Review Article

Is there a role for immunomodulatory drugs in the treatment of mantle cell lymphoma?

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Abstract: Although survival has improved in patients with mantle cell lymphoma (MCL) during the last two decades, thanks to intensified approach upfront and with anti-CD20 targeted treatment, the disease is still regarded as incurable and for the elderly/unfit patient population, there is need for more tolerable and effective treatment options. Immunomodulatory drugs (IMiDs) have demonstrated activity in MCL and could be regarded as attractive components of combinatory regimens for MCL, in light of their broad spectrum of activity and the potency to synergize with monoclonal antibody treatment. This review focus on the role of lenalidomide (L) as single agent in R/R MCL and in combinatory regimens. To date, one can conclude that L is an active agent in MCL, preferably when combined with anti-CD20 antibody, and may have a role as upfront treatment of elderly/unfit patients. Moreover, regimens including lenalidomide in combination with immunochemotherapy and in chemo-free regimens have shown activity, albeit associated with an increased risk of dose-limiting toxicity in untreated patient populations. Randomized trials evaluating the addition of L upfront, and phase I/II trials on L combined with other novel agents such as BTK- and bcl-2 inhibitors are underway and will further bring insight into the role of IMiDs in MCL.

Keywords: Lenalidomide; mantle cell lymphoma (MCL); immunomodulatory drugs (IMiDs)

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Introduction

Immunomodulatory drugs (IMiDs) refer to thalidomide and its derivatives. To date, three agents are available for use, thalidomide, pomalidomide and lenalidomide (CC-5013) of which lenalidomide is the one with approval status by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in mantle cell lymphoma (MCL) (1,2). Furthermore, a number of novel immunomodulatory agents, such as CC-122, CC-223 and CC-292, are currently evaluated in phase I trials in patients with chronic lymphocytic leukemia (CLL), and non-Hodgkin lymphoma (NHL). This overview aims to discuss the role of lenalidomide in MCL based on reported data as well as to provide a glance of how ongoing studies and future analysis will clarify the optimal use of these agents in MCL.

IMiDs exhibit a spectrum of anti-tumoral effects

IMiDs are associated with several properties, including direct anti-proliferative and anti-angiogenic effects on tumor clones as well as immunomodulatory actions associated with enhanced anti-tumoral activity mediated by the host immune system (*Figure 1*). Although mostly studied in multiple myeloma (MM), mechanisms of action (MOA) have been confirmed in *in vitro* and *in vivo* models on B cell lymphoma (3-5). The immune activating capacity of IMiDs

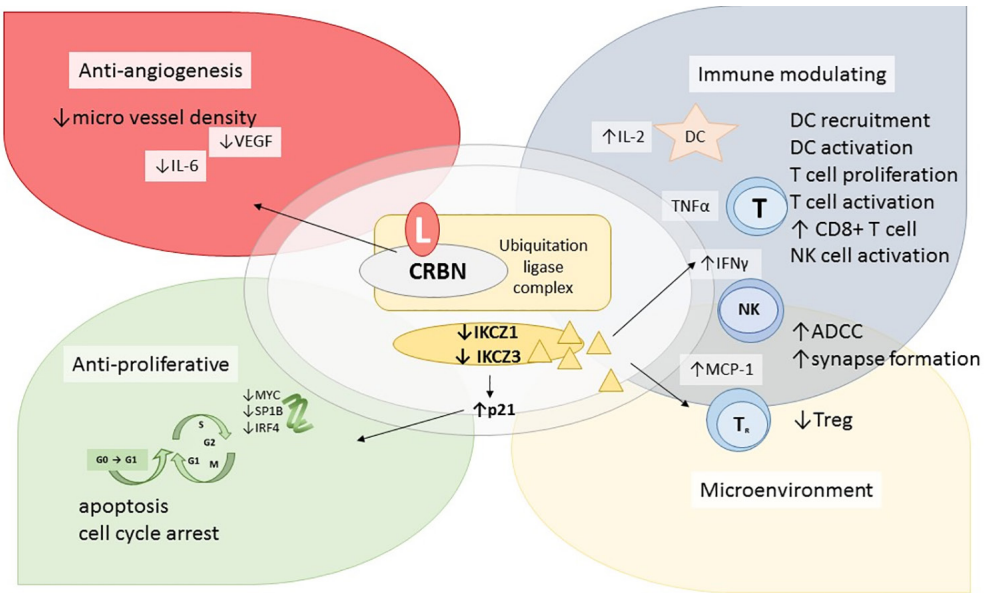

Figure 1 Schematic presentation of mechanism of action of lenalidomide. L, lenalidomide; CRBN, cereblon; IKCZ1, Ikaros; IKCZ3, Aiolos; DC, dendritic cell; T, T cell; NK, natural killer; IL-2, interleukin 2; TNFα, tumor necrosis factor α; IFNγ, interferon γ; MCP-1, monocyte chemotactic protein-1; Treg, T regulatory cell; MYC, MYC proto-oncogene; SP1B, Sp1 gene B; VEGF, vascular endothelial growth factor; IL-6, interleukin 6.

