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Life-threatening Dermatologic Adverse Events in Oncology

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Abstract

Background: The incidence of life-threatening toxicities such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are inconsistently reported. The potential association of anticancer agents with SJS or TEN has not been systematically investigated.

Methods: We searched the literature (Ovid:1950-June 2013 and PubMed:1948-June 2013) using terms for SJS/TEN and anticancer therapy. Primary case reports, case series, and clinical trials were included. Additionally, MedWatch, Food and Drug Administration Adverse Event Reporting System (FAERS), was searched (1968-August 2012) for SJS/TEN reports associated with anticancer therapies. Proportional reporting ratios (PRR>2, N>3) and empirical Bayes geometric mean (EBGM>2, N>3, lower 95% confidence interval (EBGM_{0.05} >2) were used as thresholds to constitute a signal of association between SJS/TEN and anticancer drugs.

Results: There were 45 SJS and 37 TEN cases associated with 17 and 22 anticancer drugs in the literature, respectively. Among cases in FAERS, significant signals were associated with SJS for bendamustine and with TEN for bendamustine, busulfan, chlorambucil, fludarabine, lomustine, and procarbazine .

Conclusion: Several drugs reported in published literature to be associated with SJS/TEN were not found to have significant signals in FAERS. Proactive pharmacovigilance to detect and define

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safety signals serves to assist oncology practitioners in the recognition of possible, yet uncommon, serious and/or life-threatening skin reactions.

Keywords

Stevens-Johnson syndrome; Toxic Epidermal Necrolysis; Chemotherapy; Adverse Drug Event

Introduction

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are rare but severe mucocutaneous blistering disorders that represent distinct entities within a spectrum of a single disease with common causes and mechanisms [1-3]. The incidences of SJS and TEN are estimated to be in the ranges of 1-6 and 1-3 cases per million person-years, respectively [4,5]. Despite their rare occurrence, increased recognition, and improved management, overall mortality remains significant, ranging from 1-10% for SJS and 20-40% for TEN, respectively [6-9]. Contrary to this, non-life threatening dermatologic toxicities such as alopecia, nail abnormalities, or rashes secondary to anticancer drugs are frequently reported, with well described incidence, occurring in a majority of patients for some agents [10]. Moreover, while the association of various anticancer drugs with rare, yet clinically significant life-threatening serious adverse events (SAEs) such as SJS or TEN have been anecdotally reported, the association has not been systematically examined. In the clinical realm, the putative association of oncology drugs with SJS or TEN may lead to physician and patient distress with consequent alterations in therapy, all of which may preclude additional dosing and affect clinical outcome.

There are various approaches to recognizing an association and assessing the risk between drugs and SAEs [11]. Information obtained from clinical trials and case reports may serve as one step in identifying potential association. However, interpretation of such data for association is limited, and epidemiologic studies deriving sufficient data are usually necessary to identify associations and establish causality [11]. In addition to these traditional methods, various data mining algorithms have been designed to assist with the assessment of rapidly growing databases of spontaneously reported SAEs [12]. The United States Food and Drug Administration Adverse Event Reporting System (FAERS) utilizing MedWatch represents one such database that can be analyzed utilizing data mining algorithms [13]. While this method may not be sufficient to identify true associations, and particularly doesn't establish causality, it does serve as an additional tool to identify disproportionality in rates of reports that may warrant further investigation [14]. This study aimed to examine the relationship between anticancer agents and SJS or TEN by analyzing data from peer-reviewed published literature as well as the FAERS database.

Materials and Methods

A literature search was performed through June 2013 (Ovid from 1950 and PubMed from 1948) using the terms: Stevens Johnson syndrome, toxic epidermal necrolysis, cancer drug therapy, and chemotherapy drugs. In addition, each anticancer agent reported in this paper was searched separately using appropriate terms. Ovid was utilized to accomplish Embase search. We included only reports with anticancer drugs used specifically for treatment of any cancer, except when such information was not provided. Histologic confirmation of SJS or TEN was not required for a report to be included in the results. Primary case reports and reports from clinical trials, or as part of post-marketing surveillance, were included in the results. All published peer-reviewed literature from the search was reviewed (reports were limited to English language only with inclusion of selected non-English reports with English language abstracts) to identify drugs that were administered within 8 weeks of rash onset

and/or concomitantly with the anticancer agent to which SJS/TEN was attributed. Other parameters such as concomitant radiotherapy and SJS/TEN outcomes were noted when available. In addition, as part of the RADAR (Research on Adverse Drug events And Reports) project [15], the FAERS database was searched for reports of SJS and TEN in association with anticancer agents as suspect drugs from 1968 through August 2012 (the most recent date for available FAERS data release) [16].

