Management of Adverse Events From the Combination of Rituximab and Lenalidomide in the Treatment of Patients With Follicular and Low-Grade Non-Hodgkin Lymphoma

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Abstract

Frontline treatment for patients with indolent non-Hodgkin lymphoma often includes immunochemotherapy. Although the disease of most patients responds to initial treatment, relapse is common. Recent results from the phase 3 Augment trial showed that combining rituximab with the immunomodulatory drug lenalidomide (R^2) significantly improved efficacy over rituximab monotherapy in patients with recurrent non-Hodgkin lymphoma. As a result of these data, R^2 was approved in the US (Food and Drug Administration) and Japan (Pharmaceuticals and Medical Devices Agency) for previously treated adult patients with follicular and marginal zone lymphoma; and by the European Medicine Agency and the Swiss Agency for Therapeutic Products (Swissmedic) for previously treated adult patients with follicular lymphoma. R^2 has also been studied as initial treatment, where results have been comparable, but not superior, to chemoimmunotherapy. The resulting expanded use of R^2 reinforces the need for a detailed review of its safety profile and management, as presented here. Tolerability of R^2 has been consistent among trials, with most adverse events (AEs) being predictable and manageable. Hematologic AEs, particularly grade 3/4 neutropenia; low-grade cutaneous reactions, such as rash; and gastrointestinal AEs represent the most common AEs associated with R^2. The general R^2 safety profile and optimal strategies for AE management are discussed.

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Introduction

The past 15 years have witnessed a dramatic shift in the treatment of follicular and low-grade non-Hodgkin lymphomas (NHL), from chemotherapy to chemoimmunotherapeutic regimens, and now biological and targeted strategies. The first agent that suggested the possibility of a chemotherapy-free approach was rituximab, a chimeric anti-CD20 monoclonal antibody initially studied in the relapsed/refractory setting where responses were achieved in the disease of almost half of patients, with acceptable toxicity.[1-4] Subsequent studies demonstrated single-agent activity as initial treatment, with some responses being durable.[4-7] In the SAKK study, in which induction rituximab was administered for 4 weeks followed by a dose every 2 months for 4 cycles in patients whose disease responded to induction rituximab, the event-free survival was 45% at 8 years.[8]

In an attempt to improve on those results, a series of clinical trials of biological doublets were initiated. Investigators from the Cancer and Leukemia Group B (CALGB) first studied the combination of rituximab and the anti-CD80 monoclonal antibody galiximab. In a series of 61 previously untreated patients, the overall response rate (ORR) was 72.1%, and the complete response (CR)/unconfirmed CR rate was 47.6%; outcomes correlated with the Follicular Lymphoma International Prognostic Index (FLIPI).[9] These investigators subsequently combined rituximab with the anti-CD22 monoclonal antibody epratuzumab and treated 59 previously untreated patients with follicular lymphoma (FL). The ORR was 88.2% with 42.4% CRs, many of which were durable.[10] Both of these regimens were extremely well tolerated, with few untoward effects.[9,10]

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The next partner selected for rituximab was lenalidomide. Lenalidomide is an immune-mediated inflammatory disease immunomodulatory agent that was found to be active in vitro and in vivo against B-cell lymphoma cells of various subtypes, including diffuse large B-cell lymphoma, FL, and mantle-cell lymphoma (MCL).[11-16] Clinical studies demonstrated single-agent activity against a variety of both indolent and aggressive histologies.[17-25] Combining lenalidomide and rituximab (R^2) enhanced antibody-dependent cellular cytotoxicity, immune synapse formation, monocyte-mediated killing, and direct cytotoxicity against FL cells.[12,26-28] The combination was first tested in the clinic by CALGB investigators in 91 patients with relapsed FL in a randomized trial against single-agent lenalidomide; a third arm of single-agent rituximab was discontinued as a result of poor accrual.[29] The ORR and CR rates for R^2 versus lenalidomide alone favored the combination arm (R^2: 76% ORR and 39% CR; lenalidomide: 53% ORR and 20% CR), and median time to progression (R^2: 2 years; lenalidomide: 1.1 year) significantly favored the combination. In the lenalidomide-alone and R^2 arms, grade 3/4 adverse events (AEs) were reported in 58% and 52% of subjects, respectively, with neutropenia and fatigue predominating in the R^2 arm.[29]

