Clinical experience with lenalidomide alone or in combination with rituximab in indolent B-cell and mantle cell lymphomas

J. Ruan1*, B. Shah2, P. Martin1 & S. J. Schuster3

1Division of Hematology and Medical Oncology, Weill Cornell Medical College, New York; 2Division of Hematology and Medical Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa; 3Division of Hematology and Medical Oncology, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, USA

Received 13 November 2015; revised 17 February 2016; accepted 29 March 2016

Lenalidomide is an oral immunomodulatory drug with significant activity in indolent B-cell and mantle cell lymphomas. Lenalidomide has a manageable safety profile whether administered as a single agent or in combination with rituximab. The combination of lenalidomide with rituximab, known as the ‘R2’ regimen, enhances efficacy over what has been shown with monotherapy and has demonstrated activity in patients considered resistant to rituximab. Tolerability of these regimens has been consistent among studies. Asymptomatic neutropenia is the most common grade 3/4 adverse event, typically managed by dose interruption, followed by dose reduction once neutrophils have recovered. Nonhematologic toxicities (e.g. fatigue) are generally low-grade, manageable with concomitant treatment, and/or lenalidomide dose modification. More frequent with R2, immune-related symptoms such as rash and tumor flare are important to recognize as lenalidomide-associated treatment effects in patients with lymphoma who require supportive care and potential dose modifications. Severe tumor flare reactions with painful lymphadenopathy are not typically observed outside of chronic lymphocytic leukemia/small lymphocytic lymphoma. Venous thromboembolism is uncommon in lymphomas, though prophylaxis is recommended. The general safety profile, differences between lenalidomide monotherapy and R2 treatment, and optimal strategies for managing adverse events are discussed here.

Key words: lenalidomide, mantle cell lymphoma, non-Hodgkin lymphoma, rituximab, safety

Introduction

Lenalidomide is an oral immunomodulator with significant clinical activity demonstrated in multiple phase II trials of relapsed/refractory B-cell lymphomas [1, 2] and mantle cell lymphoma (MCL) [3, 4]. This led to the pivotal MCL-001 study [5] and the subsequent randomized study of lenalidomide versus investigator’s choice (IC) in relapsed/refractory MCL (MCL-002) [6]. Combined analyses of patients with MCL, who were treated with lenalidomide showed consistent activity with predictable safety [7, 8]. Based on preclinical synergy with the anti-CD20 monoclonal antibody rituximab [9, 10], lenalidomide plus rituximab (R2) was investigated in patients with both newly diagnosed and relapsed/refractory indolent non-Hodgkin lymphoma (iNHL) and MCL [11, 12]. This review focuses on the safety profile of lenalidomide monotherapy and R2 combination therapy and communicates optimal strategies for managing adverse events (AEs), while efficacy outcomes are also reviewed.

Mechanistic rationale

Lenalidomide exhibits antineoplastic and antiproliferative effects against malignant B cells [9, 13, 14], including follicular lymphoma (FL) and MCL [15–17], and modulates immune cells within the lymph node microenvironment [18]. Cereblon, the direct molecular target for lenalidomide, partners with ubiquitously expressed E3 ubiquitin ligase [19, 20]. Combination of lenalidomide and rituximab led to expansion and recruitment of natural killer (NK) cells to the tumor and augmented rituximab-associated antibody-dependent cellular cytotoxicity (ADCC) in lymphoma xenograft models [10, 21, 22]. The inclusion of lenalidomide with rituximab demonstrated significant activity in patients with rituximab-resistant lymphoma and was associated with reduction of peripheral blood T-regulatory cells, potentially enhancing rituximab-induced ADCC by NK cells [23]. Systemic increases of CD8+/PD−1+ T cells, NK/T, and dendritic cells in peripheral blood were detected in patients during the initial
phase of R² therapy, suggesting increased trafficking of activated immune cell subsets to the tumor [24].