Proportional reporting ratios (PRR) ($PRR > 2$, $N > 3$) and empirical Bayes geometric mean (EBGM) lower 95% confidence interval ($EBGM_{0.05} > 2$, $N > 3$) were used as thresholds, constituting signals for disproportionate reporting of SJS or TEN for the selected anticancer drugs [12]. Data from the FAERS or other voluntary adverse event reporting system can be used to estimate whether a particular adverse event for a drug may be a “signal” that the event occurs in a greater frequency among patients receiving the drug than would be expected by chance. There are several estimates commonly used and all use similar methodology [17,12,18]. The proportional reporting ratio (PRR) is the simplest and easiest to perform. The PRR is a statistical aid based on the proportionate approach that is based upon the stability of a large database. It involves calculation of the proportions of specified reactions for drugs of interest where the comparator is all other drugs in the database. Judgment about whether or not there is a signal and its strength is made on the basis of three pieces of information: (1) the PRR value and the 95% confidence interval of the PRR, (2) the chi square value for the 2 by 2 table, and (3) the number of cases reported. A signal is defined as a PRR of 2 or greater, a chi square of at least 4, and 3 or more cases.[17]

An alternative is the empiric Bayes geometric mean (EBGM) which is a quantitative method that decreases the relative importance of small numbers of reports that may be subject to greater statistical variability. Thus EBGM decreases the signal to noise ratio and provides a value that is less prone to false positive signals.[17] Similar to the PRR, the EBGM mean values with 95% confidence intervals are used to determine whether the number of cases in AERS were relatively greater than for other drugs. If the EBGM confidence interval at the 0.05 cutoff is greater than 2 and number of cases > 1 , the signal is considered positive.[14]

Limitations

The limitations of the PRR and EBGM stem from the voluntary nature of adverse drug reaction reporting to the FDA. It is reported that fewer than 10% of adverse drug reactions are reported to spontaneous reporting systems such as MedWatch.[19] Health professional reasons such as lack of awareness and lack of time are associated with under-reporting.[19] Additional factors such as publicity associated with a specific adverse drug reaction, its seriousness, market size, and the inability to verify a drug/reaction relationship also impact the likelihood of the event being added to the system.[20] Since PRR/EBGM represent an estimate of the comparative reporting rates for specific reactions to individual drugs, these rates may be affected by under-reporting that may be disproportionate between drugs. [17,12] Therefore the PRR/EBGM is not used as definitive evidence, but as a finding that, with supporting information signal that a relationship between the drug and reaction exists. Additional factors such as consistency of the event descriptions and causality indicators (e.g. timing between exposure and event, dechallenge, rechallenge, blood levels), and biological explanation of the event should be used to verify the signal-event relationship.[21]

The FAERS database search methodology was based upon the SJS and TEN reaction terms and all anticancer drug names. MedWatch reports included those in which anticancer agents were used to treat cancer or other non-cancer diseases. Drugs used to treat cancer symptoms (e.g. pain) or side effects of treatment (e.g. anti-nausea agents, infection) were not included in the FAERS searches. Furthermore, the anticancer agent had to be listed as the primary or

secondary suspect drug in FAERS, as determined by the reporter. Anticancer drugs listed as concomitant drugs in the MedWatch report were therefore excluded.