Given the results favoring R^2, several studies were initiated in previously untreated patients. Martin et al[30] of CALGB/Alliance treated 66 patients, 51 of whom completed 12 cycles of the combination. The ORR was 95% with 75% CRs. At a median follow-up of 5 years, the 5-year progression-free survival (PFS) was 70%. There was no association between FLIPI and PFS.[30] Fowler et al[31] treated 110 patients with the combination, including 50 with FL. The ORR was 90% with 63% CR. For the FL population, the ORR was 98% with 87% CR. The median PFS for the entire cohort was 53.8 months; however, the PFS for the FL population was 78.5% at 3 years. The Swiss and Nordic groups published results of a randomized trial (SAKK 35/10) in previously untreated patients in which rituximab monotherapy was compared to R^2 continued for only 18 weeks.[32] The combination resulted in a higher CR/unconfirmed CR rate at 6 months (36% vs. 25%) and, with a median follow-up of 4 years, a longer PFS of 5 versus 2.3 years, although without a difference in overall survival. Varying response rates across these frontline trials may be partly attributed to differences in criteria (2007 IWG criteria[33] for CALGB/Alliance vs. 1999 IWG criteria[34] for others) as well as differences in patient populations in need of therapy per Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria[35,36] (required for eligibility in SAKK 35/10 and Relevance).

The efficacy and tolerability of R^2 led to international randomized trials, including Relevance, in which R^2 was compared directly with rituximab + chemotherapy (R-chemo), using either CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisolone), or bendamustine, in 1030 previously untreated patients with advanced FL.[37] The two arms had similar results with respect to ORR (61% for R^2 vs. 65% for R-chemo), CR (48% vs. 53%), 3-year PFS (77% vs. 78%), and overall survival (94% for both groups at 3 years). Safety results showed that R^2 was better tolerated overall, with the notable exception of cutaneous reactions (7% vs. 1% grade 3/4 AEs).[37]

In the Augment study, R^2 was compared to rituximab + placebo (R-placebo) in relapsed and refractory FL and marginal zone lymphoma (MZL) patients, and was associated with a prolongation of PFS and overall survival in favor of R^2, leading to US Food and Drug Administration and Japan Pharmaceuticals and Medical Devices Agency (PMDA) approval in this population, as well as approval by the European Commission and the Swiss Agency for Therapeutic Products (Swissmedic) for the FL population.[38,39]

Because R^2 is now an approved regimen for adult patients with previously treated FL and MZL,[40] managing the potential toxicities becomes a relevant issue for maintaining its efficacy while reducing the adverse consequences. The recommendations that we present here reflect the consensus of the authors, all of whom are experts in the management of lymphoma who are integrally involved in the development of the R^2 regimen.

Discussion

Hematologic AEs

The most common toxicities with R^2 across studies are hematologic (Table 1). Overall, AEs lead to discontinuation of R^2 in approximately 9% to 11% of patients (Table 1), often as a result of grade 3/4 neutropenia. Although not frequent with lenalidomide as a single agent, these AEs are not appreciably more common with R^2. In CALGB 50401, grade 3 and 4 neutropenia occurred in 16% and 0, respectively, with lenalidomide alone, and were 16% and 4% with the combination.[29] In frontline phase 2 studies, grade 3 and 4 neutropenia were relatively uncommon at 25% and 10%, respectively, reported by Fowler et al,[31] 15% and 6% reported by Martin et al,[30] and 32% (grades 3 and 4 combined) in the Relevance trial.[37] In contrast, when R^2 was compared to rituximab alone, there was a notable difference. In the Augment study, grade 3/4 neutropenia occurred in 50% of patients with R^2 versus 13% with rituximab alone.[38] Growth factors were administered to 36% of the R^2 group versus 12% in the R-placebo group. All incidences of grade 3/4 neutropenia in the R^2 group recovered to grade 1 or less, with a median time of 9 days. The dose of rituximab could not be reduced; if rituximab was discontinued as a result of toxicity, lenalidomide or placebo was continued as per the study protocol. Lenalidomide was held and restarted at the next lower dose (5 mg increments) if the event resolved to a lower grade or was discontinued as specified in the protocol. Only 5 patients had neutropenia leading to lenalidomide discontinuation. For all grade 4 neutropenia or grade 3 neutropenia that was sustained for ≥ 7 days or associated with fever (temperature 38.5°C), complete blood counts were monitored every 7 days, growth factor administration was permitted, and lenalidomide was restarted if the toxicity resolved to grade 2 or less.