**safety of lenalidomide and R²**

The safety profiles of single-agent lenalidomide and R² are mainly based on single-arm phase II trials. Two comparative trials evaluated R² with lenalidomide in recurrent FL (CALGB 50401) [11] and R² with rituximab in untreated FL (SACK 35/10) [25]. Unless otherwise specified, in most studies, lenalidomide was administered days 1–21 of 28-day cycles until disease progression, unacceptable toxicity or withdrawn consent.

**relapsed/refractory MCL and iNHL**

The MCL-001 study enrolled 134 patients with MCL whose lymphoma had relapsed or was refractory to bortezomib (median 4 prior treatments) to receive lenalidomide 25 mg/day on days 1–21 of each 28-day cycle [5]. Overall, 58% of patients received ≥3 cycles with an average dose of 20 mg/day lenalidomide. Neutropenia, thrombocytopenia, and anemia were the most common grade 3/4 hematologic AEs (Table 1); neutropenia and thrombocytopenia were the most common reasons for dose modification or discontinuation. Other AEs of interest included rash (22%, mostly grade 1/2; 1% grade 3), tumor flare reactions (TFRs, 10%, all grade 1/2 and mainly in cycle 1), and venous thromboembolic events (VTEs, 7%; 5% grade 3/4). VTEs were principally seen in patients not receiving thromboprophylaxis (i.e. aspirin or low-molecular-weight heparin). With the knowledge that patients with MCL are known to have an inherently higher risk for developing secondary malignancies (SPMs) [26,27], after a median follow-up of 13.4 months, 3 patients (2%) in the MCL-001 study were observed with invasive SPMs [5]. This is similar to the 2.1/100 person years age-adjusted incidence for newly diagnosed invasive cancers in individuals aged ≥65 years according to the US Surveillance, Epidemiology, and End Results (SEER) program [28].

The MCL-002 study randomized 254 patients with MCL 2:1 to receive lenalidomide 25 mg/day on days 1–21/28 or single-agent IC (cytarabine, rituximab, gemcitabine, fludarabine, or chlorambucil) [6]. The safety profile for lenalidomide was consistent with that shown in MCL-001 (with the same dosing regimen). Grade 3/4 neutropenia was more common with lenalidomide (44% versus 34%), whereas grade 3/4 thrombocytopenia was higher with IC (18% versus 28%). TFRs were only observed with lenalidomide (10% overall; 2% grade ≥3). After a median follow-up of 15.9 months, invasive SPMs were similarly reported in 4% and 5% of patients in the lenalidomide and IC arms, respectively.

A study in the UK in 26 patients examined lenalidomide at the same initial 25 mg/day dose on days 1–21/28 for six cycles similar to the above MCL-001 and MCL-002 studies, then lowered the dose to 15 mg/day on days 1–21/28 for maintenance in patients with at least stable disease [29]. The main grade ≥3 AEs were hematologic (62% neutropenia, 42% thrombocytopenia, and 15% anemia) and manageable with dose reduction with/without growth factor support. Nonhematologic AEs were generally low-grade, with the exception of a 42% grade ≥3 infection rate, including one grade 5 Pneumocystis jiroveci infection.

In combination with rituximab at a standard dose of 375 mg/m² (weekly ×4, cycle 1 only), the maximum-tolerated dose for lenalidomide was identified as 20 mg for 44 patients with relapsed/refractory MCL [12]. Patients had received a median of 2 prior regimens; all were previously treated with rituximab, and 27% received prior bortezomib. Grade 3/4 AEs with R² were mostly hematologic, including 66% neutropenia, grade 3 febrile neutropenia in 2 patients (5%), and grade 3/4 thrombosis/thromboembolism in 3 patients (7%). Grade 1/2 nonhematologic AEs in ≥50% of patients included fatigue, constipation, neuropathy, dyspnea, non-neutropenic infection, rash, myalgia, hyperglycemia, and diarrhea.

