Lenalidomide in relapsed or refractory mantle cell lymphoma: overview and perspective

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***Abstract*:** Lenalidomide, a novel immunomodulatory agent, was approved by the US Food and Drug Administration for the treatment of myelodysplastic syndrome and relapsed multiple myeloma. Data from preclinical studies paved the way for clinical trials of lenalidomide in mantle cell lymphoma (MCL). Initial phase I and II clinical trials of lenalidomide alone and as part of combination regimens in patients with relapsed/refractory MCL have shown promising results. Its immunomodulatory, T cell costimulatory, anti-inflammatory and anti-angiogenic actions working together in the tumor cell microenvironment seem to be responsible for its enhanced antitumor efficacy. Lenalidomide's nature of action and safety profile favor it over other agents studied in relapsed/refractory MCL. This review summarizes the data from preclinical and clinical studies of lenalidomide in relapsed/refractory MCL and compares the results with those of other novel agents being used for relapsed/refractory MCL.

Keywords: immunomodulatory agents, lenalidomide, mantle cell lymphoma

Introduction

Mantle cell lymphoma (MCL) was considered almost incurable until it was discovered that thalidomide, an almost forgotten compound till then, can in fact achieve better remission rates in relapsed cases of MCL with fewer toxicities [Damaj *et al.* 2003; Kaufmann *et al.* 2004]. Thalidomide was first introduced in the late 1950s, but it was not used for decades after it was found to cause severe birth defects, including phacomelia. In the 1990s, it was found that thalidomide has anti-angiogenic properties which renewed interest by researchers in this agent as a treatment for cancer. Subsequent studies showed that thalidomide possesses antitumor effects and can be used to treat various cancers [Kumar *et al.* 2002].

Although thalidomide possesses anti-angiogenic, anticancer and immunomodulatory effects, including inhibition of tumor necrosis factor-α (TNFα), treatment is associated with some severe side effects, including peripheral neuropathy and venous thromboembolism [Chaudhry *et al.* 2002; Mileshkin *et al.* 2006, Palumbo *et al.* 2011]. Besides this, intense monitoring is required to prevent pregnancy, due to its teratogenic effects. Therefore, research was driven to generate novel thalidomide analogs with enhanced antitumor, anti-angiogenic and immunomodulatory effects and better tolerability profile [Aragon-Ching *et al.* 2007]. This led to the generation of a novel class of thalidomide analogs known as immunomodulators (IMiDs), with enhanced immunological and anticancer properties but lacking the severe toxicities associated with thalidomide [Bartlett *et al.* 2004; Knight, 2005; Aragon-Ching *et al.* 2007]. Lenalidomide is one of the IMiDs that has shown promising antitumor efficacy in a wide range of malignancies, especially B-cell hematological malignancies [Chanan-Khan and Cheson, 2008]. Lenalidomide (Revlimid®) is a structural analog of thalidomide that possesses an additional amino (NH_2) group at position 4 of the phthaloyl ring and removal of the carbonyl (C=O) at position 2. Lenalidomide was approved by the US Food and Drug Administration (FDA) in 2005 for the treatment of myelodysplastic syndrome (MDS) with 5q deletion, with or without other cytogenetic abnormalities. It was subsequently approved for use in combination with dexamethasone to treat relapsed/refractory multiple myeloma (MM). Because of its efficacy in myeloma, lenalidomide is also being studied in other B cell

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malignancies, including MCL, with promising initial results.

MCL is an aggressive variant of B cell non-Hodgkin's lymphoma (NHL) and its incidence in the US has been rising steadily during the past three decades [Zhou *et al.* 2008]. It carries a poor prognosis compared to other NHL subtypes with a median overall survival (OS) of 5–7 years with recent advances [Perez-Galan *et al.* 2011]. Median age at diagnosis is 68 years and most patients are diagnosed at an advanced stage of the disease [Zhou *et al.* 2008]. There is no standard consensus for treating MCL. The most common frontline chemotherapy is R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone) or R-HyperCVAD (rituximab plus hyperfractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone alternating with cytarabine and methotrexate) [Lenz *et al.* 2005; Romaguera *et al.* 2010; Kluin-Nelemans *et al.* 2012]. The highest complete response (CR) rate for newly diagnosed MCL remains 34–61% [Lenz *et al.* 2005; Nickenig *et al.* 2006; Delarue *et al.* 2008; Geisler *et al.* 2008; Damon *et al.* 2009]. However, this comes at the expense of several hematological and non-hematological toxicities. Stem cell transplantation has improved outcomes, but it is not curative in all the patients [Khouri *et al.* 1998]. In addition, many patients are not eligible for stem cell transplantation due to their advanced age or associated comorbid conditions.