Results

Search of peer-reviewed literature yielded 46 reports of SJS in association with 18 anticancer agents [22-54]. Similarly, 37 reports of TEN associated with 22 anticancer agents were identified [55-82,46,83-89] (Table 1). A majority of SJS or TEN reports were in published literature. However, one TEN and 11 SJS reports associated with lenalidomide in patients with an underlying malignancy were reported to the pharmaceutical company in the setting of a published clinical trial [46]. SJS in association with docetaxel[31] (N=1), tegafur-gimeracil-oteracil potassium (TS-1)[47] (N=1), methotrexate[34] (N=2), gemcitabine[38] (N=1), and fludarabine[42] (N=1), and TEN in association with bivatuzumab mertansine[83] (N=1) and treosulfan[84] (N=1) were also reported in the setting of clinical trials. In 31 reports of SJS, patients were exposed to other drugs either concomitantly or within 8 weeks of the anticancer agent(s), but prior to the reaction (Table 2). Similarly, in 27 TEN reports, exposure to other drugs and/or radiation was reported (Table 3). Among SJS reports, the outcome was available in 38 reports, 9 of which were fatal. Five (63%) of the 9 reports of fatality were attributed to SJS. Similarly, the outcome was available for 38 TEN reports, among which there were 16 (50%) deaths, with 13 (41%) attributed to TEN.

Search of the FAERS database yielded 2098 reports of SJS and 1555 reports of TEN associated with anticancer drugs. Of these, 6 FDA approved drugs were reported at rates sufficient to produce significant signals (Table 4). Among the 6 chemotherapies with significant signals for TEN, reports for 2 (chlorambucil and procarbazine) were also identified in the literature. In contrast, all the anticancer agents that were identified in peer-reviewed literature, except lenalidomide, bivatuzumab mertansine, TS-1, peplomycin, and mithramycin, were also found in the FAERS database in association with SJS or TEN. However, these agents did not satisfy safety signal criteria ($PRR > 2$, $N > 3$ and $EBGM_{0.05} > 2$, $N > 3$) and were not included in results. Table 5 displays the other cancer drugs reported as suspect drugs for TEN and/or SJS, but the number of cases were insufficient to result in significant signals.

For the anticancer drugs identified in the FAERS database (Table 4) associated with less than 10 adverse reaction reports and a significant signal, we further examined the reports for evidence of concomitantly administered drugs. In all cases except for one report of bendamustine associated with SJS, patients were exposed to other drugs, including those commonly associated with SJS/TEN, such as allopurinol, sulfonamide antibiotics, anti-convulsants, and corticosteroids.

Discussion

SJS and TEN are severe and potentially fatal disorders involving mucosal and cutaneous tissue that are characterized by extensive epidermal detachment associated with keratinocyte necrosis. Their classification is based on the percentage of Total Body Surface Area (TBSA) of epidermal detachment [3]. Involvement of less than 10% of TBSA is termed SJS, while epidermal detachment greater than 30% may be characterized as TEN. SJS/TEN overlap syndrome includes cases that affect between 10 and 30 % of TBSA [3]. There is typically a prodromal period with flu-like symptoms followed by onset of rash. Characteristic erythematous dusky-red macules typically involve the trunk, neck, face, and extremities. Histological analysis reveals full thickness epidermal necrosis, often with dermal-epidermal attachment. It should be emphasized that histology is rarely diagnostic in itself, but rather is

used as an aid to confirm the clinical picture. Greater than 90% of patients have involvement of oral, ocular, and genital mucosa [90,91]. In the past, SJS and TEN were conceptualized to represent a part of the spectrum including clinical entities such as erythema multiforme major (EMM) and the two terms (SJS and EMM) were used interchangeably. It is now widely accepted, however, that SJS and TEN differ from EMM both in clinical presentation and underlying etiologies [92]. Where it was indistinguishable in the past, these reports have been included for review.

Drugs are still the predominant cause of SJS, ranging from 50% to 80%, with other less common etiologies including infection, vaccination, and chemical exposure [93,90]. Similarly, at least 80% of TEN cases are associated with drug exposure [93]. The most frequent suspect drugs for SJS/TEN are sulfonamide antibiotics, anticonvulsants, non-steroidal anti-inflammatory drugs (NSAIDs), allopurinol, and corticosteroids [4,94-96].

Our search of peer-reviewed literature revealed multiple cases reporting a potential association of anticancer drugs with SJS and TEN, including conventional cytotoxic and novel targeted agents (Table 1). The interpretation of these results, however, is not without limitations and should be performed with caution. Among identified reports in our study, fourteen were published [33-36,45,88,57,75,77,78,80,87,86,85] prior to the introduction of the currently used classification system, which is based on the degree of BSA involvement, and would have been categorized differently at present. Moreover, the diagnosis was made on clinical grounds in the majority of cases, without a histopathologic confirmation. In a case of interleukin-induced TEN, the biopsy revealed bullae underneath the stratum corneum without a true dermoepidermal separation, and authors categorized this as a “TEN-like reaction” [57]. In another case, the diagnosis of TEN in association with chlorambucil was made despite the histopathologic findings of chronic vasculitis.

