer patients. It is important to recognize SCAR reactions earlier, distinguish SCARs from other nonfatal dermatologic toxicities, and discontinue causative agents rapidly. Further studies are needed to investigate specific pathomechanisms and develop proper management for this lethal disease in particular in these high-risk cancer patients.

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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