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Sean Singer, BS[1];* Sally Y. Tan, MD, MPH[1,2];* Anna K. Dewan, MD, MHS[3]; Matthew Davids, MD, MMSc[4]; Ann S. LaCasce, MD, MMSc[4]; Steven P. Treon, MD, PhD[5], Nicole R. LeBoeuf, MD, MPH[6]

1 Harvard Medical School, Boston, MA

2 Department of Internal Medicine, Brigham & Women's Hospital, Boston, MA

3 Vanderbilt University Medical Center, Nashville, TN

4 Center for Hematologic Oncology, Dana-Farber Cancer Institute, Boston, MA

5 Bing Center for Waldenström's Macroglobulinemia, Dana-Farber Cancer Institute, Boston, MA

6 Center for Cutaneous Oncology, Department of Dermatology, Dana-Farber/Brigham & Women's Cancer Center, Boston, MA

*denotes co-first authorship

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Corresponding Author:
Nicole LeBoeuf, M.D., M.P.H.
Dana-Farber/Brigham and Women's Cancer Center
Center for Cutaneous Oncology
450 Brookline Avenue
Boston, MA 02115
Email: nleboeuf@partners.org
Phone: (617) 632-6571
Fax: (617) 394-2645

Abstract

Background

Ibrutinib is an oral inhibitor of Bruton's tyrosine kinase (BTK) that is FDA-approved for several lymphoproliferative disorders and chronic GVHD.

Objective

To characterize cutaneous eruptions arising from ibrutinib and highlight overlap with epidermal growth factor receptor inhibitor (EGFRi)-induced dermatologic adverse events (dAEs).

Methods

Single-center retrospective cohort of patients referred to the Skin Toxicities Program for management of cutaneous eruptions while taking ibrutinib.

Results

Among 19 patients, cutaneous eruptions manifested as facial-predominant papulopustular eruptions, petechiae or ecchymoses, photosensitivity, panniculitis, xerosis, and clinical staphylococcal overgrowth. The majority of patients were able to continue ibrutinib therapy with focused management of their cutaneous toxicities.

Limitations

This study represents cases at a single tertiary care center and is limited to patients referred for toxicity.

Conclusions

With the exception of petechiae, the cutaneous toxicities of ibrutinib overlap with those associated with selective EGFR inhibitors. We observed that these reactions can be successfully managed using approaches for EGFR inhibitor-induced cutaneous adverse events.

Capsule Summary

- Ibrutinib is an inhibitor of Bruton's tyrosine kinase that is FDA-approved for several lymphoproliferative disorders and chronic GVHD.
- Cutaneous toxicities from ibrutinib overlap with those of epidermal growth factor inhibitors (EGFRi), may appear unusual due to platelet dysfunction, and can be managed using the same approaches used to treat EGFRi-induced toxicities.

Introduction:

Ibrutinib is an oral, selective, irreversible Bruton's tyrosine kinase inhibitor (BTKi) that is FDA-approved for the treatment of chronic lymphocytic leukemia (CLL), mantle cell lymphoma (MCL), Waldenström's macroglobulinemia (WM), and chronic graft versus host disease (GVHD).[1–4] Cutaneous toxicities from ibrutinib are reported in up to 47% of patients,[1,4] and the most commonly reported reaction patterns of these toxicities include rash, petechiae or ecchymoses, panniculitis, and hair/nail changes.[5,6] These dermatologic adverse events (dAEs) can result in ibrutinib dose interruption, reduction or require management with drugs resulting in other side effects, all impacting the patient's overall care.

In this study, we further characterize cutaneous toxicities secondary to ibrutinib and draw similarities between the reaction patterns seen with ibrutinib to those seen with epidermal growth factor inhibitors (EGFRi).

Methods

Our study was granted approval by the Partners Institutional Review Board. Cases were collected from a cohort referred to see an oncodermatologist in the Skin Toxicities Program at the Dana-Farber/Brigham and Women's Cancer Center; those patients referred for suspected cutaneous toxicity or rash from ibrutinib were included. Patients who were on ibrutinib but were referred for other disorders (i.e. graft versus host disease management) were excluded.