The main difficulty in attempting to identify anticancer therapies that may potentially serve as triggers stems from the frequent co-administration of not only multiple anticancer agents but also drugs that are known to have strong associations with these cutaneous reactions (e.g. sulfonamide antibiotics, corticosteroids, allopurinol). In the majority of published case reports patients were exposed to multiple agents (Table 2 and 3). In fact, in a case of TEN in the setting of cladribine therapy, intrinsic imputability (possible cause between drug and clinical event) scores were “likely” for concomitantly administered sulfonamide antibiotics. Similarly, in one case of SJS developing during therapy with imatinib, according to Naranjo’s algorithm [97] (a questionnaire designed for determining the causality in evaluation of an adverse reaction to a drug), SJS was “possible” due to imatinib and “probable” due to lansoprazole [23]. Of note, in all 4 cases of TEN associated with thalidomide, systemic corticosteroids were administered [65-68]. Although, corticosteroids have been reported as common triggers of SJS/TEN, their role as triggers is not clearly defined and there is a high potential for confounding [95]. However, a recently introduced algorithm of drug causality for epidermal necrolysis (ALDEN) demonstrated corticosteroids to be “probably causal” in their relation to SJS/TEN [98]. Although multiple authors have attempted to attribute reactions to a particular anticancer agent either alone or in combination with other agents, causality remains difficult to ascertain.

Cancer patients often have co-morbidities and multi-organ involvement by the underlying disease, which add to the overall complexity of each individual case analysis. It is also likely that in some cases interaction between different anticancer agents may contribute to the development of SJS/TEN. To improve our ability to optimally interpret case reports, thorough documentation of clinical history, renal and hepatic functions, and exposure to all drugs with precise dates in chronological order, when possible, should be performed. In

addition, the process of identifying the offending agent requires knowledge of the individual drug's and relevant metabolite's half-life and the temporal relationship to the onset of rash.

Several cases in which no other concomitant drugs were reported and an anticancer agent was presumed to be the offending agent were also identified. This was particularly noted with imatinib associated SJS, where in 5 of 8 cases it was the only agent to which the patient was exposed [22,24,25,28,50]. However, while case reports may heighten our suspicion of a specific association, by themselves, they are insufficient to establish causality [11]. Furthermore, in many instances, insufficient clinical information may be provided, thereby limiting detailed analyses. In the identified published case reports, management strategies ranged from only supportive care to various combinations of systemic steroids, intravenous immunoglobulin (IVIG) therapy, and/or systemic antibiotics, which is consistent with the generally accepted approach to treatment of SJS/TEN. In many cases granulocyte colony stimulating factor (GCSF) was administered for concomitant neutropenia, which is a frequent complication of chemotherapy treatment. For cases where outcome was available, estimated mortality attributed to SJS and TEN was 16% and 40%, respectively, which reflects mortality to these syndromes [6-9].

FAERS utilizes MedWatch as a voluntary adverse event (AE) reporting system that is primarily directed toward post-marketing surveillance. AEs associated with prescription and over-the-counter FDA-approved drugs, biologics, medical devices, and nutritional products are reported using MedWatch. Despite the availability of the FAERS database for reporting and obtaining information on a variety of adverse effects from drugs, biologics, and nutritional products, its interpretation is not without limitations. First, duplicate reports are possible in a case of a single drug reaction. To detect duplicate reports for a single drug reaction patient demographics (age, gender), date of reporting, reported diagnosis, outcomes, and patients' concomitant drug lists were assessed. Duplicate reporting within a single drug/reaction was not identified for any of the drugs that met our safety signal criteria (Table 4). Additionally, some patients had both SJS and TEN reactions reported. In these situations, the reports were included in the analysis of both SJS and TEN drugs. Second, calculations of incidence, for example, cannot be performed based on these data. This is partially because it is not mandatory to report adverse drug events (ADEs) or to establish causality prior to reporting to FAERS database. Also, utilization data are not available in the FAERS. Both health-care workers and consumers can submit reports, thus data are often incomplete for appropriate analysis [99], and may not consistently include a listing of all concomitantly administered drugs. Given these limitations, PRR and EBGm are accepted methods for identifying signals from FAERS data [12].