could be regarded as the most important and reproducible mechanism, as demonstrated by activated dendritic cells (DC) and increased secretion of interleukin 2 (IL-2) leading to recruitment and activation of T cells, natural killer (NK) cells and activated pro-inflammatory response by secretion of cytokines, such as tumor necrosis factor α (TNF-α), interferon gamma (INFγ) and monocyte chemotactic protein-1 (MCP-1) (3). A fundamental point in all these actions is the intracellular binding to cereblon (CRBN), which is involved in the formation of a ubiquitination ligase complex (6). Treatment with lenalidomide has been demonstrated to induce ubiquitination and degradation of two transcription factors, Ikaros and Aiolos (IKCZ1 and IKCZ3), and thereby altering the expression of several genes involved in proliferation and activity of B and T cells, such as increased levels of p21 and reduced expression of MYC proto-oncogene protein (MYC), Sp1 gene B (SP1B) and interferon regulatory factor 4 (IRF4) proteins (7,8). Degradation of IKCZ1 and IKCZ3 has also been correlated with increased IL-2 secretion by T cells, increased levels of $CD8^+$ cytotoxic T cells, decreased levels of T regulatory cells and recruitment and activation of NK cells, altogether representing an activation of the immune response (3,8).

Furthermore, IMiDs have demonstrated a capacity to overcome tumor-related evasion, by restoring the reduced immunologic synapse formation between the T cell and the tumor cell, as observed in in *in vitro* assays on follicular lymphoma (FL) and CLL (9,10).

The anti-angiogenic effects have been described as reduced micro vessel density and may be explained by depletion of macrophages and monocytes involved in lymphoma-related angiogenesis (3,11).

IMiDs may synergize with dexamethasone and/or anti-CD20 antibody treatment

A synergistic activity of lenalidomide and dexamethasone in MCL cell lines and patient-derived MCL cells was demonstrated by Qian *et al.* with higher grade of cell cycle arrest, higher expression of pro-apoptotic proteins such as caspases, Bcl-2 and Bax, higher rate of apoptotic cells and decreased tumor growth upon combination of these two agents (12).

Targeting CD20 by a monoclonal anti-CD20 antibody, i.e., rituximab, has been proved to be highly active in MCL and constitutes a backbone of primary treatment. Upfront addition of rituximab to chemotherapy, is associated with superior survival in retrospective analysis

of large population-based cohorts and randomized trials have demonstrated prolonged disease control and improved survival when given as maintenance after immunochemotherapy (13-16).

The MOA of anti-CD20 antibody treatment include complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and direct cell death via apoptosis, of which ADCC, mediated by different effector cells of the immune system, is regarded as one of the more important in the activity in NHL and MCL as reviewed by Boross *et al.* (17).

Based on the enhanced T cell activity upon treatment with lenalidomide, *in vitro* models have investigated whether lenalidomide could increase the immune-mediated cytotoxicity induced by monoclonal anti-CD20 antibody treatment. A first report in 2005 described a tendency of synergistic effect of CC-5013 (lenalidomide) when combined with rituximab *in vitro* (18). Wu *et al.* demonstrated a synergistic effect on NK-cell mediated cell killing by pre-treatment of NK cells with lenalidomide, with increased cytotoxicity of anti-CD20 coated lymphoma cells and increased release of IFNγ (19). Similar studies confirmed the enhanced NK cell activity and ADCC by combination of immune modulators including lenalidomide and rituximab in B cell lymphoma and MCL *in vitro* and *ex vivo* models, as shown by increased recruitment of NK cells, increased levels of IL-2 and increased expression of CD16 and IFNγ in NK cells (3,20).

Lenalidomide in MCL

Single agent may induce response in R/R MCL

The initial trials evaluating single agent lenalidomide, NHL-002 and NHL-003, were designed for NHL and MCL patients constituted a subgroup of the study population. Both trials used 25 mg daily for 12 months treatment (NHL-002) or until PD (NHL-003) and primary endpoints were overall response rate (ORR). Based on the promising activity in the subgroups of MCL patients demonstrating ORR of 47% and 53% respectively (*Table 1*), trials designed for MCL patients were initiated (21,38).