The CALGB 50401 study randomly assigned 91 assessable patients with recurrent FL (after prior rituximab) to lenalidomide or R² [11]. Lenalidomide was administered at 15 mg/day, cycle 1 and then escalated to 20 mg/day, cycles 2–12 if tolerated; rituximab 375 mg/m² was given weekly ×4 during cycle 1 in the R² arm. Notably, more patients receiving R² completed the planned 12 cycles of treatment (63% versus 36%). Overall, grade 3/4 AEs were similar for the R² and lenalidomide arms (52% versus 58%; 11% versus 9% grade 4; Table 1), although a lower incidence of thrombosis was observed with R² (4% R² versus 16% lenalidomide; P = 0.157). Although correlations were limited by small sample sizes and the nonrandomized use of prophylaxis, these data emphasize that it is important to consider the use of thrombosis prophylaxis in high-risk patients.

In a separate study of R² in relapsed/refractory iNHL, lenalidomide 20 mg/day was given with rituximab 375 mg/m² weekly ×4 beginning day 15 in cycle 1 [30]. Two of the first four patients enrolled, both previously heavily treated and with bulky disease, developed grade 3 tumor lysis syndrome (TLS) within the first 2 weeks on 25 mg lenalidomide. As a result, the protocol was amended to reduce the starting dose of lenalidomide from 25 to 20 mg and incorporate allopurinol prophylaxis alongside electrolyte monitoring. No subsequent cases of TLS were reported. Grade 3/4 toxicity was mainly hematologic, although fatigue was reported in 23% of patients and hyponatremia in 9% (Table 1).

In 50 patients with rituximab-resistant iNHL or MCL receiving R², lenalidomide was administered at 10 mg/day continuously, with weekly rituximab during cycle 3 [23,31]. The first 27 patients also received low-dose dexamethasone (10 mg once weekly). The most common grade 3/4 AEs were neutropenia and hypokalemia (Table 1). Pulmonary embolism was reported in two patients (4%). Dose interruptions due to tumor flare and rash in the first two cycles of treatment were significantly fewer with dexamethasone (P = 0.035).

**previously untreated MCL and iNHL**

Based on its activity in relapsed/refractory disease, R² was subsequently evaluated in previously untreated non-Hodgkin lymphoma (NHL). A total of 110 patients with advanced-stage, untreated iNHL received R² consisting of lenalidomide 20 mg, days 1–21 and rituximab 375 mg/m², day 1 of each 28-day cycle for 6 cycles and continued for up to 12 cycles in responders [24]. Patients with small lymphocytic lymphoma (SLL) initiated lenalidomide at a dose of 10 mg, with 5-mg dose escalations monthly, to reduce the risk of TFR. Grade 3/4 neutropenia was
<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>Treatment</th>
<th>All grade 3/4 AEs</th>
<th>Grade 3/4 hematologic AEs (≥5%)</th>
<th>Grade 3/4 nonhematologic AEs (≥5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph II MCL-001 [5]a</td>
<td>R/R MCL after prior bortezomib (N = 134)</td>
<td>Lenalidomide</td>
<td>66%</td>
<td>Neutropenia (43%), thrombocytopenia (28%), anemia (11%)</td>
<td>Pneumonia (8%), fatigue (7%), diarrhea (6%), dyspnea (5%)</td>
</tr>
<tr>
<td>Ph II MCL-002 [6]a</td>
<td>R/R MCL (N = 170)</td>
<td>Lenalidomide</td>
<td>–</td>
<td>Neutropenia (44%), thrombocytopenia (18%), anemia (8%), leukopenia (8%)</td>
<td>None above 5%</td>
</tr>
<tr>
<td>Ph II MCL UK study [29]b</td>
<td>R/R MCL (N = 26)</td>
<td>Lenalidomide</td>
<td>–</td>
<td>Neutropenia (62%), thrombocytopenia (42%), anemia (15%)</td>
<td>Infection (42%)</td>
</tr>
<tr>
<td>Ph I/II R² dose-finding [12]c</td>
<td>R/R MCL (N = 44)</td>
<td>R²</td>
<td>–</td>
<td>Neutropenia (66%; 5% grade 3 febrile), lymphopenia (36%), leukopenia (30%), thrombocytopenia (23%)</td>
<td>Thrombosis/thromboembolism (7%) and 5% (2 patients) each abdominal pain, fatigue, pleural effusion, rash, myalgia, hyperglycemia</td>
</tr>
<tr>
<td>Ph II CALGB 50401 [11]d,e</td>
<td>Recurrent FL after prior rituximab (N = 91)</td>
<td>Lenalidomide (n = 45)</td>
<td>58%</td>
<td>Neutropenia (16%)</td>
<td>Fatigue (9%), thrombosis (16%)</td>
</tr>
<tr>
<td>Ph II R² [30]f</td>
<td>R/R iNHL (N = 30)</td>
<td>R² (n = 46)</td>
<td>52%</td>
<td>Neutropenia (20%)</td>
<td>Fatigue (13%), thrombosis (4%)</td>
</tr>
<tr>
<td>Ph II R² [23]g</td>
<td>Rituximab-resistant iNHL or MCL (N = 50)</td>
<td>R²</td>
<td>–</td>
<td>Neutropenia (55%), lymphopenia (45%)</td>
<td>Fatigue (23%), hypokalemia (9%)</td>
</tr>
</tbody>
</table>