Using our pre-defined thresholds for signals of disproportionate reporting, we have identified multiple anticancer drugs reported in association with SJS/TEN in the MedWatch database (Table 4). The majority of these agents, however, were not found in association with SJS/TEN in our search of the peer-reviewed literature. This discrepancy may be partially due to the fact that our search of the FAERS database included chemotherapy drugs used to treat both cancer and non-cancer diseases, while our search of the literature was limited to cases of cancer treatment. Moreover, several studies have demonstrated a significant and widespread underreporting of drug adverse effects in healthcare, which has been estimated to exceed 90% [100,19,101]. The discrepancy in the number of cases between the sources used in our search may reflect the existing underlying inconsistencies and inadequacy of reporting in general. The chosen threshold for our data mining algorithms ($PRR > 2$, $N > 3$) and ($EBGM_{0.05} > 2$, $N > 3$) may be too "sensitive", resulting in an increased number of identified associations that may not necessarily have clinical significance. To further investigate potential confounding factors, we explored if other drugs, including those commonly associated with SJS or TEN, were concomitantly administered with anticancer

agents that were associated with less than 10 cases of SJS or TEN. With the exception of one case of SJS associated with bendamustine, other co-administered drugs or anticancer therapies were reported for each case. In many instances, patients were exposed to drugs with an established association with SJS or TEN, such as anti-epileptic agents, sulfonamide antibiotics, and allopurinol. Thus, the interpretation of these cases is difficult and the degree to which anticancer agents contributed to the development of an AE is uncertain. These results are similar to what we observed in peer-reviewed literature. This highlights the difficulty in assessing potential offending agents in cancer patients, since in most cases there is exposure to multi-drug regimens that may include the most common causes of SJS/TEN such as allopurinol and sulfonamide antibiotics.

Published case reports and data mining algorithms from FAERS should not be utilized for defining specific associations in a vacuum. The associations identified should be assessed for pathologic mechanisms and verification using comprehensive patient care datasets. Our objective is to highlight an area in oncology that thus far has not been systematically investigated, and perhaps identify specific anticancer drugs having disproportionately increased frequency in association with SJS or TEN. It has been previously shown that data mining algorithms may have the advantage of identifying reported associations before their appearance and recognition in published literature approximately 30% of time [14]. Even if a significant signal is detected after reports have started circulating in published literature, these data may also serve as an additional method for further defining the level of suspicion [14].

It is critical to establish causality, since attribution to drugs is made erroneously in up to 24% of patients with a suspected cutaneous drug reaction [102]. This flawed attribution has been clearly demonstrated in the oncology clinical research realm, in which up to 50% of AEs attributed to a study drug were reported in the placebo arm of a trial [103]. Directing our attention to specific anticancer agents with the help of data mining algorithms or a critical review of published literature helps identify those that may warrant further investigation. This knowledge can result in earlier consideration of certain anticancer drugs in the differential diagnosis of a patient with SJS/TEN. Making a timely and a correct diagnosis can facilitate discontinuation of a suspected drug, in which case morbidity associated with reactions may be diminished [90]. On the other hand, correctly establishing a negative attribution will allow patients to receive additional necessary therapy. All of this would be expected to optimize attribution and safety in both clinical trials and patient care.

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Table 1

SJS and TEN cases from peer-reviewed literature inclusive of Ovid (1950-June 2013) and PubMed (1948-2013)