Although recent advances in treatment have slightly increased remission rates; recurrence and relapse are very common. Relapse is also a major cause of death in patients with MCL. Despite the fact that intensive frontline regimens and salvage programs can achieve an overall response rate (ORR) of nearly 90%, the majority of patients still relapse [Herrmann *et al.* 2009]. Bortezomib, a first generation proteasome inhibitor, was the first drug approved by the FDA for use in MCL patients who have received at least one prior therapy. The response rates still remain low and many patient relapse while on bortezomib, as we will see later. This emerging need for novel chemotherapeutic options that could induce prolonged responses and increase survival with fewer side effects led to thorough research into lenaliodomide in MCL patients. Extensive research led to FDA approval of lenalidomide for MCL patients whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib. Recently, ibrutinib (Bruton's tyrosine kinase inhibitor) has been approved for treatment of relapsed MCL as well. In this review, we discuss the preclinical and clinical experience with lenalidomide as a promising therapeutic option for patients with relapsed and/or refractory MCL.

Mechanism of action of lenalidomide in MCL

In vitro and *in vivo* experimental studies have shown that lenalidomide works through multiple mechanisms, including direct tumor cytotoxicity, inhibition of angiogenesis and osteoclastogenesis, and disruption of stromal cell-derived signals from the tumor microenvironment [Chanan-Khan and Cheson, 2008]. In addition, lenalidomide acts as an immunomodulator by activating immune cells, especially natural killer (NK) and T cells. Compared with thalidomide, lenalidomide exerts superior anti-inflammatory and immunomodulatory actions [Aragon-Ching *et al.* 2007].

Lenalidomide stimulates proliferation and activation of antitumor T cells effective against MCL cells [Gaidarova *et al.* 2008]. Lenalidomide inhibits interleukin-1β (IL-1β) and TNF-α induced activation of IκB kinase (IKK) from nuclear factor-κB (NF-κB), preventing its nuclear translocation and induction of genes that function in metastasis, angiogenesis, cellular proliferation, inflammation and protection from apoptosis [Keifer *et al.* 2001]. Further, lenalidomide exhibits significant anti-angiogenic effects including interaction with tumor microenvironment, endothelial cells and vascular endothelial growth factor (VEGF) [Dredge *et al.* 2002, 2005; Vallet *et al.* 2008]. Recently it was also found that tumor lymphangiogenesis contributes to the progression of lymphomagenesis and that lenalidomide is effective in decreasing MCL growth specifically and metastasis by inhibiting recruitment of MCL-associated macrophages [Song *et al.* 2013].

Hernandez-Ilizaliturri and colleagues first studied the combination of lenalidomide and rituximab in aggressive lymphoma [Hernandez-Ilizaliturri *et al.* 2005]. They found that *in vitro* lenalidomide induced growth inhibition and apoptosis of lymphoma cells. In the mouse model, lenalidomide enhanced the antitumor effects of rituximab and augmented NK cell function. In addition, the combination increased the median survival of the lymphoma-bearing mice compared with rituximab alone. Lenalidomide has also been shown to