Data was retrospectively collected on patients who were seen between July 2016 and September 2018 and included demographic information, oncologic history, clinical morphology and timing

of cutaneous toxicity, management of ibrutinib dosing following development of toxicity, treatment and response of cutaneous eruption, and concurrent photosensitizing medications. Time to cutaneous toxicity was calculated as the number of weeks from the date of first dose of ibrutinib to the initial date of the eruption. Concurrent photosensitizing medications were recorded if the patient was on these treatments at the time of initial presentation to oncodermatology or in the preceding 4 weeks.

Results

19 patients were included in this study (Table 1) with a mean age of 70 (range: 39-88 years). 13 patients (68.4%) were male. 10 patients (52.6%) received ibrutinib for CLL, 6 patients (31.6%) for WM, 2 patients (10.5%) for MCL, and 1 patient (5.3%) for refractory GVHD. The mean time to development of cutaneous toxicity was 16.1 weeks (range: 1-120 weeks) after initiating ibrutinib.

The clinical morphologies of cutaneous toxicities from ibrutinib were varied. 10 patients (52.6%) had papules and pustules primarily affecting the cheeks and nose that appeared weeks to months after initiating ibrutinib therapy (Figure 1); several occurred or flared after sun exposure. 10 patients (52.6%) were found to have marked xerosis, 4 (21.1%) with eczematous changes. 4 patients (21.1%) had clinical staphylococcal overgrowth with honey-colored crusts or fissured nares (Figure 2a), and 2 (10.5%) had brittle nails. 2 patients (10.5%) developed a pityriasis rosea-like eruption (Figure 2b) while another 4 (21.1%) patients had panniculitis (Figure 2c). 8 patients (42.1%) developed petechiae, ecchymoses, or purpura (Figure 2d). 8 patients (42.1%)

were on concurrent photosensitizing medications within 4 weeks of presentation for ibrutinib toxicity.

Each ibrutinib toxicity was treated based on the clinical phenotype present. Sun protection and emollients were recommended to all 19 patients. Of 10 patients with papulopustular eruptions, 6 (60%) improved with oral tetracyclines with or without topical steroids, 3 (30%) improved with topicals alone, and 1 (10%) improved after observation without medical intervention. Once clear, oral antibiotics were tapered to the lowest dose that maintained clearance. For 4 patients with clinical staphylococcal overgrowth, dilute bleach baths and mupirocin were recommended for decolonization. The 4 patients with panniculitis were managed with non-steroidal anti-inflammatory drugs (NSAIDs), and 1 with more severe panniculitis required prednisone, pentoxifylline, hydroxychloroquine and ultimately ibrutinib discontinuation.

Among our cohort, 16 patients (84.2%) were able to be successfully managed without discontinuation of ibrutinib, while 2 (10.5%) reduced their ibrutinib dose for other indications with resultant resolution of their cutaneous eruptions. Only 1 patient (5.3%) discontinued ibrutinib for a dermatologic adverse event, refractory panniculitis.

Discussion:

In our study, cutaneous eruptions on ibrutinib manifested as facial-predominant papulopustular eruptions, petechiae or ecchymoses, photosensitivity, panniculitis, xerosis, and clinical staphylococcal overgrowth. With the exception of petechiae, these overlap with the cutaneous toxicities associated with selective EGFR inhibitors.[7,8] This cohort highlights the range of ibrutinib-associated cutaneous toxicities, describes the papulopustular eruption as a result of

ibrutinib therapy, and – by connecting the observed reaction patterns – allows us to draw a parallel to the skin findings classically associated with EGFR inhibitors.