*Lenalidomide 25 mg/day given on days 1–21 every 28 days; patients with creatinine clearance ≥30 to <60 ml/min received lenalidomide 10 mg/day according to the same schedule.

*Lenalidomide 25 mg/day given on days 1–21 every 28 days for six cycles followed by low-dose maintenance in responding patients with lenalidomide 15 mg/day on days 1–21 of every 28 days until disease progression.

*Lenalidomide 20 mg/day given on days 1–21 every 28 days plus rituximab 375 mg/m² weekly for 4 weeks in cycle 1.

*Lenalidomide 15 mg/day in cycle 1, then 20 mg/day in cycles 2–12; administered on days 1–21 every 28 days.

*Lenalidomide 15 mg/day in cycle 1, then 20 mg/day in cycles 2–12; administered on days 1–21 every 28 days plus rituximab 375 mg/m² weekly for 4 weeks in cycle 1.

*Lenalidomide 20 mg/day administered on days 1–21 every 28 days plus rituximab 375 mg/m² weekly for 4 weeks starting on day 15 of cycle 1.

*Lenalidomide 10 mg daily (continuous 28-day cycles) plus rituximab 375 mg/m² weekly for 4 weeks in cycle 3 only; 27 patients also received dexamethasone 10 mg once weekly.

–, not reported; AE, adverse event; FL, follicular lymphoma; iNHL, indolent non-Hodgkin lymphoma; MCL, mantle cell lymphoma; Ph, phase; R², lenalidomide + rituximab; R/R, relapsed/refractory.
Table 2. Most common grade 3/4 adverse events in clinical studies of $R^2$ regimen

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients</th>
<th>$R^2$ regimen</th>
<th>Grade 3/4 hematologic AEs ($\geq 5%$)</th>
<th>Grade 3/4 nonhematologic AEs ($\geq 5%$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PH II $R^2$ [32]</td>
<td>iNHL (N = 65), FL (N = 65)</td>
<td>Lenalidomide 20 mg/day on days 1–21 and rituximab 375 mg/m² weekly during cycle 1 and then on day 1 of cycles 4, 6, 8, 10, and 12</td>
<td>Neutropenia (19%), lymphopenia (11%)</td>
<td>Rash (29%), tumor flare (11%), serum sickness-like infusion reaction associated with rituximab (8%), fatigue (8%), infusion reaction associated with rituximab (8%)</td>
</tr>
<tr>
<td>PH II $R^2$ [33]</td>
<td>MCL (N = 38)</td>
<td>Lenalidomide 15 mg/day on days 1–21 of each 28-day cycle</td>
<td>Neutropenia (13%), anemia (11%)</td>
<td>Rash (29%), tumor flare (11%), serum sickness-like infusion reaction associated with rituximab (8%), fatigue (8%)</td>
</tr>
</tbody>
</table>