In previously untreated MCL, the risk of grade 3/4 neutropenia has been reported as 42% with R^2.[42] However, the incidence of febrile neutropenia was extremely low, as was the risk of serious infections. Thus, there was no indication for the prophylactic use of growth factors or antibiotics.

The risk of thrombocytopenia is also quite low. In CALGB 50401, there were 4% episodes of grade 3/4 thrombocytopenia with the combination versus 16% with lenalidomide alone.[29] In Augment, grade 3/4 thrombocytopenia occurred in 1% with rituximab alone versus 2% with R^2.[38]

Table 1 AEs in R^2 Arms Reported in ≥ 4 Trials and ≥ 40% Any Grade in Any Trial

Study	Leonard[38] (2019 Augment)		Morschhauser[37] (2018 Relevance)		Martin[30] (2017 CALGB 50803)		Becnel[41] (2019)[a]		Fowler[31] (2014)[a]		Ruan[42] (2018)		Ruan[42] (2018)		Chong[43] (2015)	
Phase	3		3		2		2		2		2		2		2	
Patient type	FL/MZL		FL		FL		MZL		FL/MZL/SLL		MCL		MCL		Indolent B-cell and MCL	
Line of therapy	R/R		1L		1L		1L		1L		1L (induction)		1L (maintenance)		Rituximab resistant	
No. of patients	176		507		65		30		110		36		36		50	
Hematologic AEs	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Neutropenia	58%	50%	75%	32%	55%	21%	60%	33%	76%	35%	68%	42%	66%	42%	34%	34%
Anemia	16%	5%	66%	0	38%	0	25%	0	63%	0	47%	8%	32%	3%	8%	4%
Thrombocytopenia	15%	2%	53%	2%	45%	1%	37%	3%	51%	3%	29%	11%	37%	5%	12%	8%
Nonhematologic AEs	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**	**Any Grade**	**Grade 3/4**
Diarrhea	31%	3%	37%	2%	39%	2%	48%	0	50%	0	53%	0	55%	0	38%	4%
Constipation	26%	0	35%	1%	27	2	48%	0	52%	0	45%	0	18%	0	32%	0
Cough	23%	1%	NR	NR	NR	NR	63%[b]	5%[b]	49%[b]	5%[b]	53%	0	24%	0	14%	0
Fatigue	22%	1%	23%	1%	84%	6%	93%	0	90%	4%	76%	11%	39%	3%	62%	2%
Upper respiratory infection	18%	1%	9%	0	28%	2%	10%	0	23%	2%	24%	0	45%	0	8%	0
Edema	13%	0	14%	0	NR	NR	50%	0	44%	1%	39%	0	13%	0	NR	NR
Rash	11%	1%	29%	4%	40%	8%	40%	5%	58%	7%	68%	29%	16%	0	26%	4%
ALT increased	10%	2%	NR	NR	45%	2%	NR	NR	NR	NR	24%	3%	16%	3%	NR	NR
Dizziness	NR	NR	NR	NR	NR	NR	38%	0	44%	1%	18%	0	8%	0	NR	NR
Pain or myalgia	NR	NR	14%	0	18%	4%	60%	10%	82%	9%	16%	3%	11%	0	18%	0
Patients discontinuing R^2 as result of AE (%)	9%		11%		9%		10%		NR		NR		NR		NR	

Abbreviations: AE = adverse event; ALT = alanine transaminase; FL = follicular lymphoma; MCL = mantle-cell lymphoma; MZL = marginal zone lymphoma; NR = not reported; R^2 = lenalidomide + rituximab; R/R = relapsed/refractory; SLL = small lymphocytic lymphoma.
[a]Publications are from the same study (ClinicalTrials.gov, NCT00695786).
[b]Includes cough, dyspnea, and pulmonary (other).

Hematologic AE Recommendations

Guidelines for management of neutropenia are outlined in Figure 1 and call for interrupting lenalidomide on the basis of neutrophil counts; however, real-world experience has shown that administering growth factors may allow these patients to continue to receive lenalidomide, particularly during the induction phase for the first 6 months. Additionally, lowering the dose of lenalidomide to 10 mg at later time points may mitigate most neutropenia. For patients with grade 4 neutropenia or grade 3 neutropenia that is sustained for $\geq$ 7 days or associated with fever (38.5°C), complete blood counts should be monitored at least weekly. Lenalidomide may be restarted when toxicity resolves to grade 2 or less. Subsequent growth factor support is recommended for patients with a history of neutropenic fever or infection, as well as for those with recurrent neutropenia with reinstitution of lenalidomide. Guidelines for the management of lenalidomide associated thrombocytopenia are outlined in Figure 2.