Ibrutinib-associated cutaneous toxicities have been observed in 3-47% of patients treated for CLL and 2-15% of WM and MCL patients, reported as 'rash' or 'bruising'.[1,4] Additional morphologies in prior studies and case reports include vasculitis-like lower extremity papules, panniculitis, pityriasis rosea-like dermatitis, brittle nails, and hair changes.[5–7] Nearly all dAEs described in clinical trials were grades 1-2; only one patient required dose reduction for a grade 3 rash.[1–4] Patients with ibrutinib-associated eruptions have been managed with oral and topical corticosteroids, oral antihistamines, dose reduction, and treatment delays.[9–11]

While some of the toxicities in our patients are similar to those that have been previously reported, 10 of our patients developed acneiform papulopustular reactions that appeared weeks to months after initiating ibrutinib therapy. Several of these occurred or flared after sun exposure, which closely resembles a commonly described phenomenon in patients on EGFRi.[7] Of note, 7 patients reported photosensitivity, which manifested as flaring of their papulopustular eruptions or sunburn-like erythema. While several of these patients were also taking concurrent potentially photosensitizing medications, the papulopustular flares and the timing of eruptions lead us to conclude that ibrutinib was the more likely culprit. Additionally, ibrutinib is known to inhibit platelet aggregation by interfering with glycoprotein VI signaling, which may contribute to the development of petechiae or ecchymoses and alter the appearance of inflammatory skin conditions, as was seen in case 2 (Figure 1c).[12]

The non-petechial ibrutinib-associated cutaneous toxicities in our cohort resemble the well-described dermatologic toxicities associated with EGFR inhibitors. EGFR-associated papulopustular eruptions appear on the face, scalp and upper trunk, are dose-dependent and affect most patients.[13] Additional effects of EGFRi that show overlap with the dAEs seen in our cohort include xerosis, which can lead to eczematous dermatitis, staphylococcal overgrowth, photosensitivity, panniculitis, and hair/nail changes.[7,8] EGFR regulates growth and maturation within the epidermis and inhibition leads to growth arrest, premature differentiation of basal keratinocytes, and release of inflammatory cytokines.[14] Treatment prior to initiation of EGFRi with doxycycline, topical steroids, emollients and sun protection significantly decreases grade ≥2 skin toxicities[16] and reactive approaches were mirrored in our cohort.

Notably, patients were managed by approaching the clinical phenotype as we would dAEs from EGFR inhibitors.[7] Those with papulopustular eruptions were managed with a combination of topical antibiotics and topical steroids in addition to sun protection and emollients; patients with more severe reactions also received oral tetracyclines. Xerosis and photosensitivity were managed with liberal use of emollients and sun protection. Dilute bleach baths and mupirocin were used for decolonization in those with clinical findings of staphylococcal overgrowth,[17] while panniculitis was managed in most cases with non-steroidal anti-inflammatory drugs (NSAIDs).

The dAEs seen in our patients on ibrutinib support the possibility that it may have off-target activity against EGFR in the skin. Pre-clinical studies have shown that ibrutinib may have EGFR inhibitory effects in non-small cell lung cancer cells carrying mutations in the EGFR gene. In

these cell lines, there was a dose-dependent effect, ibrutinib prolonged survival and suppressed cancer growth in mouse models *in vivo*.[18] Interestingly, children with BTK mutations develop X-linked agammaglobulinemia that predisposes to pulmonary and skin infections. Skin infections are not uncommon during ibrutinib therapy and may be a contributing explanation for the clinical staphylococcal overgrowth observed (honey colored crusts, fissured nares). This alone, though, would not explain the additional adverse events. It is important to note that only 2 patients were cultured in the study as clinical findings were diagnostic, so it is difficult to definitely draw conclusions about the role of skin infections in our cohort.

Our findings must be interpreted in the context of our study design. This is a retrospective analysis of patients referred for consultation to oncodermatologists in the Skin Toxicities Program of a single institution, and as such additional studies are necessary to determine the generalizability of our results. Milder dAEs were likely managed by treating oncologists and general dermatologists. The retrospective nature of this study also leads to variability in the work up done across cases, some diagnoses based on clinical findings, others supported by culture or biopsy data.

Conclusion

While the clinical appearance and response to therapy of the dAEs seen in these cases resemble the eruptions classically associated with selective EGFR inhibitors, the severity and extent of the papulopustular eruption does appear milder and more rosacea-like in these cases. Further research is needed to determine whether the mechanism of these dAEs is indeed via an EGFR-

mediated pathway, the host and environmental factors at play, and whether the severity of such cutaneous eruptions may predict response to treatment.

