Characteristics and management of rash following lenalidomide and rituximab in patients with untreated indolent non-Hodgkin lymphoma

Low-grade rash may occur with lenalidomide, rituximab, or their combination (R^2) in non-Hodgkin lymphoma (NHL). From our phase II study of R^2 in previously untreated indolent lymphoma (n=110), 52 (47%) patients had rash, which was associated with pruritus in 22 (42%). Worst grade 1, 2, and 3 rash was found in 19%, 21%, and 7%, respectively. Grade 1/2 rash was effectively managed with observation, antihistamines and/or topical steroids, and resolved within a median of 7-9 days. Grade 3 rash was manageable through lenalidomide interruption and prednisone treatment, with successful R^2 rechallenges. Practical recommendations described here for rash management enable optimal R^2 treatment in patients with previously untreated indolent lymphoma.

Indolent lymphomas constitute one-third of all types of NHL, with the most common form being follicular lymphoma (FL), followed by small lymphocytic lymphoma and marginal zone B-cell lymphoma.[1] Optimal treatment for newly diagnosed indolent lymphomas remains to be determined. For patients with advanced stage disease requiring treatment, first-line rituximab alone or in combination with chemotherapy is recommended.[2]

Lenalidomide is an oral immunomodulator with single-agent activity in relapsed/refractory indolent lymphoma.[3] Preclinical studies indicate that lenalidomide has multiple antitumor and antiproliferative mechanisms of action and suggest possible synergy between lenalidomide and rituximab, thereby providing the basis for clinical evaluation of the combination.[4] Multiple phase II studies in relapsed/refractory and newly diagnosed indolent lymphoma show that R^2 is active and well tolerated.[5-8]

Although not considered a prominent adverse event for either agent, rash has the potential to affect quality of life negatively and to hinder optimal treatment. Rash has generally been observed as a grade 1/2 adverse event with few

Table 1. Baseline characteristics, treatment, and outcomes of patients with grade 3 rash.

Hist., age, sex	Past medical history (atopy history)	Prior drug allergies (symptom)	Other cause possible	Cycle at rash onset	Rash morphology	Associated symptoms	Rash distribution	Rash treatment	Duration of lenalidomide	Rash duration, days	Lenalidomide rechallenge, outcome
FL 78M	Hypertension, reflux (None)	Diflunisal (rash)	None	5	NR	Myalgia	Neck, arms, trunk	Lenalidomide held, antihistamines, topical hydrocortisone 1%	21	14	Rechallenged, no recurrence
FL 47F	None (None)	None	Nystatin	2	Maculo-papular	Pain, fever, arthralgia	Arms, trunk, legs	Lenalidomide held, antihistamines, oral prednisone 20 mg x 3 d	7	2	Rechallenged while on daily antihistamine prophylaxis, no recurrence
FL 54F	Seizures (None)	Sulfa (lip swelling)	None	1	NR	Fever	Entire body	Lenalidomide held, antihistamines	7	6	Rechallenged, grade 1 with daily antihistamine prophylaxis, recurrence cycle 9
FL 55F	Hypothyroiditis, meningioma (None)	Sulfa (rash)	None	2	Erythematous	Pruritus	Arms, trunk	Lenalidomide held, antihistamines, oral prednisone 20 mg x 3 d	7	4	Rechallenged, no recurrence
MZL 74F	Hypertension (None)	None	None	1	NR	Myalgia	Neck, arms, trunk	Lenalidomide held, antihistamines, topical triamcinolone 1%	14	12	Rechallenged, no recurrence
MZL 64F	None (None)	None	Possible sun exposure	1	Raised red papules	–	Arms, trunk (80% BSA), legs,	Lenalidomide held, oral prednisone 20 mg x 3 d, IM methylprednisone*	withdrawn	15	Withdrawn from study, no rechallenge
SLL 55M	Past hepatitis B (None)	None	None	2	Macular erythematous	–	Face (periorbital), neck	Antihistamines, topical hydrocortisone 1%	7	6	Rechallenged, no recurrence
SLL 60F	Osteoarthritis, fibromyalgia, irritable bowel syndrome, emphysema, hyperPTH (Asthma)	Codeine, cephalexin, metronidazole, penicillin, phenobarbital, Sulfa (rash)	Allopurinol likely	1	Maculo-papular	Arthralgia, pruritus	Entire body (90% BSA)	Lenalidomide held, antihistamines, IM methylprednisone*	14	13	Rechallenged, no recurrence

*BSA: body surface area; d: days; F: female; FL: follicular lymphoma; IM: intramuscular; M: male; MZL: marginal zone lymphoma; NR: not reported; PTH: parathyroidism; SLL: small lymphocytic lymphoma; hist: histology. *Dose of methylprednisone was unknown.*

grade 3/4 occurrences in patients with relapsed/refractory NHL treated with lenalidomide[3,9] or in relapsed/refractory[10] or newly diagnosed FL patients treated with rituximab.[11,12] The objective of this report is to describe our experience with rash and share best practice for its management during R^2 therapy in patients with previously untreated indolent NHL.

