Inadequate and delayed characterization of cutaneous reactions for US Food and Drug Administration–approved oncologic drugs from 2011–2020 leading to medication discontinuation

To the Editor: Cutaneous reactions are common adverse events (AE) in oncologic drug clinical trials and a frequent reason for discontinuation. Although properly diagnosing cutaneous AEs and keeping patients on oncologic therapy is increasingly appreciated, many cutaneous AEs are not detailed in subsequent studies until long after their discovery, leading to unnecessary drug cessation and suboptimal management.[1-3] We aimed to evaluate the extent to which cutaneous adverse events are described in oncologic trials and measure the delay from identification of a rash to its full characterization in the literature—parameters anecdotally appreciated as lacking but not examined in prior studies.

We used CenterWatch to identify all US Food and Drug Administration (FDA)-approved anticancer drugs from 2011 to 2020. For each drug, we queried PubMed/MEDLINE to identify the first published phase III trial and first published dermatologic study describing any of the drug's cutaneous AEs if present in trials. We noted which trials provided any, even minimal, insight into rash morphology and which provided defined dermatologic diagnoses. We calculated the time difference between publication of the initial phase III trial and the initial clinical report and between FDA-approval and initial clinical report (Supplemental Fig 1 available via https://data.mendeley.com/datasets/stjkfxhbkh/1).

Of 98 FDA-approved anticancer drugs from 2011 to 2020, 56 met inclusion criteria. Twenty-five trials (44.6%) provided no additional details outside of "rash." The remaining 31 (55.4%) provided any morphologic descriptions, of which 22 (39.3%) provided defined dermatologic diagnoses. Nearly 60% of trials discontinued treatment because of rash (Table I).

Thirty-five drugs had subsequent studies detailing their cutaneous AEs. The average lag time from phase-III trial to literature characterization was 12.1 months. The average lag time from FDA approval to literature characterization was 20.5 months. When stratifying trials into 27 "earlier" (2011-2015) and 29 "later" trials (2016-2020), later trials more frequently described rash morphology (31.0% vs. 18.5%) and had lower lag times from trial to literature report (median 7 vs 14 months).

Table I. Characteristics of phase III clinical trials and subsequent literature reports

Characteristic	No. of drugs	% of drugs
Total phase III trials with cutaneous AE	56	100.0
No description of cutaneous AE	25	44.6
Minimal characterization of cutaneous AE	31	55.4
Specific dermatologic diagnosis*	22	39.3
Listed "rash" as an AE	46	82.1
Described "rash" morphology	16	34.8
Common AE excluding "rash"	—	—
Hand-foot syndrome*	12	21.4
Pruritus	11	19.6
Erythema	7	12.5
Acneiform dermatitis	6	10.7
Dry skin	6	10.7
Herpes/Zoster*	5	8.9
Squamous cell carcinoma of skin*	5	8.9
Hyperkeratosis	4	7.1
Vitiligo*	4	7.1
Basal cell carcinoma of skin*	4	7.1
Discontinued treatment due to rash	22	56.4†
Explained treatment of cutaneous AE	17	30.4
Grade III-V "rash" listed	32	57.1
First in class drugs	14	25.0
Minimal characterization	7	50.0
Specific dermatologic diagnosis	6	42.8
Dermatologic report in literature	35	62.5
Provided histopathologic findings	28	80.0
Discontinued therapy due to rash	14	40.0
Lag time from FDA approval‡		
Report prior to FDA approval	3	8.6
0-2.0 y	13	37.1
2.0-4.0 y	13	37.1
4.0-6.0 y	6	17.1
Lag time from phase III trial		
Report prior to phase III trial	6	17.1
0-2.0 years	18	51.4
2.0-4.0 years	5	14.3
4.0-6.0 years	6	17.1

*Indicates adverse events classified as specific, actionable dermatologic diagnoses.
†Calculated as a proportion of the 39 trials that detailed which adverse events led to discontinuation.
‡Seventeen drugs with literature characterization (49%) were granted accelerated FDA approval before publication of phase III trials.