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Abbreviations

BTKi = Bruton tyrosine kinase inhibitor

CLL = Chronic lymphocytic leukemia

WM = Waldenstrom's Macroglobulinemia

GVHD = Graft versus host disease

dAE = Dermatologic adverse event

EGFRi = Epidermal growth factor receptor inhibitor

NSAID = Non-steroidal anti-inflammatory drug

Author Contributions: Nicole LeBoeuf had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: All authors.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Singer, Tan, Dewan.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: N/A.

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Study supervision: Dewan, LeBoeuf.

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This study was approved by the Partners Healthcare Institutional Review Board, protocol 2015P001336/BWH.

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Figure Legend

Figure 1. Clinical presentations of Cases 1 and 2. A, Clinical presentation of Case 1. Papulopustular eruption of bilateral cheeks, nose and forehead. B, Follow-up for Case 1. Resolution of facial lesions after treatment with oral doxycycline 100mg twice daily and mupirocin 2% ointment to nares. C, Clinical presentation of Case 2**.** Round petechiae and ecchymoses of the cheeks and chin at sites of prior pustules. D, Follow-up for Case 2. Resolution of facial ecchymoses with time, after resuming ibrutinib with doxycycline 100mg twice daily, clindamycin 1% lotion applied daily and sun protection daily to prevent rash recurrence. The patients in both Cases 1 and 2 provided written consent for publication of clinical images.

Figure 2. Additional cutaneous toxicities associated with ibrutinib beyond facial-predominant papulopustular eruptions. A, erythema and yellow crusting of lid margin consistent with staphylococcal blepharitis as seen in EGFRi-induced overgrowth. B, oval pityriasiform papules and plaques resembling pityriasis rosea similar to previous report.[7] C, tender erythematous subcutaneous nodules consistent with panniculitis with visible background xerosis both seen with EGFR inhibition. D, purpuric papules and petechiae on the lower extremities as previously reported[1].

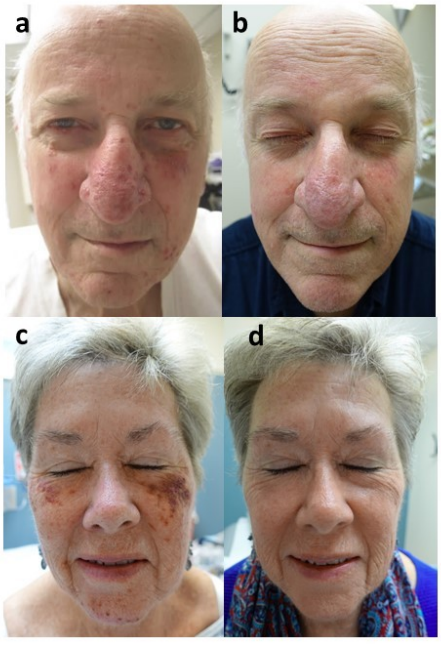
Table 1. Summary of clinical findings and management of EGFRi-like cutaneous toxicities associated with ibrutinib.