increase recruitment of NK cells to tumor sites which is mediated by stimulation of dendritic cells and modification of the cytokine microenvironment that causes augmentation of rituximab-associated antibody-dependent cellular cytotoxicity (ADCC) [Reddy *et al.* 2008]. Lenalidomide potentiates the effects of rituximab more strongly than thalidomide [Richardson *et al.* 2010]. It also increases peripheral blood mononuclear cell (PBMC) mediated cytotoxicity. This enhanced PBMC activity can lead to tumor cell apoptosis. Increase of NK cells and NK-T cells from the PBMC population play an essential role in this process [Zhu *et al.* 2008]. Lenalidomide delayed the tumor growth and improved the survival of MCL-bearing mice when used with dexamethasone as well as rituximab [Zhang *et al.* 2009; Qian *et al.* 2011]. Lenalidomide also enhanced dexamethasone-induced G0/G1 arrest. The combination of lenalidomide with dexamethasone as well as with rituximab induces apoptosis of lymphoma cells through mitochondrial signaling pathways. Lenalidomide sensitizes tumor cells and enhances rituximab-mediated cytotoxicity of MCL cells. Daily treatment with lenalidomide increased NK cells by 10-fold in MCL-bearing SCID mice [Zhang *et al.* 2009]. The combination of lenalidomide and rituximab enhances the NK-cell mediated synapse formation and cell killing which can become dysfunctional as part of immune evasion by lymphoma cells [Gaidarova *et al.* 2009]. Additionally, lenalidomide induces capping of CD20 and cytoskeleton proteins of malignant B cells which increases their immune recognition by rituximab and its overall activity [Gaidarova *et al.* 2010]. Moros and colleagues studied the activity of lenalidomide in *in vitro* and *in vivo* models of bortezomib-resistant MCL and showed that single-agent lenalidomide is preferentially effective in MCL cases resistant to bortezomib by targeting C-Myc-driven tumorigenesis [Moros *et al.* 2012]. Lenalidomide has also shown to partially overcome resistance exerted by lymphoma cells towards other chemotherapeutic agents like rituximab and bortezomib [Reddy *et al.* 2006, Moros *et al.* 2012].

In summary, lenalidomide has antitumor activity in MCL as a single agent as well as in combination, mainly with rituximab. Preclinical success led to study of its efficacy and safety in clinical trials. Lenalidomide has been studied in clinical trials as a single agent and in combination with other agents with proven activity in MCL as described below.

Activity of single-agent lenalidomide in MCL

Table 1 reports the published data on activity of lenalidomide in relapsed MCL patients from phase II clinical trials of single-agent lenalidomide in patients with relapsed and/or refractory NHL. Lenalidmide has not been studied as a monotherapy in front-line settings of MCL.

NHL-002 was the first trial studying single-agent lenalidomide in patients with relapsed/refractory aggressive NHL [Wiernik *et al.* 2008]. In this multicenter phase II study, lenalidomide was administered as 25 mg per day orally for day 1 to 21 of a 28-day cycle. Lenalidomide receiving patients (n = 49) had an ORR of 35% with a median duration of response (DOR) of 6.2 months. Median progression-free survival (PFS) was 4 months. Activity and safety data among MCL patients has been published separately with a longer follow up [Habermann *et al.* 2009]. ORR among 15 patients with relapsed/refractory MCL was 53%; 20% of them had a CR. Median PFS among MCL patients was 5.6 months.

The subsequent clinical trial, NHL-003, an international phase II study, enrolled 217 patients with relapsed/refractory aggressive NHL and reported an ORR of 35%, with a median PFS of 3.7 months and median DOR or 10.6 months [Witzig *et al.* 2011]. Zinzani and colleagues recently presented long-term safety and efficacy data of MCL patients from the NHL-003 trial. Among 57 patients with relapsed/refractory MCL, 35% had a response and 12% had a CR with a median DOR of 8.8 (5.5–23) months. The median PFS among MCL patients was 16.4 (7.1 to not reached) months [Zinzani *et al.* 2013]. Vose and colleagues analyzed data from the NHL-002 and NHL-003 trials and showed that the potential of achieving a response to lenalidomide appears to be independent of prior history of stem cell transplantation (SCT) [Vose *et al.* 2013]. In this retrospective analysis, lenalidomide had an ORR of 63% [CR/unconfirmed CR (uCR) 26%] in patients with relapsed and/or refractory MCL who had at least one SCT done prior to receiving lenalidomide in both trials. Eve and colleagues studied a slightly different lenalidomide regimen in a phase II multi-center study among 26 patients with relapsed refractory MCL [Eve *et al.* 2012]. Patients received 25 mg per day of lenalidomide for 6 cycles followed by low-dose maintenance lenalidomide (15 mg) in responding patients. The study demonstrated an ORR of 31% with a

Table 1. Clinical experience with single agent lenalidomide in MCL.