Safety comparisons across studies are inherently limited by differences in patient populations, types of NHL, study designs, and dosing regimens. Nevertheless, the safety profile of lenalidomide appears generally consistent whether administered as a single agent or in combination with rituximab. Neutropenia is the most common grade 3/4 AE, more frequent in patients with MCL, but without a clinically significant increase in fever or infections. In preliminary results from comparative studies, grade 3/4 neutropenia was elevated when comparing rituximab versus $R^2$ (5\% versus 19\%) in previously untreated FL (SAKK 35/10) [25], though it was similar for lenalidomide versus $R^2$ for patients with recurrent FL [11]. Immune-related symptoms such as rash and TFR may reflect immune recalibration in patients with lymphoma and are important to recognize as lenalidomide-associated treatment effects that require supportive care and potential dose modifications.

Clinical perspectives on monitoring and managing toxicities

Dosing schedules

The dose of lenalidomide generally averages 20 mg/day (days 1–21) for each 28-day cycle when combined with standard-dose rituximab.
in NHL. Lenalidomide was started at a dose of 10 mg in patients with SLL to minimize TFR risk and subsequently escalated monthly in 5-mg increments [24]. Because lenalidomide is excreted primarily unchanged by the kidneys, lower starting doses are recommended in patients with moderate (10 mg daily) and severe (15 mg every 48 h) renal impairment [5, 34]. In the Ruan et al. study, 36% of patients tolerated dose escalation from 20 to 25 mg/day lenalidomide, whereas 42% required dose reduction to ≤15 mg [33]. To ensure optimal treatment with lenalidomide or \( R^2 \), the treating physician should consider TLS and VTE prophylaxis, particularly for those at higher risk of such complications. A guideline for monitoring and treatment of these and other AEs is provided in Figure 1.

**cytopenias**

As noted above, grade 3/4 myelosuppression is recognized as the most common AE with single-agent lenalidomide and \( R^2 \). In the MCL-001 study, neutropenia was observed throughout treatment, although thrombocytopenia decreased after the first two cycles; thus, monitoring of complete blood counts is recommended weekly in cycle 1, every 2 weeks in cycle 2, and monthly in subsequent cycles [5, 34]. Specified dose reductions or interruptions are based on significant neutrophil or platelet count changes (Figure 1). Prophylaxis for neutropenia and thrombocytopenia is not required, but patients may be given growth factor support or platelet transfusions to correct severe/prolonged cytopenias or neutropenic fever.

**Figure 1.** Monitoring and management strategies for common AEs in patients receiving lenalidomide or \( R^2 \). AE, adverse event; CBC, complete blood count; LMWH, low-molecular-weight heparin; NHL, non-Hodgkin lymphoma; NSAIDs, nonsteroidal anti-inflammatory drugs; \( R^2 \), lenalidomide + rituximab; SLL, small lymphocytic lymphoma; TFR, tumor flare reaction; TLS, tumor lysis syndrome.
immune-related reactions
TFR generally occurred during the first cycle of lenalidomide, with few events evident during later cycles [5]. None were serious in nature, allowing treatment to continue with minimal interruption or modification. It is clinically important to recognize and differentiate TFR, which tends to be associated with painful swelling and other inflammatory symptoms, from disease progression to prevent premature treatment termination. Grade 3/4 rash occurred more frequently with R² than lenalidomide in early treatment cycles, particularly in previously untreated patients. To date, the incidence of any-grade rash was reported as 22% (1% grade 3) with lenalidomide in relapsed/refractory MCL (MCL-001) [5], 61% (5% grade 3) with R² in relapsed/refractory MCL [12], and 29% grade 3/4 with R² in previously untreated MCL [33]. Mild-to-moderate rash following lenalidomide ± rituximab was generally manageable with antihistamines or low-dose corticosteroids [5]. A focus on the incidence of rash from a recent study of previously untreated iNHL patients receiving R² reiterated the observation that rash was generally low grade in nature, though pointed out that rash has the potential to negatively affect a patient’s quality of life [35]. With the upfront management strategies outlined by Fowler et al., including patient education, occurrences of grade 1/2 rash may be effectively mitigated with supportive care alone, while grade 3 rash may require dose modification to allow for re-exposure to R² treatment. In a phase II study for relapsed/refractory iNHL and MCL, the inclusion of low-dose dexamethasone (10 mg weekly) with R² may in part abrogate both TFR and rash [23]. Patients in the dexamethasone arm encountered fewer dose interruptions due to TFR and rash during the initial 8 weeks of lenalidomide (P = 0.035), with the incidence of rash following R²-dexamethasone registered at 26% overall and 4% grade 3/4.

