Cutaneous Reactions in Clinical Trials for Oncologic Drugs: An Increasing Need for Dermatologic Involvement

Jason J. Yang[1] BS, Naomi So[2] MD, Nolan J. Maloney[2] MD, Julia Arzeno[1] MD, Katherine K. Clifton[3] MD, Daniel Q. Bach[1] MD MPH

[1]Division of Dermatology, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California, USA
[2]Department of Dermatology, Stanford University School of Medicine, Palo Alto, California, USA
[3]Division of Oncology, Department of Medicine, Washington University School of Medicine, St Louis, MO, USA

Background

- Cutaneous reactions are among the most common adverse events (AE) and reasons for discontinuation of oncological drugs in clinical trials and clinical practice. 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.
- This lack of knowledge leads to unnecessary drug cessation and suboptimal management. Early dermatologic intervention to treat these adverse effects may be able to decrease discontinuation rates.
- Though anecdotally appreciated as lacking in the literature, prior studies have neither examined the extent to which rashes are described in clinical trials nor measured the time lag before they are first characterized in the literature.

Methods

- We utilized the CenterWatch database to identify all anticancer drugs approved by the Food and Drug Administration (FDA) within the last 10 years (2011-2020, inclusive).
- Analgesics, antiemetics, and other non-oncologic drugs were excluded. Drugs without any dermatologic AEs, modified versions of past drugs, and past drugs recently approved but for a new indication were also excluded.
- For each drug, we queried the PubMed/MEDLINE database using Medical Subject Headings (MeSH) to identify the first published phase III or combination phase II/III study.
- To evaluate adequate characterization of a rash, we noted how many trials provided any, even minimal insight into a rash morphology and how many provided definitive dermatologic diagnoses.
- To identify the first dermatologic study describing the drug's AEs, the PubMed/MEDLINE database was queried using MeSH terms, taking note of rash latency, morphology, and whether AEs led to treatment discontinuation.
- We calculated the time difference between publication of the initial phase III trial and publication of the first clinical report describing any of the drug's cutaneous AEs, as well as the time difference between FDA approval and initial clinical report.

Results

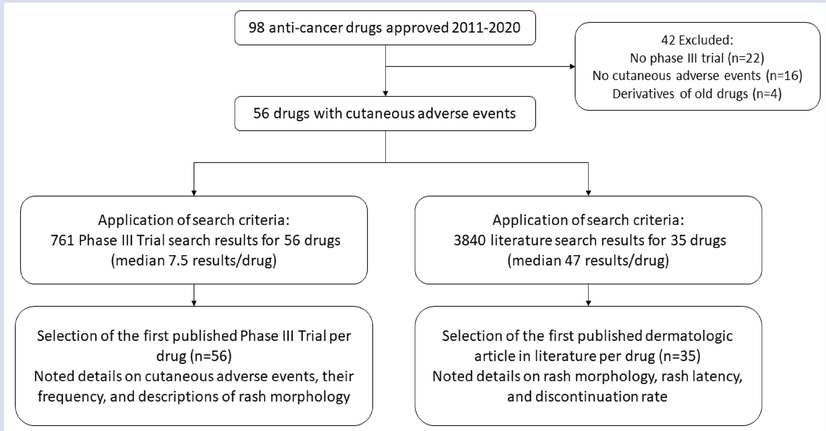

Figure 1: Study methodology

Common AE excluding "rash"	# of drugs	% of drugs
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

§ Indicates adverse events classified as specific, actionable dermatologic diagnoses
† Calculated as a proportion of the 39 trials detailing which adverse events led to discontinuation

Table 1: Common cutaneous adverse effects excluding rash: Hand-foot syndrome, herpes or herpes zoster, squamous or basal cell carcinoma, and vitiligo were considered specific, actionable dermatologic diagnoses. Abbreviations: HFS = hand-foot syndrome (palmar-plantar erythrodysesthesia), SCC = squamous cell carcinoma of skin, BCC = basal cell carcinoma of skin

Characteristic	# 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
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 years	13	37.1
2.0 – 4.0 years	13	37.1
4.0 – 6.0 years	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

Abbreviations: AE = adverse event
‡ 17 drugs with literature characterization (49%) were granted accelerated FDA approval prior to publication of Phase III trials.

Table 2: Characteristics of phase III clinical trials and subsequent literature reports: Fifty-six anticancer drugs had phase III trials reporting cutaneous adverse events. Twenty-five (44.6%) trials reported a rash without any additional details. 60% of trials discontinued treatment due to rash. The time lag averaged 12.1 months after the phase III trial and 20.5 months after federal approval.

Discussion

- Our review of clinical trials of anticancer drugs with cutaneous AEs from 2011-2020 demonstrates that only half of clinical trials have any appreciable description of rashes and that there is a prolonged one to two-year lag from identification of a rash to its characterization.
- The lag time and lack of dermatologic detail appears to slowly have improved over the last decade as later studies (published 2016-2020) began to incorporate the delayed findings from earlier studies (published2011-2015), but the absolute percentage remains low (31% vs. 18% describing rash).
- Many therapies are discontinued due to rash, often without dermatologic consultation. Studies show weak agreement between referring clinicians and consulting dermatologists on discontinuation – in cases of disagreement, dermatologists recommended against discontinuation 86.4% of the time.
- Early dermatology consultation and intervention has been shown to decrease treatment interruption rates and improve outcomes (e.g. rash recurrence), patient quality of life, and treatment adherence

Limitations:

- Adverse events leading to discontinuation were often not described or described incompletely to identify rash as a cause for discontinuation.
- We did not examine other channels such as conference presentations or FDA drug watch reports that may have provided earlier insight into cutaneous reactions for clinicians.

Conclusion

- Information on cutaneous reactions to new oncologic drugs in clinical trials is sparse and delayed in its characterization in literature.
- Our study points out not only the deficit and delay in providing sufficient assessment of these cutaneous AE for oncologic drugs, but also highlights the importance of early and more comprehensive involvement of dermatologists in the creation and study of these life-saving drugs
- Earlier involvement of dermatologists can facilitate early characterization and management of these eruptions and reduce unnecessary discontinuation of oncologic drugs.

*The authors have no outside interests to disclose