Drug	Cases <i>n</i>	Drug	Cases <i>n</i>
Lenalidomide [46,51,54]	13	Thalidomide[68,67,66,65]	4
Imatinib [26-28,24,25,23,22,50]	8	Procarbazine [80,87,79]	3
Docetaxel[31,32,30,29]	4	Methotrexate[63,64,62]	3
Thalidomide[49]	3	Mithramycin[85,86]	3
Methotrexate[33,34]	3	Gemcitabine[61,60]	2
Bleomycin[36,35]	2	Cytarabine[59,58]	2
Mechlorethamine[39]	1	Pemetrexed[81,82]	2
Paclitaxel[40]	1	Cetuximab[71,70]	2
Rituximab[41]	1	Chlorambucil [55,88]	2
Fludarabine[42]	1	Aldesleukin (IL-2)[56,57]	2
Temozolomide[43]	1	Docetaxel[74]	1
Gemcitabine[38]	1	Doxorubicin[75]	1
Capecitabine[44]	1	Imatinib[76]a	1
Cladribine[37]	1	Asparaginase[77]	1
Etoposide[45]	1	6-mercaptopurine[78]	1
TS-1 (tegafur-gimeracil-oteracil potassium)[47]	1	Cladribine[72]	1
Peplomycin[48]	1	Denileukin[73]	1
Verumafenib [53]			
Cetuximab * [52]		TS-1 (tegafur-gimeracil-oteracil potassium) [89]	
Total	46	Lenalidomide[46]	1
		Bivatuzumab mertansine[83]	1
		Treosulfan[84]	1
		Bortezomib[69] ^a	1
		Total	37

^aReported severe epidermal necrolysis

* SJS/TEN overlap

Table 2

Published SJS cases in which patients were exposed to multiple drugs inclusive of Ovid (1950-June 2013) and PubMed (1948-2013)

Author	Suspect Drug	Concomitantly administered drugs/therapy within 8 weeks of onset of skin reaction
Severino[23]	Possible to imatinib and probable to lansoprazole according to Naranjo scale	Lansoprazole
Hsiao[26]	Imatinib	Allopurinol ^a , TMP/SMX ^a , conditioning with busulfan, cyclophosphamide
Hsieh[27]	Imatinib vs allopurinol vs combination	Allopurinol, hydroxyurea
Sawada[29]	Docetaxel	Metoclopramide ^{ab} , famotidine ^{ab}
Kattan[31]	Docetaxel	Estramustine, zoledronic acid
Cuthbert[33]	Methotrexate	Folinic acid, vitamin B12, folic acid, bleomycin ^b , cyclophosphamide ^b , doxorubicin ^b , vincristine ^b , prednisolone ^b
Lee [104]	Methotrexate	procarbazine, dexamethasone, allopurinol, omeprazole
Moe[34]	Methotrexate	Dexamethasone, vincristine, leucovorin, L-asparaginase ^c or 6-mercaptopurine ^s
Giaccone[35]	Bleomycin	Cisplatin, vinblastine
Brodsky[36]	Bleomycin	Cisplatin, vincristine, metamizole sodium (NSAID)
Newman[39]	Topical nitrogen mustard	Naproxen ^a , estrogen ^a , triamterene/hydrochlorothiazide ^a
Hiraki[40]	Paclitaxel	Carboplatin
Lowndes[41]	Rituximab	Chlorpheniramine
Sarma[43]*	Temozolomide and radiotherapy	Phenytoin ^{ab} , diclofenac ^{ab} , radiation, dexamethasone
Talamonti[38]	No specifically presumed culprit	Gemcitabine, 5-FU, radiation
Sendur[44]	Capecitabine	Cyclophosphamide ^c , doxorubicin ^c , fluorouracil ^c
Jameson[45]	Etoposide	Methotrexate, cyclophosphamide ^b , doxorubicin ^b , vincristine ^b , acetaminophen ^b , codeine ^b , compazine ^b
Castaneda[46] ^ψ	Bortezomib in one case	Dexamethasone (8 reports), allopurinol (2), moxifloxacin (1), levofloxacin (1), bortezomib (2), cyclophosphamide (1)
Siniscalchi [105]	Lenalidomide in combination with dexamethasone	dexamethasone
Allegra [106]	Lenalidomide in combination with prednisolone	prednisolone
Lambertini* [107]	Rituximab plus bendamustine	bendamustine

* SJS/TEN overlap

^ψ 11 reports

^aPatients received these drugs for at least 3 months prior to onset of skin toxicity

^bContinuation and/or reinstitution of these drugs after resolution of SJS/TEN did not induce a skin reaction

^cAdministered shortly prior to onset of skin toxicity but difficult to establish the precise time of administration in relation to the onset of the rash