venous thromboembolism
Venous thromboembolic events were reported in small percentages of patients receiving lenalidomide or R². To reduce risk, thromboprophylaxis has been recommended with a regimen based on initial assessment of the patient’s underlying risk. Low-dose aspirin or low-molecular-weight heparin (LMWH) has been used for patients at lower risk, whereas LMWH or dose-adjusted warfarin may be considered for patients at higher risk [5, 36]. In MCL-001 and CALGB 50401, high-risk was defined as a history of thromboembolic events, use of concomitant medications that increased risk, or a known hypercoagulable state [5, 11].

fatigue/asthenia
Fatigue/asthenia, although generally low grade, may be a common issue reported in lenalidomide single-agent and R² trials throughout therapy. Since treatment is typically given over longer periods of time than chemotherapy, patients may need to expect persistent but tolerable symptoms, while some may require dose adjustments for quality-of-life reasons. In the Ruan et al. study which provided maintenance treatment with rituximab and a lower dose of lenalidomide (15 mg) following induction therapy, both the total and grade ≥3 incidences of fatigue (66% and 8% during induction versus 32% and 0 during maintenance) decreased at maintenance with the lower lenalidomide dose [33]. In addition, response quality continued to deepen with the maintenance dose. Therefore, to encourage compliance and ensure long-term treatment benefit, it is important to balance efficacy and toxicity with dose adjustment when indicated, especially in patients who have attained responses.

second primary malignancies
Based on findings in patients with multiple myeloma [37] and an increased risk for SPMs in patients with MCL [26, 27], long-term monitoring is an important aspect of lenalidomide therapy. The incidence of invasive SPMs with single-agent lenalidomide from the pivotal MCL-001 study in relapsed/refractory MCL was similar to the background age-adjusted incidence of newly diagnosed invasive cancer reported by US SEER [5, 38], and comparable for patients receiving lenalidomide and IC monotherapy (4% and 5%, respectively) in MCL-002 [6]. In R² studies, reported SPMs are an infrequent occurrence in newly diagnosed patients with iNHL [24] and patients with previously untreated MCL [33]. Other R² studies have not reported SPMs to date.

efficacy of lenalidomide and R²
The goal of the early lenalidomide monotherapy studies was to determine whether the treatment was active and tolerable to patients with relapsed/refractory disease, who may be heavily pretreated with limited treatment options. As reviewed above, the safety profile for lenalidomide and subsequent evaluation of R² treatment is manageable with a consistent safety profile. Table 3 provides detailed efficacy findings from the studies reviewed above.