Infection

Infections are not an uncommon consequence of treatment with R^2. In the frontline CALGB experience,[30] grade 1/2 mostly sinopulmonary infections were reported in 18 of 65 patients, 6 of which were grade 3 and none of which were grade 4. No infections were reported in the MD Anderson frontline experience.[44]

In the Relevance trial,[37] a higher percentage of patients in the R-chemo group had infections of any grade (12% vs. 5%) and grade 3/4 infections (4% vs. 2%) than in the R^2 group that were associated with grade 3/4 neutropenia, although more patients in the R-chemo group received concomitant antimicrobial agents.

Zucca et al[32] reported on their short course of R^2 versus rituximab monotherapy in untreated patients. The combination arm was associated with infections in 30% of patients compared to 18% with the single agent. In the combination arm, there were 4% grade 3 infections; 5% skin infections with no grade 3%; 17% upper respiratory infection with 1% grade 3%; and 5% urinary tract infection, including 3% grade 3. There were no grade 4 infections.

In the Augment trial in relapsed and refractory indolent NHL,[38] upper respiratory infection (R^2 vs. R-placebo arms: any grade, 18% vs. 13%; grade 3/4%, 1% vs. 2%, respectively) and influenza (any grade, 10% vs. 4%; grade 3/4%, 1% vs. 0) were reported. Neutropenia-related infections were reported in the CALGB 50401 comparison of R^2 versus lenalidomide alone (grade 3/4%, 2% vs. 4%).[29]

In untreated MCL, Ruan et al[42] noted mostly grade 1 or 2 upper respiratory infections in 45%, urinary tract infection in 21%, sinusitis in 13%, and cellulitis in 11% of patients. These were managed on an outpatient basis. Seven patients experienced grade 3 infections that required a brief hospitalization with intravenous antibiotics; 3 patients (8%) had pneumonia, 1 with recurrent urinary tract infections and 1 with West Nile virus encephalitis.