Table 3

Published TEN cases in which multiple drugs were administered inclusive of Ovid (1950-June 2013) and PubMed (1948-2013)

Author	Suspect Drug	Concomitantly administered drugs/therapy within 8 weeks of skin reaction
Rajkumar [65]	Thalidomide in combination with dexamethasone	Dexamethasone
Horowitz [66]	Thalidomide	Phenobarbital ^a , divalproex sodium, dexamethasone, nizatidine, diphenhydramine, bisoprolol
Eo [67]	Thalidomide	Dexamethasone
Colagrande [68]	Thalidomide	Ramipril ^a , amlodipine ^a , thyroxine ^a , aspirin ^a , allopurinol ^a , prednisone
Jones [79]	Procarbazine	Lomustine ^b , vincristine ^b
Yang [62]	Methotrexate with contribution from TMP/SMX	TMP/SMX, 6-MP, leucovorin
Stone [64]	Methotrexate	Folinic acid, prednisolone ^b , vincristine ^b , doxorubicin ^b , cyclophosphamide ^b , L-asparaginase ^b , intrathecal methotrexate ^b , cytarabine ^b
Eyster (2 reports)	Mithramycin	1.) Dexamethasone, radiation, cephalothin 2.) Dexamethasone, radiation, diazepam
Purpora	Mithramycin	Radiation
Sommers [60] [*]	Combination of gemcitabine and radiation	Radiation
Mermershtain [61]	Gemcitabine	Cyproterone ^a , triptorelin ^a
Bosch-Barrera [81]	Pemetrexed in combination with carboplatin and vitamins	Quetiapine ^a , valproic acid ^a , multivitamin, vitamin B12, folic acid, dexamethasone, carboplatin
Then C, et al and Scheinplug K, et al. [108,109]	Pemetrexed in combination with cisplatin	Cisplatin
Tummino [82]	Pemetrexed	Vitamin B12 and folic acid
Lee [71]	Cetuximab with minocycline	Cisplatin ^c , corticosteroids ^c , antihistamines ^c , serotonin 5-HT3 ^c , radiation ^c , minocycline
Segura Huerta [56]	IL-2 (probable according to Naranjo scale)	Dexamethasone, omeprazole, morphine, subcutaneous heparin, radiation
Wiener [57] ^ψ	IL-2	Acetaminophen ^c , diphenhydramine ^c , prochlorperazine ^c , meperidine ^c
Dourakis [74] [§]	Docetaxel	Methylprednisolone
Solberg [75]	Doxorubicin interacting with whole-body radiation	Radiotherapy, trimethoprim-sulfamethoxazole, allopurinol, doxorubicin, cytarabine
Schaich [76] [†]	Imatinib in combination with conditioning regimen and stem	Conditioning with fludarabine and

Author	Suspect Drug	Concomitantly administered drugs/therapy within 8 weeks of skin reaction
	cell transplant	busulfan
Rodriguez [77]	L-asparaginase	Prednisone ^a , allopurinol ^a , compazine isoniazid ^a amikacin, carbenicillin
Meunier [72]	Likely secondary to sulfonamide antibiotic and not cladribine	Sulfonamide antibiotic
Polder [73]	Denileukin	Corticosteroids ^d , vancomycin ^e
Castaneda [46]	Lenalidomide	Dexamethasone, tamoxifen, alendronate
Scheulen [84]	Treosulfan	5-hydroxytryptamine receptor Antagonists, dexamethasone, antibiotics and antimycotic agents (unknown type), PBSCT, cyclophosphamide ^b , GCSF

* Described as SJS/TEN overlap

^ψ Described as a severe generalized drug eruption that resembled TEN

[§] Described as TEN-like reaction Described as severe epidermal necrolysis

^a Patients received this drug(s) for at least 4 months prior to onset of skin toxicity

^b Continuation and/or reinstitution of these drugs after resolution of SJS/TEN did not induce a skin reaction

^c Administered shortly prior to onset of skin toxicity but difficult to establish the precise time of administration in relation to the onset of the rash

^d Administered to treat the first episode of denileukin induced rash

^e Administered between the first episode of the rash and TEN

Table 4

SJS and TEN cases for anticancer drugs from the FAERS database (1968 to October 2012) found to have significant signals.