With single-agent lenalidomide in prospective studies of patients with relapsed/refractory MCL, three studies showed overall response rate (ORR) 28%–40%, with 5%–8% of patients achieving a CR/CRu [5, 6, 29]. The median duration of response (DOR) was consistently above 16 months, and median progression-free survival (PFS) was 3.9–8.7 months. Compared with other single-agent IC of therapy, lenalidomide showed significantly improved PFS (primary end point) by 39% (median PFS was 8.7 months for lenalidomide versus 5.2 months with IC; P = 0.004) [6]. Subsequent evaluation of lenalidomide combined with rituximab (R²) demonstrated improved efficacy outcomes in relapsed/refractory MCL [12], iNHL [11, 30], and in patients who were considered resistant to prior rituximab [23] (Table 3). Indolent NHL patients from the CALGB 50401 study receiving R², compared with lenalidomide alone, achieved higher ORR (76% versus 53%) and CR rates (39% versus 20%), and significantly longer time to progression (2.0 versus 1.1 years, P = 0.0023) [11].

In the first-line setting, efficacy outcomes of R² continue to show favorable improvement over the relapsed/refractory setting (Table 3). Among 103 assessable iNHL patients, the ORR was 90%, CR was 63%, and 3-year PFS was 75% [24]. Among 57 assessable patients with previously untreated FL from the CALGB 50803 study, R² produced an ORR of 93% and CR of 72% [32]. Preliminary analysis for the SAKK 35/10 study at week 23 for intent-to-treat patients showed 36% CR/Cru for R² versus 25% for rituximab (P = 0.056) with follow-up ongoing [25]. Among 36 assessable patients with previously
tional role for bendamustine in combination with "
ination of other possible combinations has evaluated the poten-
median follow-up of 30 months [33].
untreated MCL, $R^2$ produced an ORR of 92% and 64% CR. The median DOR and PFS had not been reached after a median follow-up of 30 months [33].

**ongoing studies**

$R^2$ has a consistent safety profile with enhanced efficacy comparable with single-agent lenalidomide. Promising activity was reported with lenalidomide plus first-line R-CHOP in iNHL [39, 40] and in aggressive lymphoma [41, 42]. Additional examination of other possible combinations has evaluated the potential role for bendamustine in combination with $R^2$ (B-$R^2$) in MCL. While the B-$R^2$ triple combination has demonstrated high activity in the first-line and relapsed/refractory settings [43, 44], its clinical utility, limited by a high rate of grade 3–5 infections, remains to be further defined.

Combination regimens typically use active agents with complementary mechanisms of action and nonoverlapping toxicity profiles, but in some cases unexpected toxicity with novel biologic combination may be encountered. Idelalisib, a specific inhibitor of phosphatidylinositol-3-kinase-δ, has significant single-agent activity and has been safely combined with rituximab in iNHL [45, 46]. Phase I trials designed to combine idelalisib with $R^2$ were stopped due to unexpected toxicity suggestive of cytokine release syndrome, an uncommon IL-6-mediated toxicity, in relapsed/refractory FL and MCL [47] and serious hepatotoxicity in a small cohort of seven patients with relapsed/refractory indolent NHL [48]. Biologic triple combinations continue to be explored within clinical trials for iNHL/MCL, such as in a phase I study of first-line $R^2$ with ibrutinib in stage II-IV FL (Alliance A051103; NCT01829568), which is expected to provide results in the near future. As further data emerge, there is considerable
potential for lenalidomide-inspired combinations to contribute toward improved outcomes in iNHL/MCL.

These and other studies have led to further evaluation of $R^2$ in combination with chemotherapy and other targeted agents in a multitude of phase II/III clinical trials that have been reported in detail by Gribben et al. [18]. A few notable studies to mention include a large phase III international trial conducted on behalf of the MCL network with $R^2$ maintenance (versus rituximab alone) in elderly MCL patients (NCT01865110), a phase III Italian trial where lenalidomide is investigated for maintenance after autologous stem cell transplantation (NCT02354313) in advanced MCL, the phase III RELEVANCE trial for previously untreated FL with $R^2$ versus R-chemotherapy followed by R maintenance (NCT01650701), and a phase II Nordic Lymphoma Group study of $R^2$+ibrutinib (NCT02460276). Eventual data maturation of these studies will shed light on a head-to-head comparison of efficacy of frontline $R^2$ with R-chemo in FL, as well as delineating the optimal maintenance strategies for MCL.