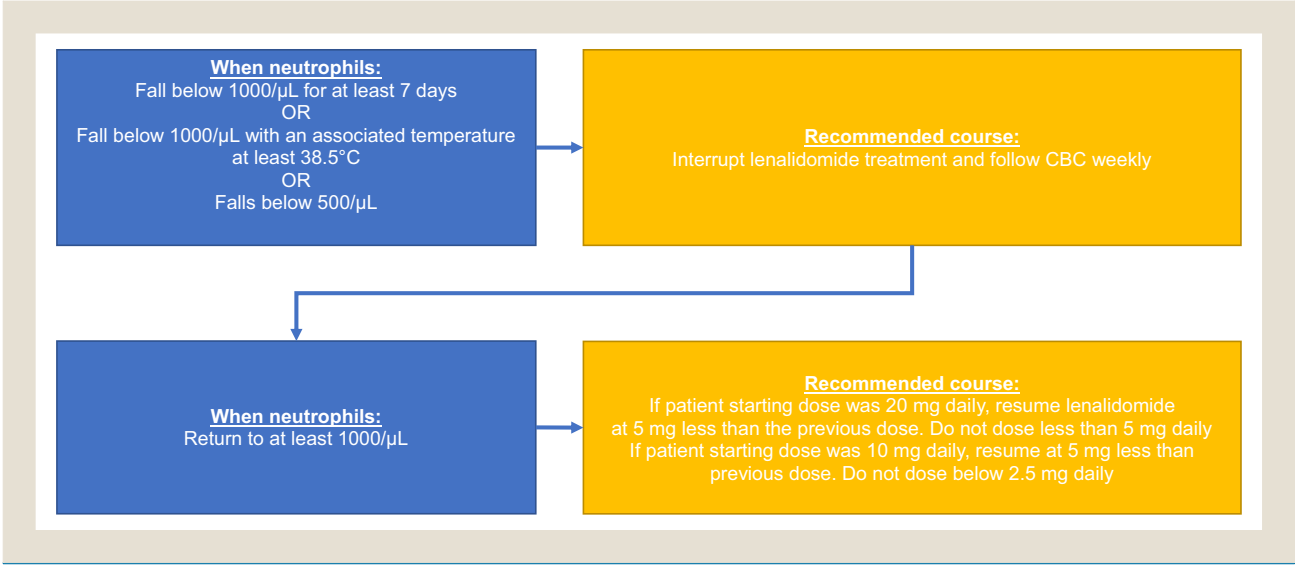
Infection Recommendations

Although severe infections are uncommon, low-grade infections do affect quality of life. Because there is no clear pattern to the infections, there are no specific recommendations for their prevention or management, other than the potential provision of growth factors. Given the infrequency, diverse nature, and usual lack of severity of infections, prophylactic antimicrobial therapy is generally not recommended. For patients who experience recurrent infections, determination of quantitative immunoglobulin levels should be considered, with supplemental immunoglobulin administration for those with levels below 600 mg/dL to prevent recurrent sinopulmonary infections.

Rash

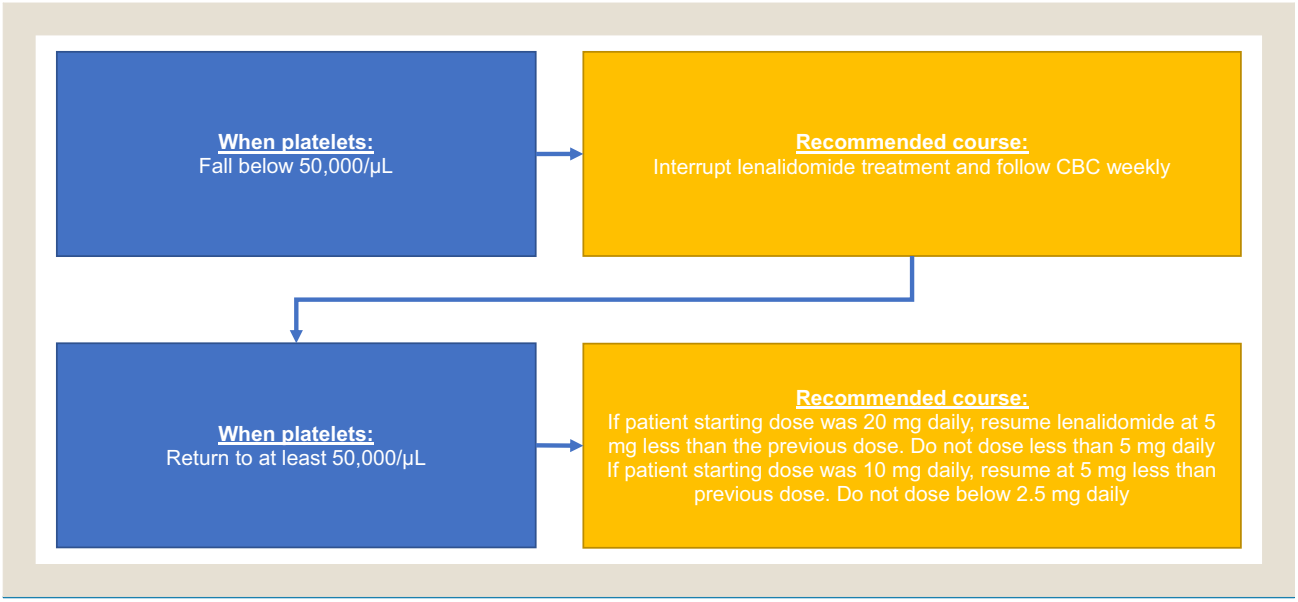
Rash is one of the more problematic adverse effects of R^2. It not only raises cosmetic issues but may have an adverse effect on patient quality of life. In the report of Fowler et al,[31] rash was observed in 47% of patients, including 7% with grade 3. Pruritus was reported

Figure 1 Management of Neutropenia During Lenalidomide Treatment in FL or MZL



Abbreviations: CBC = complete blood count; FL = follicular lymphoma; MZL = marginal zone lymphoma.

Figure 2 Management of Thrombocytopenia During Lenalidomide Treatment in FL or MZL



Abbreviations: FL = follicular lymphoma; MZL = marginal zone lymphoma.

in 42%, while an additional 11% experienced pruritus without rash. Rash occurred most frequently during the first cycle (71%), while the second cycle had 17% and third/subsequent cycles only 12%. The rash tended to be maculopapular and localized on the extremities and/or trunk. The authors were unable to distinguish patients with or without rash on the basis of pretreatment characteristics. Unfortunately, the development of rash did not correlate with response to treatment. The need to reduce or interrupt the dose was infrequent, and the rash tended not to recur with retreatment.[45]

In the frontline study of Fowler et al,[31] rash occurred in 58% of patients, including 7% with grade 3. Martin et al[30] reported rash in 40%, including 8% with grade 3. In the Relevance trial, 29% of patients reported a rash, including 4% with grade 3/4.[37] Zucca et al[32] reported 77 previously untreated patients with FL who received a short course of R^2, with 27% reporting a rash, including 5% with grade 3.