Drug	Cases	Signals					
		<i>PRR</i>	<i>PRR Lower 95% CI</i>	<i>PRR Upper 95% CI</i>	<i>EBGM</i>	<i>EBGM Lower 95% CI</i>	<i>EBGM Upper 95% CI</i>
SJS							
Bendamustine	27	4.32	2.96	6.31	3.85	2.59	5.57
TEN							
Fludarabine	43	2.88	2.13	3.89	2.72	2.01	3.63
Procarbazine	24	5.21	3.49	7.76	4.90	3.14	7.22
Busulfan	19	3.04	1.94	4.77	2.69	1.68	4.12
Chlorambucil	12	4.87	2.77	8.56	4.32	2.23	7.54
Bendamustine	10	3.25	1.75	6.05	2.58	1.35	4.55
Lomustine	14	16.29	9.71	27.37	14.14	7.23	23.19

AERS, Adverse Event Reporting System; PRR, proportional reporting ratio; EBGM, empirical Bayes geometric mean; CI, confidence interval

Table 5

Drugs with Non-Significant Signals Associated with SJS and/or TEN

Drug	Cases Reported in the FAERS	Signals					
		<i>PRR</i>	<i>PRR Lower 95% CI</i>	<i>PRR Upper 95% CI</i>	<i>EBGM</i>	<i>EBGM Lower 95% CI</i>	<i>EBGM Upper 95% CI</i>
SJS							
Bleomycin	13	0.98	0.57	1.69	0.98	0.68	1.36
Bevacizumab	5	0.07	0.03	0.18	0.07	0.03	0.17
Chlorambucil	10	2.08	1.12	3.85	1.81	0.95	3.19
Cetuximab	7	0.21	0.10	0.44	0.22	0.09	0.42
Cisplatin	24	0.27	0.18	0.41	0.28	0.18	0.41
Docetaxel	64	1.08	0.85	1.38	1.05	0.85	1.23
Doxorubicin	47	0.51	0.38	0.68	0.51	0.38	0.67
Etoposide	41	0.77	0.57	1.05	0.83	0.64	1.05
Fludarabine	26	0.89	0.61	1.31	0.93	0.68	1.23
Hydroxyurea	21	1.36	0.88	2.08	1.14	0.83	1.55
Imatinib	40	0.92	0.67	1.30	0.94	0.72	1.195
Interferon	81	0.63	0.50	0.78	0.65	0.52	0.79
Methotrexate	196	0.67	0.58	0.77	0.68	0.59	0.78
Pemetrexed	11	0.69	0.38	1.24	0.85	0.57	1.19
Vemurafenib	0	-	-	-	-	-	-
Vincristine	50	0.71	0.54	0.94	0.74	0.57	0.95
Temozolomide	41	2.24	1.65	3.04	2.14	1.56	2.88
TEN							
bevacizumab	6	0.20	.09	0.455	0.215	0.09	0.43
bleomycin	6	0.88	0.40	1.96	0.95	0.62	1.38
Busulfan	19	3.05	1.95	4.78	2.70	1.69	4.12
Cetuximab	8	0.55	0.28	1.11	0.71	0.38	1.11
Cisplatin	40	0.89	0.65	1.211	0.91	0.70	1.17
Doxorubicin	63	1.35	1.04	1.71	1.23	0.99	1.52
etoposide	46	1.68	1.25	2.24	1.48	1.13	1.96
Gemcitabine	43	1.41	1.05	1.90	1.30	0.98	1.69
hydroxyurea	9	1.13	0.59	2.18	1.02	0.69	1.47
interferon	19	0.47	0.30	0.74	0.47	0.29	0.72
methotrexate	187	1.26	1.09	1.46	1.22	1.06	1.40
Tamoxifen	28	1.11	0.76	1.63	1.05	0.78	1.38
Vemurafenib	1	-	-	-	-	-	-
vinblastin	9	1.79	0.98	3.44	1.24	0.76	2.19
vincristine	78	2.19	1.75	2.74	2.14	1.7	2.65

CI=Confidence Interval; EBGM=Empirical Bayes Geometric Mean; FAERS=Food and Drug Administration Adverse Event Reporting System; PRR=Proportional Reporting Ratio; SJS=Stevens Johnson syndrome; TEN=Toxic Epidermal Necrosis