Study	Dose	No. of patients	Prior lines of therapy	ORR	CR/ uCR	Median PFS, months	Median DOR, months	Most common grade 3/4 adverse events
Lenalidomide in relapsed/refractory MCL								
NHL-002 [Habermann *et al.* 2009]	25 mg/d PO; days 1–21	15	4 (2–7)	53%	20%	5.6	13.7	Neutropenia (40%), thrombocytopenia (33%)
NHL-003 [Zinzani *et al.* 2013]	25 mg/d PO; days 1–21	57	3 (1–13)	35%	12	8.8 (5.5-23)	16.34 (7.1 to NR)	Neutropenia (46%), thrombocytopenia (30%)
Eve *et al.* [2012]	25 mg/d PO, days 1–21 for 6 cycles followed by 15 mg maintenance	26	3 (2–7)	31%	8%	14.6 (7.3–21.9)	22.2 (0–53.6)	Neutropenia (62%), thrombocytopenia (42%), infection (42%)
Lenalidomide in bortezomib-resistant MCL								
EMERGE [Goy *et al.* 2013]	20 mg/d PO, days 1–21	134	4 (2–10)	28%	8%	4 (3.6–5.6); OS 19 (12.5–23.9)	16.6 (7.7–26.7)	Neutropenia (43%), Thrombocytopenia (28%)

CR, complete response; DOR, duration of response; MCL, mantle cell lymphoma; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by month; uCR – unconfirmed CR.

median DOR of 22.2 months. Median PFS was 3.9 months without maintenance lenalidomide and 14.6 months with maintenance lenalidomide, providing evidence for further study of lenalidomide in maintenance settings to achieve a longer disease-free period.

Lenalidomide showed activity in bortezomib-resistant cells as we saw earlier. Goy and colleagues conducted a phase II, multicenter, single-arm, open-label study (MCL-001 'EMERGE' study) to study the safety and efficacy of single-agent lenalidomide in subjects with MCL who relapsed on or were refractory to bortezomib, a proteasome inhibitor approved in treatment of relapsed/refractory MCL (n = 134) [Goy *et al.* 2013]. Single-agent lenalidomide demonstrated a response among 28% of subjects with a median DOR of 16.6 [95% confidence interval (CI) 7.7–26.7] months. Median time to response was 2.2 months and median time to progression was 5.4 (3.7–7.5) months by central review. Median PFS was 4 (3.6–5.6) months and OS was 19 (12.5–23.9) months. The most common grade 3/4 adverse events were neutropenia (43%), thrombocytopenia (28%) and anemia (11%). This was the first clinical study to demonstrate activity of lenalidomide in bortezomib-resistant patients providing way for larger phase III study for its approval for bortezomib-resistant MCL patients.

Lenalidomide is better tolerated than its parent compound thalidomide [Richardson *et al.* 2002]. Previous clinical trials in relapsed/refractory NHL using lenalidomide as a single agent have reported the following hematological and nonhematological toxicities: grade 3/4 hematologic adverse events occurring in at least 5% of patients include neutropenia, thrombocytopenia, leukopenia, anemia and febrile neutropenia; and grade 3/4 nonhematological adverse events were rarely reported and were manageable [Wiernik *et al.* 2008; Witzig *et al.* 2011]. Among all grade 3 or 4 toxicities, neutropenia is the most common hematological toxicity (40–46%) [Goy *et al.* 2013]. However, the incidence of febrile neutropenia is lower (2–6%) [Reeder *et al.*; Witzig *et al.* 2011; Wang *et al.* 2012]. Thrombocytopenia also is common (28–30%), but did not culminate into serious events in any studies. All hematological toxicities were manageable and reversible upon discontinuation of lenalidomide. Thalidomide is associated with a high incidence of peripheral neuropathy [Mileshkin *et al.* 2006], but recent studies of lenalidomide have shown that the incidence of grade 3/4 neuropathy in lenalidomide-naïve patients is very low (0.4–1%). In addition, lenalidomide maintenance did not significantly increase the incidence of grade 3/4 peripheral neuropathy [Wang *et al.* 2008; Attal *et al.* 2012].

Activity of lenalidomide in combination regimens in MCL

As lenalidomide enhanced the antitumor activity of other agents in preclinical studies and as it showed promising activity as a single-agent in MCL, interest was driven to study lenalidomide in combination with other active agents for treating MCL. Lenalidomide has been combined with dexamethasone, rituximab and bortezomib in respective clinical trials (Table 2).