Ruan et al[42] reported a series of patients with MCL who received R^2 as initial treatment. Rash occurred in 68% of patients, of which 29% were grade 3 or worse. During the maintenance phase, rash was noted in only 16% of patients, with no grade 3 cases. Kiesewetter et al[46] reported on 50 patients with untreated or previously treated mucosa-associated lymphoid tissue lymphoma. Rash occurred in 46% of patients but was grade 3 in only 3 of 48 patients.

In the relapsed setting, Leonard et al[29] reported grade 3 rash in 4% of patients with R^2, which was similar to that reported for lenalidomide alone (2% with grade 3%, 2% with grade 4; no overall risk was provided). In the Augment trial, any grade rash was reported in 11% of patients, but only 1% was grade 3/4.[38] In recurrent nonfollicular indolent NHL, Sacchi et al[47] reported rash in 23% of patients, including 3% with grade 3. These data suggest that the frequency may be higher in previously untreated patients, perhaps because of a more intact immune system.

Angioedema and severe cutaneous reactions including Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS) have been reported rarely in patients with multiple myeloma treated with lenalidomide and are potentially fatal.[48,49] DRESS may present with a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy along with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. Patients with a history of grade 4 rash associated with thalidomide treatment should not receive lenalidomide. Lenalidomide interruption or discontinuation should be considered for grade 2/3 skin rash.[40] Lenalidomide must be discontinued for angioedema, grade 4 rash, or exfoliative or bullous rash, or if Stevens-Johnson syndrome, toxic epidermal necrolysis, or DRESS are suspected and should not be resumed even when these reactions have resolved.[40]

The likelihood of rash appears to increase when other drugs are added to the combination. Ujjani et al[50] combined R^2 with ibrutinib in a phase 1 trial in previously untreated FL. Rash was reported in 82% of patients and was grade 3 in 36%, but there were no grade 4 cutaneous reactions. Notably, rashes occurred at each dose level. Two patients withdrew from the study because of the rash. Almost all rashes were maculopapular, although one was pustular. The onset was typically during cycle 1 but occurred as late as cycle 4. Trimethoprim/sulfamethoxazole was implicated in one patient because the rash disappeared along with discontinuation of the antibiotic. Although allopurinol was recommended at the start of treatment and could be discontinued at the discretion of the treating physician, there was no apparent correlation between the administration of allopurinol and the likelihood of rash.[50]

Rash Recommendations

Fowler et at[45] published recommendations for the management of rash associated with R^2, which are shown in Table 2.

Table 2 Management of Rash During Lenalidomide Treatment in Follicular Lymphoma or Marginal Zone Lymphoma

Rash Grade	Recommended Course
1	No dose adjustment.
2	No dose adjustment, but consider supportive measures. These might include daily oral antihistamines. If this approach is unsuccessful, recommend a short course of steroids, prednisone 10 mg by mouth for 3 days or hydrocortisone 20 mg in the morning and 10 mg at night, along with antihistamines to be continued for the duration of lenalidomide treatment.
3	Hold the dose for a week if it occurs within the first 15 days; otherwise hold for the remainder of the cycle. Supportive measures as noted above should be initiated. If the rash resolves to less than grade 1, restart the same dose through day 21. If it only resolved to grade 2, restart next cycle at the next lower dose level. If it does not resolve to less than grade 3, withhold further dosing and refer the patient to dermatology.
4 or desquamating rash	Discontinue lenalidomide and initiate supportive measures.