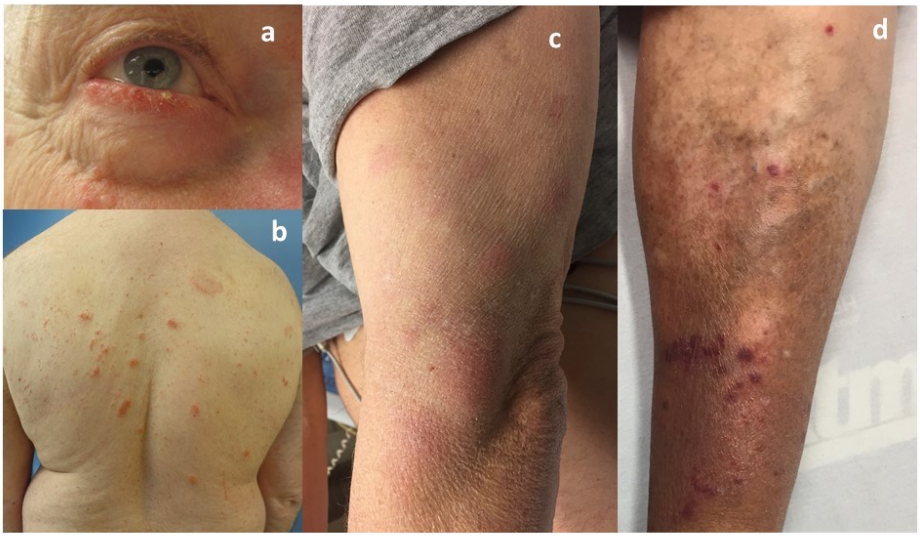
Case #	Age	Sex	Malignancy	Clinical Presentation of Cutaneous Toxicities from Ibrutinib	Timing of Cutaneous Eruption After Ibrutinib Initiation	Treatment Beyond Sun Protection and Emollients	Ibrutinib Dosing	Concurrent potentially photosensitizing drugs
1	70s (Case 1)	Male	MCL	• Pruritic, erythematous, papulopustular eruption of the bilateral cheeks, chin, nose and eyes **(Figure 1a and 1b)** • Ecchymoses • Eczematous dermatitis on trunk and arms • Photosensitivity • Clinical staphylococcal overgrowth **(Figure 2a)**	2-3 weeks; flared months later in the setting of sun exposure	Doxycycline 100mg BID, desonide 0.05% cream BID to face; mupirocin 2% ointment to nares; erythromycin 2% ointment daily near eyes	Continued	Furosemide
2	60s (Case 2)	Female	WM	• Papulopustular eruption on bilateral cheeks and chin; flares of pustules in the sun **(Figure 1c and 1d)** • Residual ecchymoses after pustules regressed • Xerosis • Photosensitivity • Onychodystrophy and brittle nails • Hair changed from curly to straight and brittle	4 months after starting ibrutinib, flares after sun exposure	Doxycycline 100mg twice daily, clindamycin 1% lotion applied daily	Temporarily held, then resumed full dose; Later reduced to 280 mg daily due to arthralgias	Amlodipine, atorvastatin
3	50s	Female	CLL	• Episodic inflammatory papules and pustules on nose, bilateral cheeks and upper lip • Ecchymoses • Xerosis • Nail brittleness and thinning	2 weeks	Doxycycline 100mg twice daily, metronidazole 1% gel applied daily	Continued	Ciprofloxacin, sulfamethoxazole -trimethoprim, venlafaxine
4	60s	Male	WM	• Asymptomatic, papulopustular eruption on nose with surrounding telangiectasias • Culture with 2+ mixed cutaneous flora • Photosensitivity	6 weeks after starting ibrutinib	Clinical observation	Continued	None
5	80s	Male	CLL	• Papules and pustules on cheeks, nose, chin, upper chest and back • Pink scaly eczematous patches on trunk and extremities • Diffuse, severe xerosis • Petechiae on legs • Clinical staphylococcal overgrowth	1 week after starting ibrutinib	Triamcinolone 0.1% cream BID, dilute bleach baths 1-2x weekly, emollients	Temporarily reduced dose to 280 mg daily x1 month, tolerated re-escalation to full dose once on topicals	Amlodipine
6	70s	Male	CLL	• Papulopustular eruption on nasal tip, ala, upper cutaneous lip	14 months after	Doxycycline 50mg BID,	Continued	Sulfamethoxazole