We prospectively collected data on dermatologic adverse events (i.e., rash) in patients with previously untreated indolent B-cell lymphoma who received R^2 during an open-label, phase II study at the MD Anderson Cancer Center (MDACC; ClinicalTrials.gov NCT00695786). The study protocol was previously described in detail.[5] Briefly, 50 stage III-IV FL, 30 marginal zone B-cell lymphoma, and 30 small lymphocytic lymphoma patients received R^2 therapy, consisting of lenalidomide 20 mg/day PO on days 1-21 (beginning at 10 mg/day for small lymphocytic lymphoma) and rituximab 375 mg/m^2 IV on day 1 of each 28-day cycle for ≤12 cycles or until disease progression, intolerability, or withdrawal of consent. No steroids or antihistamines were used prophylactically. The study was conducted in accordance with the Declaration of Helsinki and approved by the MDACC Institutional Review Board. All patients provided written informed consent to participation in the study.

Dermatologic adverse events were evaluated in all enrolled patients and graded according to the National Cancer Institute's Common Terminology for Adverse Events, version 3.0 criteria (*Online Supplementary Table S1*).[13] Baseline characteristics of patients with and without rash were compared using the Mann-Whitney U-test or chi-squared test as appropriate. Response was determined according to the criteria of the International Working Group for Malignant Lymphomas.[14] *P*-values were two-sided, and values <0.05 were considered statistically significant.

Rash of any grade was observed in 52 (47%) patients. Grade 1 rash occurred in 21 (19%) patients, grade 2 rash in 23 (21%) patients, and grade 3 rash in eight (7%) patients; no grade 4 rash occurred. Associated pruritus was present in 22/52 patients (42%), while an additional 12 patients reported pruritus without evidence of rash. Rash occurred during the first cycle of therapy in 37/52 (71%) cases, during the second cycle in nine (17%) cases, and during the third or subsequent cycles in six (12%) cases. In most cases the rash occurred on the extremities and/or trunk and was maculopapular in appearance (Figure 1). There were no statistically differences between patients with or without rash with regards to baseline characteristics, including age (*P*=0.29), stage (*P*=0.54), hemoglobin concentration (*P*=0.66), histological subtype (*P*=0.48), presence of B symptoms (*P*=0.62), splenomegaly (*P*=0.14), or lactate dehydrogenase (*P*=0.32; *data not shown*).

Treating physicians determined supportive care for rash. Among 21 patients with grade 1 rash, lenalidomide was interrupted in one patient; the remaining 20 continued therapy. Management consisted of observation alone (n=8) or supportive measures (antihistamines, n=12).