To study the synergistic effects of lenalidomide in combination with rituximab demonstrated in preclinical studies, Wang and colleagues conducted a phase I/II clinical trial using this combination to investigate its efficacy in patients with relapsed and/or refractory MCL [Wang *et al.* 2012]. The maximum tolerated dose of lenalidomide when given in combination with rituximab was determined to be 20 mg in phase I. A total of 44 patients were enrolled in phase II, with an ORR of 57% and a median OS of 24.3 months. The median PFS was twice as long (11.1 months) with the lenalidomide–rituximab combination compared with lenalidomide alone (5.6 and 5.7 months) [Wiernik *et al.* 2008, Witzig *et al.* 2011, Wang *et al.* 2012]. Most common grade 3/4 adverse events were neutropenia (n = 29), lymphopenia (n = 16), leucopenia (n = 13 and thrombocytopenia (n = 10). These findings are promising and should be validated in a larger phase III clinical trial. Zaja and colleagues studied the combination of lenalidomide and dexamethasone among 33 patients with relapsed refractory MCL; 52% of the subjects had a response while 24% had a CR with a median DOR of 18 months. Median PFS was 12 months and median OS was 20 months [Zaja *et al.* 2012]. They reported slightly higher incidence of grade 3/4 neutropenia (53%) when lenalidomide was used in combination with dexamethasone, but this is likely due to this specific combination, as other studies using the lenalidomide–dexamethasone combination reported a similar adverse event profile, with an incidence of neutropenia near to 40% [Weber *et al.* 2007]. The incidence of thromboembolism was high in studies of lenalidomide in combination with dexamethasone in patients with myeloma and MDS [Carrier *et al.* 2011], which resulted in the FDA issuing a precautionary warning regarding thromboembolic events (deep vein thrombosis and pulmonary embolism) on the drug label. However, thromboembolic adverse events have not been seen in recent studies of lenalidomide either alone or in combination with other regimens in patients with MCL or other NHL. The high incidence of thromboembolic events reported in myeloma has been suggested to be associated with its use in combination with dexamethasone [Menon *et al.* 2008].

Morrison and colleagues conducted a phase II trial to investigate safety and efficacy of combination of lenalidomide with bortezomib (Alliance/CALGB 50501) [Morrison *et al.* 2012]. Although a higher ORR was expected, only 40% of patients responded with a 1-year PFS of 41%, while producing significant toxicity leading to treatment discontinuation in 32% of participants. Most common grade 3/4 toxicities (>10%) were thrombocytopenia (13/21), fatigue/aesthenia (21/0) and neuropathy (17/0; grade 2: 36%). Since this response was similar to that seen with single-agent lenalidomide and incidence of higher toxicity with this regimen, the authors do not recommend further studies with similar dose and schedule of combination of lenalidomide and bortezomib.

Flinn and colleagues studied combination of rituximab, lenalidomide and bortezomib in first- or second-line treatment of patients with MCL in a phase I/II trial [Flinn *et al.* 2012]. The maximum tolerated dose (MTD) of lenalidomide (10mg) in combination with bortezomib and rituximab was less than lenalidomide and bortezomib combination in MM as per study. In phase II, patients received 10 mg lenalidomide by mouth (PO) (daily on days 1–14), bortezomib 1.3 mg/m^2 intravenously (IV) (days 1, 4, 8 and 11) and rituximab 375 mg/m^2 (days 1, 8 and 15 of cycle 1; 375 mg/m^2 on day 1 of subsequent cycles). ORR was 82% with 32% of patients having a CR. Those who did not received prior treatment, ORR was 75%. At the median follow up of 16 months, 18-month PFS was 61%. Grade 3/4 events were rash (32%), thrombocytopenia (23%), neutropenia (18%) and neuropathy (18%). The authors suggest that, given the incidence of neuropathy, subcutaneous or less frequent IV dosing of bortezomib is worthy of investigation rather than the twice-weekly IV bortezomib used in this study. The LENA-BERIT trial studied lenalidomide, bendamustine and rituximab as first-line therapy for patients >65 years with MCL [Jerkeman *et al.* 2011]. The results of the phase I portion reported that addition of lenalidomide to the rituximab–bendamustine regimen leads to increased toxicity in elderly patients with MCL, although it is associated with very high response rate (ORR 100%, n = 10).

Table 2. Clinical experience with lenalidomide in combination with other agents for MCL.