Our study found that only half of clinical trials have any appreciable description of rashes, more than half discontinue therapy because of rash, and that there is a prolonged 1- to 2-year lag from identification of a rash to full characterization. The lag time and lack of dermatologic detail improved over the last decade, but the absolute percentage remains low.

These findings are significant because oncologic therapies are often discontinued without dermatologic consultation because of rash.[4] Studies show weak agreement between referring clinicians and dermatologists on discontinuation; in cases of disagreement, 86.4% of dermatologists recommended against discontinuation.[5] Early dermatology consultation/intervention has been shown to decrease treatment interruption rates and improve outcomes, quality of life, and treatment adherence.[4,5] Our findings point out the deficit and delay in providing sufficient assessment of these cutaneous AE and highlight the importance of early, more comprehensive involvement of dermatologists in the creation and study of these life-saving drugs being rapidly developed and deployed. Limitations include an inability to examine conference presentations or FDA drug watch reports that may have provided earlier insight into cutaneous AEs. Future studies are warranted to assess the effectiveness of early dermato-oncology involvement in oncologic drug clinical trials.

Jason J. Yang, BS,[a] Naomi So, MD,[b] Nolan J. Maloney, MD,[b] Julia Arzeno, MD,[a] Katherine K. Clifton, MD,[c] and Daniel Q. Bach, MD, MPH[a]

From the Division of Dermatology, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California[a]; Department of Dermatology, Stanford University School of Medicine, Palo Alto, California[b]; Division of Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO.[c]

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Correspondence to: Jason J. Yang, Division of Dermatology at UCLA, 200 Medical Plaza, Ste 450, Los Angeles, CA 90095

E-mail: jjyang@mednet.ucla.edu

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Diagnosis of gamma/delta mycosis fungoides requires longitudinal clinical observation

To the Editor: It is unclear whether epidermotropic cutaneous T cell lymphomas (CTCLs) exhibiting a T-cell receptor gamma delta (TCR$\gamma\delta$) phenotype initially presenting with patches and plaques should be considered a variant of mycosis fungoides ($\gamma\delta$-MF) or as primary cutaneous $\gamma\delta$ T cell lymphomas (PC$\gamma\delta$TCL).[1-3] Because PC$\gamma\delta$TCL is considered an aggressive lymphoma,[4] the misclassification of epidermotropic PC$\gamma\delta$TCL as MF may delay the decision to use systemic treatments. Our objective was to identify unique features that differentiate $\gamma\delta$-MF from epidermotropic PC$\gamma\delta$TCL.

We reviewed 4 patients (2 women and 2 men 39-71 years of age) from our cutaneous lymphoma clinic who presented with features resembling early-stage MF (stages IA-IB) and who had the TCR$\gamma\delta$ phenotype. The clinical courses and histopathologic and immunophenotypic profiles of each patient are described in detail (Supplemental Tables I and II available via Mendeley at https://doi.org/10.17632/fhww2x8yy6.2). Cutaneous signs preceded the first diagnostic biopsy specimen by a median of 20 months (range 6-48 months), with a median follow-up of 64 months. Stage progression was noted in 3 patients, and 1 patient died. Besides case 1, all patients presented with patches and plaques on the distal extremities or the face rather than on sun-protected areas typical for MF. When disease progressed to tumors, the localization was atypical for classic MF (ie, the face and plantar aspects of the feet; Fig 1 and Supplemental Fig S1).

Histologically, the infiltrate was indistinguishable from classic early-stage MF (Supplemental Figs S2 and S3). Immunophenotypically, cases demonstrated cytotoxic markers (granzyme B or T-cell intracellular antigen 1), a double-negative phenotype (CD4−/CD8−), an absence of TCR-βF1, positivity for TCR$\gamma\delta$, and monoclonal rearrangements