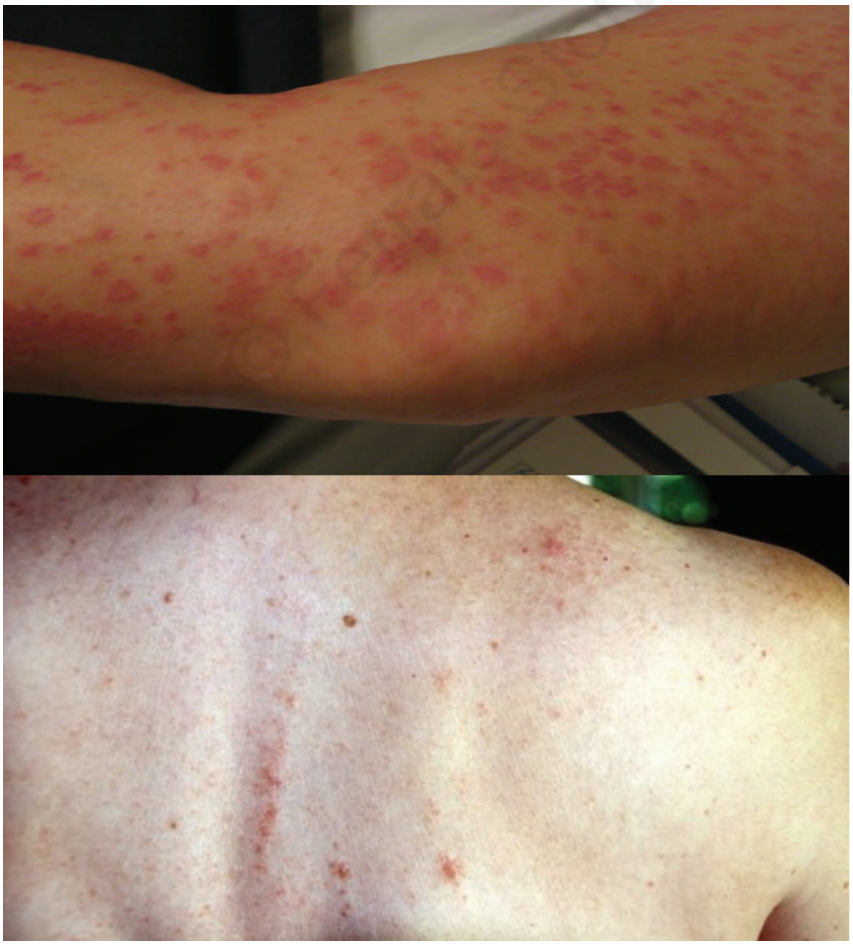

Figure 1. An illustrative example of a patient who developed rash during treatment with R^2. Top panel, forearm. Lower panel, back.

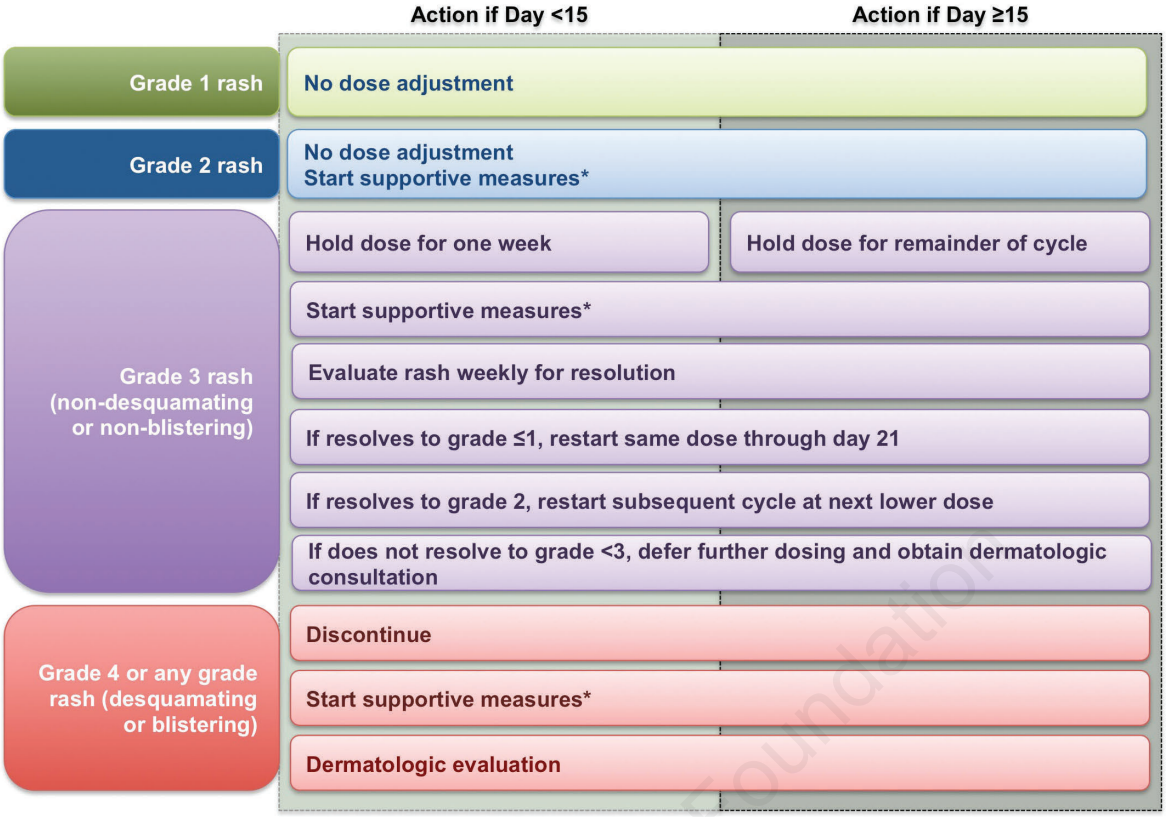

Figure 2. Recommended approach to rash management for lenalidomide and rituximab treatment in indolent NHL. *Supportive measures: 1. Initiate daily oral antihistamines: loratadine 10 mg/day PO or cetirizine 10 mg/day PO or diphenhydramine 25 mg/day PO. 2. Short courses of low-dose steroids: prednisone 10 mg PO ×3 days or hydrocortisone 20 mg PO once in the morning and 10 mg PO once in the evening ×3 days. 3. Continue daily oral antihistamines for the rest of the lenalidomide treatment