Gastrointestinal AEs

Both diarrhea and constipation are common with R^2; however, they are rarely severe. Most of these data presented are in patients with FL. In the Augment trial, diarrhea was reported in 31% of patients, including 3% with grade 3/4, and constipation was reported in 26% of patients, with no grade 3/4 episodes.[38] In the Relevance study, diarrhea occurred in 37% of patients, including 2% with grade 3/4, constipation occurred in 35% of patients, and < 1% experienced a severe episode.[37] Ruan et al[42] reported an incidence of diarrhea of 53% with no severe reactions and an incidence of constipation of 45%; none was severe. Fowler et al[31] noted diarrhea in 50% of patients, none severe; constipation was reported in 52% of patients, none severe. Martin et al[30] reported diarrhea in 39% of patients, including 2% with grade 3, and constipation in 27% of patients, including 2% severe. Zucca et al[32] noted diarrhea in 25% of patients, all episodes of which were grade 1/2. Management involves standard supportive measures for either diarrhea or constipation.[40] Of note, lipid-lowering drugs such as cholestyramine[51] and colesevelam[52] have been shown to lower rates of lenalidomide-associated diarrhea, and cholestyramine is the subject of an ongoing prospective study in multiple myeloma (ClinicalTrials.gov, NCT03767257).

Gastrointestinal AE Recommendations

For grade 3 diarrhea, lenalidomide should be interrupted but can be restarted if the constipation resolves to grade 1 or less. For grade 4 diarrhea or colitis, lenalidomide should be discontinued. Constipation should be treated with standard measures, including stool softeners and laxatives when necessary.

Peripheral Neuropathy

Peripheral neuropathy has been uncommon with R^2. In most studies there have been no episodes[29,32,47] or few reported episodes (Relevance had 7%, including < 1% with grade 3; Ruan et al[42] had 8%, including 0 with grade 3).[37] In distinction have been the frontline studies of Fowler et al,[31] with peripheral neuropathy reported in 37%, including < 1% with grade 3; and Martin et al,[30] reporting 16%, including 2% with grade 3.

Peripheral Neuropathy Recommendations

For grade 3 peripheral neuropathy, lenalidomide administration should be interrupted but can be restarted at a lower dose if it resolves to grade 1 or less.[40] For grade 4 peripheral neuropathy, lenalidomide should be discontinued.

Fatigue

Any grade fatigue has been reported frequently in many R^2 trials; however, grade 3/4 fatigue is relatively uncommon, with rates ranging from 1% to 11% (Table 1). Low-grade fatigue is often difficult for many patients because it typically continues to occur throughout lenalidomide treatment, potentially affecting their quality of life.

Thrombosis

Thrombosis is a well-described complication of lenalidomide monotherapy, although most of the published data have been in patients with multiple myeloma.[53] In lymphoma, Witzig et al[25] reviewed multiple studies including 206 patients with relapsed MCL and noted 3% of patients with deep-vein thrombosis (DVT), with one patient requiring dose interruption and 2% developing a pulmonary embolism. In diffuse large B-cell lymphoma, DVT was observed in 2.3% of 217 patients.[20] In FL, these authors reported 1% of patients with grade 3 and 2% of patients with grade 4 pulmonary embolism. Additionally, Yamshon et al[54] performed a systematic review and meta-analysis of thrombosis in patients with NHL treated with lenalidomide and found that these patients appeared to be at substantial risk of thrombotic events; overall, the rate of thrombosis per 100 patient therapy cycles was 0.77. Interestingly, single-agent lenalidomide resulted in higher rates of thrombosis (1.09 events per 100 patient therapy cycles) compared to combining lenalidomide with a biologic (0.49 events).

In CALGB 50401, in relapsed FL, 15.6% of patients receiving lenalidomide alone had thrombosis compared to 4.4% treated with the combination, suggesting a possible protective effect.[29] This risk was similar to the Augment trial in a similar population, in which 2.0% experienced a DVT event.[38] In many studies of R^2, there were no reported thrombotic episodes.[30-32,37,42,46] Nevertheless, prophylaxis is recommended for patients receiving lenalidomide with 70 to 325 mg of aspirin per day, especially for patients on birth control pills or receiving estrogen therapy.[38]

Thrombosis Recommendations

It is generally recommended that patients receiving lenalidomide receive 81 mg of aspirin per day. However, in the CALGB 50401

study,[29] patients who received R^2 actually had a lower risk of thrombotic events than those treated with lenalidomide alone. Thus, it is not clear that aspirin is needed for patients on the combined therapy. Patients with a history of venous thromboembolism may still be treated with R^2 if they are receiving therapeutic anticoagulation.