Study/regimen	Dosing	No. of patients	Prior lines of therapy	ORR	CR/uCR	Survival	Median DOR, months	Median follow up	Most common grade 3/4 adverse events
Lenalidomide in combination regimen in relapsed/refractory MCL									
LEN+DEXA [Zaja *et al.* 2012]	LEN: 25 mg/d PO, days 1–21 DEX: 40 mg/day on days 1, 8, 15, 22 (for maximum of 12 cycles)	33	3 (2–7)	52%	24%	Median PFS: 12 months Median OS: 20 months	18	N/A	Neutropenia (53%), leukopenia (25%), thrombocytopenia (22%)
LEN+RTX [Wang *et al.* 2012]	LEN: 20 mg/day PO, days 1–21 RTX: 375 mg/m^2 IV, 4 weekly doses – cycle 1 only	52	2 (1–4)	57%	36.4%	Median PFS: 11.1 months Median OS: 24.3 months	18.9	N/A	Neutropenia (29 pt), lymphopenia (16 pt), leucopenia (13 pt), thrombocytopenia (10 pt)
LEN+BTZ [Morrison *et al.* 2012]	LEN: 20 mg/d PO, days 1–14 BTZ: 1.3 mg/m^2 IV days 1, 4, 8, 11 (maximum 8 cycles)	53	1 (1–5)	40%	15%	1-year EFS 25%, 1-year PFS 41%, 1-year OS 67%	N/A	2.3 years	Thrombocytopenia (13%/21%), fatigue (21%/0), Neuropathy (17%/0)
Lenalidomide in combination regimen in MCL									
LEN+RTX+BTZ [Flinn *et al.* 2012]	LEN: 10 mg/day PO, days 1–14 RTX: 375 mg/m^2, days 1, 8, 15 of cycle 1 and then day 1 of subsequent cycles BTZ: 1.3 mg/m^2 IV, days 1, 4, 8, 11 (maximum 6 cycles)	22	0 (0–1)	82%	32%	18-month PFS: 61%; 18-month OS: 79%	N/A	16 (1–38) months	Neutropenia (23%) Rash (32%) Neuropathy (18%) Thrombocytopenia (18%)

BTZ, bortezomib; CR, complete response; DEX, dexamethasone; DOR, duration of response; EFS, event-free survival; IV, intravenously; LEN, lenalidomide; MCL, mantle cell lymphoma; N/A, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PO, by mouth; RTX, rituximab; uCR, unconfirmed CR.

Discussion

Managing relapsed/refractory MCL has always been a challenge, with many options being evaluated to date. Bortezomib was the first agent approved by the FDA for use in relapsed/refractory MCL followed by lenalidomide and ibrutinib, successively. The largest prospective phase II study of bortezomib in relapsed/refractory MCL (n = 155) showed an ORR of 33%, with 8% CR/uCRs and a median DOR of 9.2 months [Fisher *et al.* 2006]. Subgroup analyses of MCL cases from NHL-002 and NHL-003 reported ORR of 35–53% [Habermann *et al.* 2009; Zinzani *et al.* 2013]. We speculate that response rates with lenalidomide as a single agent are better than bortezomib, with fewer toxicities, especially peripheral neuropathy.

Single-agent lenalidomide also comparatively exhibits better efficacy than single-agent rituximab. When used as a single agent in relapsed/refractory MCL, rituximab showed an ORR in 27–34% (n = 104) [Foran *et al.* 2000; Ghielmini *et al.* 2005]. When lenalidomide and rituximab were combined, the combination was more effective than either agent alone [Wang *et al.* 2012]. Furthermore, there were very few grade 3/4 adverse events and all were manageable, with no patients discontinuing the study due to adverse events. Because the combination of lenalidomide and dexamethasone has been effective as a treatment for relapsed/refractory myeloma, the combination was tested in patients with relapsed/refractory MCL as well with an ORR of 52% and CR of 24% (n = 33). Investigators used a higher lenalidomide dose (25 mg/m^2) and achieved comparatively lower response rates compared with a recent trial of lenalidomide–rituximab [Zaja *et al.* 2012]. From the available data, we can say that lenalidomide–rituximab might be better tolerated than lenalidomide–dexamethasone.

Combination of bendamustine and rituximab has also been studied with ORRs of 92% (n = 12) and 75% (n = 16), respectively [Rummel *et al.* 2005; Robinson *et al.* 2008]. Although the response rate and efficacy are higher with the bendamustine-containing regimen, the toxicity profile of the alkylating agent, which is cytoreductive and causes significant hematoxicity, is expected to be higher than that of lenalidomide. In addition, the higher response rates found in these studies have not been confirmed in larger randomized trials.