Patients with pruritus only were treated with antihistamines. The median duration of rash was 7 days (range, 1-37). Of 23 patients with grade 2 rash, lenalidomide was interrupted in two patients and a dose reduction from 20 to 15 mg was required in one patient. The remaining 20 patients continued supportive measures with antihistamines and topical corticosteroids. The median time to rash resolution was 9 days (range, 1-71). Eight patients developed grade 3 rash; their baseline characteristics and treatment are detailed in Table 1. One patient (a 64-year old female with marginal zone B-cell lymphoma) withdrew from the study due to rash; a skin biopsy demonstrated leukocytoclastic vasculitis.

In our modest cohort, the occurrence of rash did not appear to predict response to R^2 or survival. Patients who did or did not develop rash had similar overall response rates (96% *versus* 87%, respectively; P=0.80) and complete response rates (72% *versus* 60%, respectively; P=0.80), with no statistical difference in estimated 3-year progression-free survival (73% *versus* 84%, respectively; P=0.38). This finding should be validated in studies with larger numbers of patients.

The incidence and severity of rash observed with R^2 appears slightly higher than with each agent alone when compared to other studies of patients with treatment-naive or relapsed/refractory NHL. Any-grade rash was observed in approximately 25% of patients with relapsed/refractory NHL who received single-agent lenalidomide.[9,15] Few grade 3/4 rash events have been reported in patients with mixed indolent NHL. With rituximab monotherapy, grade 1/2 rash was reported in 6/50 patients (12%),[12] and single grade 3 and 4 events were reported in newly diagnosed FL (n=35).[11] In relapsed/refractory indolent NHL, 16/166 patients (10%) experienced grade 1/2 rash, with no evidence of grade 3/4 rash following four weekly doses of rituximab 375 mg/m^2.[10] In these studies, patients treated with rituximab were allowed (but not required) to receive premedication with acetaminophen and diphenhydramine;[10-12] premedication was administered according to the physicians' discretion in the lenalidomide studies.[9,15]

In a study of relapsed/refractory mantle cell lymphoma, combination therapy with R^2 (lenalidomide 20 mg, days 1-21/28 with rituximab 375 mg/m^2/week ×4 cycle 1) was given to 44 patients, of whom 29 (66%) developed a rash, including two (5%) patients who experienced grade 3 rash.[7] No prophylaxis for rash was employed. Using a similar dosing schedule in 45 patients with relapsed/refractory diffuse large B-cell lymphoma, transformed lymphoma, or grade 3 FL, grade 1, 2, and 3 rash was observed in five (11%), three (7%) and two (4%) patients, respectively; none developed grade 4 rash. These rashes led to dose reductions of lenalidomide in three cases and discontinuation in one. With a different dosing schema for first-line R^2 in mantle cell lymphoma (lenalidomide 20 mg/day, days 1-21/28 and rituximab 375 mg/m^2/week ×4 weeks in cycle 1

and every other cycle for 12 cycles, then continued as maintenance with lower-dose lenalidomide), an early safety report described grade 3/4 rash in 26% of patients (n=38).[6]

In our experience, rash following R^2 was generally mild and transient, although dose interruption in a minority of patients and dose reduction in one patient were required. Most cases resolved with supportive care, and rash did not occur with re-exposure in the majority of patients. Although we suspect that rash may herald immune cell activation and potentially augment immunogenicity following exposure to the combination, the occurrence of dermatologic events did not predict response to the combination therapy. We recommend discussion of rash, including a suggested management approach, with patients prior to initiating combination therapy (Figure 2). In the case of grade 3 (desquamating) rash which does not rapidly resolve following drug discontinuation or supportive measures, we advise prompt referral for dermatologic evaluation.

In summary, although dermatologic events in patients with indolent NHL who receive R^2 are expected and are manageable from a physician's perspective, these overt symptoms may affect a patient's quality of life enough to warrant the patient's withdrawal from therapy. Active preparation for the occurrence and management of rash should enable optimal treatment with R^2 in previously untreated patients with indolent NHL.

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