				and chin • Photosensitivity • Clinical staphylococcal overgrowth in nares	starting ibrutinib in the setting of sun	mupirocin 2% ointment to nares BID, dilute bleach baths 1-2x weekly		-trimethoprim
7	70s	Female	CLL	• Papules and pustules on the face, upper back with central facial erythema • Inflammatory papules on upper extremities and back • Diffuse petechiae and purpuric patches across chest, abdomen and extremities • Panniculitis on upper arms • Biopsy showing mixed chronic and granulomatous inflammation with no organisms on gram stain	1-2 months after starting ibrutinib	Minocycline 100mg daily, triamcinolone 0.1% cream BID, antiseptic wash 3x weekly	Continued	Furosemide
8	70s	Male	Refractory GVHD	• Pruritic papulopustular eruption on the forehead, cheeks, nose and dorsal hands	2 week after starting ibrutinib	Doxycycline 100mg BID, triamcinolone 0.1% cream to affected areas on hands and face	Continued	None
9	60s	Female	CLL	• Pustules and papules on the cheeks and chin • Perifollicular papules on lower extremities	3 months after starting ibrutinib	Clindamycin 1% solution BID, benzoyl peroxide washes, bleach baths	Continued	None
10	80s	Male	WM	• Bilateral upper extremity edema • Xerosis with eczematous scaling of popliteal fossa • Biopsy showing intracorneal pustule with dermal chronic inflammation and numerous eosinophils • Culture with 4+ growth of MSSA	7 months after starting ibrutinib	Triamcinolone 0.1% cream BID, bleach baths, cephalexin 250mg qd for 10 day course	Continued	Atorvastatin
11	70s	Male	WM	• Asymptomatic purpuric erythema and upper extremity edema • Xerosis	2.5 years after starting ibrutinib	Clinical observation	Continued	None
12	60s	Female	CLL	• Petechiae on extremities • Geometric purpura of R upper extremity in setting of treated cellulitis • Xerosis	2 years after starting ibrutinib	Continued inpatient course of cefepime and daptomycin for cellulitis, no treatment for purpura/petechiae as self-limited	Continued	None
13	50s	Male	CLL	• Photosensitivity • Psoriasiform eruption in areas of sunburn • Biopsy consistent with psoriasis or impetiginized spongiotic / eczematous dermatitis	16 months after starting ibrutinib	Acitretin 10mg qd, desonide BID to face, clobetasol 0.05% ointment BID to trunk and extremities, sun protection	Continued	None

14	80s	Male	WM	• Photosensitivity • Inflammatory purpuric papules on lower extremities	18 months after starting ibrutinib, with sun exposure	Sun protection	Continued	HCTZ
15	30s	Female	CLL	• Panniculitis of thighs • Biopsy showing acute lobular panniculitis with associated mucin deposition • Diffuse xerosis	2 months after starting ibrutinib	Supportive care - warm compresses, ibuprofen	Continued	None
16	60s	Male	CLL	• Papulopustular eruption on forehead, cheeks • Xerosis • Pityriasis rosea or nummular dermatitis-like eruption (**Figure 2b**)	17 months after ibrutinib	Triamcinolone 0.1% cream to face and trunk BID, dilute bleach bathsilute bleach baths	Continued	None
17	70s	Male	MCL	• Panniculitis: Extremities and abdomen (**Figure 2c**) • Biopsy showing superficial granulomatous dermatitis and interstitial / perivascular inflammation; deep dermis with lobular panniculitis • Tissue cultures with no growth • Purpuric papules on the bilateral lower extremities **(Figure 2d)** • Xerosis	3 months after starting ibrutinib	Clinical observation	Continued	None
18	60s	Male	CLL	• Panniculitis: Anterior and medial lower legs • Exquisitely tender • Biopsy showing dense lobular panniculitis with neutrophilic and lymphohistiocytic inflammation, microabscess formation and focal vasculopathic changes	9 months after starting ibrutinib	Cool compresses, ibuprofen, prednisone taper, pentoxifylline 400mg TID, increased to 800mg TID, Hydroxychloroquine 200mg BID	Stopped	None
19	60s	Male	WM	• Pityriasis rosea-like papules and nummular dermatitis like oval plaques in a Blaschko distribution on the back • Biopsy showing pityriasiform and spongiotic dermatitis with eosinophils • Xerosis	7 months after starting ibrutinib	Triamcinolone 0.1% cream BID	Continued	None

WM = Waldenström's macro-globulinemia
CLL = Chronic lymphocytic leukemia
MCL = Mantle cell lymphoma
GVHD = Graft versus host disease





Capsule Summary

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- Cutaneous toxicities from ibrutinib overlap with those of epidermal growth factor inhibitors (EGFRi), may appear unusual due to platelet dysfunction, and can be managed using the same approaches used to treat EGFRi-induced toxicities.