Tumor Flare Reaction/Tumor Lysis Syndrome

Tumor flare reaction is an acute inflammatory process in which patients may experience a rapid, often painful increase in lymphadenopathy. Tumor flare reaction poses a diagnostic problem in the management of patients treated with thalidomide or lenalidomide.[55] This finding was originally described in patients with chronic lymphocytic leukemia.[56] Although initially considered unique to immunomodulatory agents, other drugs have since been associated with such events, thus confounding interpretation of response assessment.[57] Several investigators have suggested a correlation with response in chronic lymphocytic leukemia.[58] Tumor flare reaction with lenalidomide has also been reported in small numbers of patients with aggressive B-cell NHL and indolent NHL, more commonly in small lymphocytic lymphoma (17%) than in FL (5%).[19]

Tumor flare reaction has been uncommon with R^2 but may vary with histology and disease status. The frequency was 11% in the Augment and 6% in the Relevance studies.[37,38] However, it has been as high as 37% in MCL.[42]

Tumor Flare Reaction Recommendations

Tumor flare reaction tends to be transient and is self-limiting over a period of a week or two; it generally does not require drug interruption. If symptomatic, it will generally respond to nonsteroidal anti-inflammatory agents such as aspirin in the span of 2 to 3 days, although responses to steroids have also been reported. In the case of grade 3/4 toxicity, the drug should be withheld until toxicity is reduced to grade 1 or less.[40]

Fatal instances of tumor lysis syndrome (TLS) have been reported during treatment with lenalidomide. Patients at greatest risk of TLS are those with high tumor burden before treatment. In the Augment trial in FL or MZL patients, TLS occurred in 2 patients (1.1%) in the R^2 arm. TLS occurred in 1 patient (0.5%) in the Magnify trial during the R^2 induction period; the event was a serious grade 3 adverse reaction.

Table 3 Definitions of Tumor Lysis Risk Categories Adapted From CLL[59]

Risk Category	Definition
Low	All measurable LNs with largest diameter <5 cm AND <25 × 10^9/L ALC.
Medium[a]	Any measurable LN with largest diameter ≥5 and <10 cm OR ≥25 × 10^9/L ALC.
High	Any measurable LN with largest diameter ≥10 cm OR ≥25 × 10^9/L ALC AND any measurable LN with the largest diameter ≥5 cm.

Abbreviations: ALC = absolute lymphocyte count; CLL = chronic lymphocytic leukemia; LN = lymph node.
[a]Patients at medium risk with creatinine clearance < 80 mg/mL are to be managed as high risk.

TLS Recommendations

Patient risk of TLS should be assessed before therapy using criteria similar to those recommended for venetoclax therapy and managed in a similar fashion[59] (Table 3).

Other AEs

Other AEs with R^2 are infrequently reported. The occurrence of myalgias ranges from 11% to 60%, including 3% to 10% with grade 3.[41,42] Increases in alkaline phosphatase have been reported in 16% to 22% of cases, almost all of minor severity.[30,42] Similarly, elevations of alanine transaminase (ALT) have ranged from 10% to 45%, including 2% to 3% with grade 3 or higher.[30,38] For incidences of ALT or aspartate aminotransferase elevation to grade 3 or higher (> 5× upper limit of normal) or total bilirubin to grade 2 or higher (> 1.5× upper limit of normal), ALT, aspartate aminotransferase, and total bilirubin should be monitored weekly and lenalidomide resumed at the same dose if levels return to baseline in ≤ 14 days or resumed at the next lower dose after returning to baseline if recovery takes > 14 days.[40] Grade 3/4 serum sickness has also been reported in 2% to 8% of patients, leading to discontinuation of rituximab with continued single-agent lenalidomide.[30,42,60]

Conclusion

Therapy for patients with indolent NHL is rapidly evolving from chemoimmunotherapy to targeted strategies including single agents and combinations. As shown in the Relevance trial, efficacy of R^2 is often comparable to chemoimmunotherapy. The safety profile of a regimen such as R^2 also compares favorably with the single agents within the R^2 doublet and with conventional chemoimmunotherapy. Nonetheless, there are both common and unique AEs that require attention. Importantly, as multidrug targeted regimens are developed, exaggeration of expected toxicities may occur as well as some that might be unanticipated. Additionally, with some agents, immune-mediated toxicities may occur with increased frequency and severity in patients who are younger and who have received less prior therapy, perhaps as a result of a more intact immune system. Thus, such combinations should not be administered outside of a clinical trial. Nonetheless, because there are no chemotherapeutic agents in development, we need to safely develop targeted regimens as newer agents enter the clinic.

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