Temsirolimus, a mammalian target of rapamycin (mTOR) kinase inhibitor, has been studied as a single agent and in combination with other agents in MCL. In phase II trials, single agent temsirolimus has been studied with different dosing regimens: 250 mg intravenously every week with ORR of 38% [Witzig *et al.* 2005] and 25 mg intravenously every week with ORR of 41%. [Ansell *et al.* 2008]. In both studies, temsirolimus had significant dose-dependent hematological toxicities, especially thrombocytopenia (grade 3/4 thrombocytopenia: 66% with 250 mg; 39% with 25 mg regimen). Subsequently, a randomized, open-label phase III study was performed to evaluate temsirolimus in two dosing levels compared with investigator's choice therapy (n = 162) [Hess *et al.* 2009]. Temsirolimus 175 mg weekly for 3 weeks followed by 75 mg weekly was shown to have ORR of 22%, median PFS of 4.8 months and median OS of 12.8 months compared with investigator's choice therapy. Based on these results, temsirolimus gained approval for the treatment of patients with relapsed MCL in the European Union. Another study investigated the combination of temsirolimus with rituximab in relapsed/refractory MCL (n = 71), which achieved an ORR of 59% and CR of 19%. For the rituximab refractory group, the ORR was 52% [Ansell *et al.* 2011]. While the response rate for this regimen is comparable to those of the lenalidomide–rituximab combination, there were fewer CRs with the temsirolimus–rituximab combination. Furthermore, there were more grade 3 and 4 toxicities with the temsirolimus–rituximab combination, particularly thrombocytopenia and neutropenia in rituximab-refractory group.

As a novel modality, investigators are studying biologic therapy as a first-line approach in MCL patients. Recently, Ruan and colleagues published preliminary data from a phase II multicenter trial of lenalidomide and rituximab in MCL patients who are recently diagnosed and not received any chemotherapy [Ruan *et al.* 2013]. Among 31 enrolled patients, 77% achieved ORR and 40% CR at a median follow-up of 12 months. A total of 23 (87%) patients remain on study for further follow up and maintenance treatment assessment. Medial time to objective response was 2.8 months. Grade 3/4 adverse events were neutropenia (39%), rash (23%) and thrombocytopenia (13%). The authors believe that response rates may further improve with additional follow up on continued treatment. Biological therapy should be further explored in front-line settings with agents like lenalidomide and ibrutinib in MCL to improve outcomes.

FDA recently approved the Bruton's tyrosine kinase (BTK) inhibitor, ibrutinib, in the management of MCL in patients who have received at least one therapy on the basis of multi-center, international, single-arm trial enrolling 111 patients with relapsed or refractory MCL [Wang *et al.* 2013]. Ibrutinib (560 mg, once daily) achieved response rates of 68% with CR of 21% at a median follow up of 15.3 months. Grade 3 or greater hematological adverse events were few: neutropenia (16%), thrombocytopenia (11%) and anemia (10%). Estimated 18-month OS was 58% and estimated median PFS was 13.9 months (95% CI: 7 to not reached). This was a breakthrough in MCL history considering once oral dosing, tolerability and higher response rates.

At the current moment, we have novel and better modalities coming to existence in the MCL field. Ibrutinib and lenalidomide both seem to be the potential future therapies for these patients. It is difficult to compare lenalidomide against ibrutinib in absence of comparative trials. In fact, it would be interesting to know if the combination modality is superior to the current approaches – specifically standard chemotherapy.

Conclusion

Considering the poor prognosis of MCL and frequent relapse/refractory disease, novel agents with higher efficacy and better tolerability are sorely needed early in the course of the disease. Lenalidomide is a potential agent with immune-enhancing effects as evidenced in preclinical studies and further validation in recent clinical trials leading to its approval. Good overall tolerability and ability to further enhance the antitumor efficacy of the established immunotherapeutic agent, rituximab, put lenalidomide at the forefront for early consideration in relapsed and/or refractory MCL. Current evidence is definitely in favor for the extensive study of lenalidomide in combination, as maintenance regimen and even in front-line settings for MCL. Temsirolimus has been approved in the European Union, but considering its heavy toxicity profile, lenalidomide and rituximab may be a preference with the new addition of another biologic agent, ibrutinib, for further investigation as a therapeutic choice. As we quoted earlier, lenalidomide with ibrutinib and/or rituximab would be a therapeutic choice in the future. We highly recommend future phase II clinical trials of lenalidomide in combination with ibrutinib or other novel agents in relapsed and/or refractory setting of MCL in order to achieve better response rates and increase overall survival of this group of patients. Early biologic approach in chemotherapy of naïve MCL patients with immunomodulatory agents and ibrutinib should also be explored further.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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