conclusions

Combining lenalidomide with rituximab increases efficacy in MCL and iNHL while maintaining safety established by single-agent therapy. Optimal treatment with lenalidomide or $R^2$ requires consideration of prophylaxis for TLS and thromboembolic events and regular monitoring for common AEs including cytopenias and rash. Grade 1/2 AEs can generally be managed symptomatically without treatment interruption. Grade 3/4 AEs require dose modification while signs and symptoms are addressed and, once sufficiently resolved, resuming treatment as appropriate. Taking these steps will help ensure that patients with NHL receive maximal benefit from lenalidomide and $R^2$.

$R^2$ induction followed by maintenance may be an effective upfront alternative to chemotherapy for MCL patients, particularly for those who would otherwise not tolerate or wish to avoid a more intensive approach. The optimal treatment duration and potential combination with other agents remains to be defined in future prospective studies. In FL, the ongoing RELEVANCE study will provide valuable insight regarding the appropriate patient population for induction and maintenance strategies in the upfront setting.

To date, there are no prospectively established clinical–pathological parameters or biomarkers that can reliably predict treatment response to lenalidomide. This may reflect the mechanistic difference between a pleotropic biologic agent such as lenalidomide, which targets tumor microenvironment, from conventional combination chemotherapy. In the MCL-001 study, subgroup exploratory analysis showed a correlation between higher lactate dehydrogenase with lower response rates and DOR, and Ki-67 >50% was associated with lower CR rate, DOR, and survival [5, 49]. Given the significantly higher CR rates to $R^2$ in first-line settings compared with historical controls in relapsed/refractory iNHL and MCL, it is conceivable that patients with more resistant disease and a compromised immune microenvironment may be less likely to respond to lenalidomide. More prospective correlative studies are needed to identify clinically predictive biomarkers for response and survival in patients treated with lenalidomide-based biologic combinations.

In practical terms, the success of lenalidomide alone or the $R^2$ regimen relies on long-term adhesion to the outpatient treatment program, facilitated by a physician–patient team strategy to balance efficacy with safety management. Given that most of the dose-dependent adverse effects occur within the first few cycles of treatment, initiating treatment at lenalidomide dose of 20 mg or lower with a gradual dose ramp-up in subsequent cycles if tolerated may be appropriate for high-risk patient populations, including those with poor performance status, advanced age, risk for tumor lysis, and reduced bone marrow reserve. In patients deriving clinical benefit from treatment (stable disease, partial response, and CR), maintenance therapy at a low dose of lenalidomide either alone or in combination with rituximab may continue to improve response quality and duration in patients with MCL.

acknowledgements

The authors received editorial support in the preparation of this manuscript from Julie Kern, PhD, CMPP, and Barry Weichman, PhD of Bio Connections LLC, funded by Celgene Corporation. The authors directed development of the manuscript and are fully responsible for all content and editorial decisions for this manuscript.

funding

Assistance for editorial support in the preparation of this manuscript was funded by Celgene Corporation (no grant number).

disclosure

Authors report the following disclosures of potential conflicts of interest, including:

- Research funding: JR (Celgene, Janssen, Pharmacyclics, Seattle Genetics), BS (DeBartolo Institute for Personalized Medicine, Incyte, Rosetta Genomics, Seattle Genetics), PM (Millennium, Teva), and SS (Celgene)
- Honoraria received directly from an entity: JR (Celgene for advisory board and speaking), BS (Celgene), and PM (Janssen)
- Consulting, speaker’s bureau, or advisory board meeting: JR (Celgene, Janssen, Pharmacyclics, Seattle Genetics), BS (Acetylon, Bayer, Celgene, Pharmacyclics, Spectrum), PM (Acerta, Celgene, Genentech, Gilead, Janssen, Novartis), and SS (Celgene)

references