In the MCL-001 trial, 134 patients who relapsed after prior treatment with bortezomib received lenalidomide 25 mg daily until progression. At a median follow-up (FU) time of 9.9 months, 28% had responded with a median duration of response (DOR) time of 16.6 months (95% CI, 7.7 to 26.7 months) (26). Another trial, reported by Eve *et al.*, evaluated 6 cycles of lenalidomide, 25 mg daily, followed by maintenance lenalidomide 15 mg daily, in 29 included patients, demonstrating 31% ORR, and a median DOR of 22 months (23).

These results lead to US FDA approval of lenalidomide to patients with MCL who had relapsed after treatment with bortezomib (39). A subsequent randomized phase III trial (MCL-002; SPRINT) compared lenalidomide with investigator's choice in 292 patients (2:1 lenalidomide: investigator's choice) which demonstrated a benefit in the lenalidomide group leading to approval in Europe by EMA (2). Objective response rate in the lenalidomide group was 40% and median progression-free survival (PFS) was 8.7 months, compared to 11% and 5.2 months in the investigator's choice group. Although the median DOR was longer in the lenalidomide group, no significant difference in overall survival between the groups could be demonstrated (27,40).

A long term analysis on 206 MCL patients included in the initial trials NHL-002, NHL-003 and MCL-001 after a median FU time of 6.8 years, 7.6 years and 52.2 months respectively, demonstrated a best ORR of 33%, complete remission rate (CRR) 11% and a median DOR of 16.6 months (22).

Lenalidomide in combination with dexamethasone and anti-CD20 antibody

Based on the preclinical demonstration of increased cell cycle arrest and apoptotic activity by combination of lenalidomide and dexamethasone, this regimen was evaluated in a phase II trial, demonstrating 52% ORR in 33 patients with MCL (12,28).

Given the enhanced immune activity by lenalidomide and an anti-CD20 antibody *in vitro*, the combination of rituximab and lenalidomide (R2) was explored in clinical trials. Wang *et al.* reported data from the initial phase I/II trial on R/R MCL patients, combining rituximab and lenalidomide, with somewhat higher response rates; ORR 57% and CRR 36%, compared to single agent lenalidomide. All patients had previously received rituximab, of which nine patients had received rituximab as maintenance therapy and eight patients as part of the latest regimen (29,41).

Chong *et al.* investigated the potency of lenalidomide to re-sensitize previously rituximab resistant/refractory disease. Fifty patients with B cell lymphoma, previously defined as resistant/refractory to rituximab, received two cycles of pre-treatment with lenalidomide followed by the

Table 1 Overview of reported trials with lenalidomide in MCL

Regimen	Ref	Trial	Phase	Diagnosis	Dose L*	n MCL	Dose L in M	ORR (CRR)	md DOR	md FU time	PFS	OS
Single agent lenalidomide	(21,22)	NHL-002	II	R/R NHL	25 mg	15 (49 tot)		53% (20%)	14 m (4 NR)	NR	md 6 m	
	(23)	UK (Eve)	II	R/R MCL	25 mg	26	15 mg	31% (8%)	22 m	23m	ITT: md 4 m; M: md 15 m	md 10 m
	(24)	NHL-003	II	R/R aggr. NHL	25 mg	57 (217 tot)		53% (20%)	16 m (7 NR)	Resp pts 20 m		
	(25,26)	MCL-001 (EMERGE)	II	R/R MCL post-BOR		134		28% (8%)	17 m	10 m	md 4 m	md 19 m
L *vs.* investigator's choice	(27)	MCL-002 (SPRINT)	III, rand	R/R MCL	25 mg	170		68% (40%)	16 m	41 m	md 9 m	md 28 m
					Inv.'s choice	84		9% (11%)	10 m		md 5 m	md 21 m
L + dexamethasone	(28)		II	R/R MCL		33		52% (24%)	18 m		md 12 m	md 20 m
L + rituximab (R2)	(29)	NCT 00294632	I/II	R/R MCL	MTD: 20 mg	44		57% (36%)	md 18.9 m (17.0 NR)	23 m	md 11 m	md 24 m
	(30,31)		II	Untreated MCL	I: 20 mg c 1, 25 mg c 2–12; R†	38	15 mg, R†/8 w 3 y	61%	–	68 m	3-y PFS 80.3%; 5-y PFS 64%	3-y OS 92%; 5-y OS 77%
L + obinutuzumab	(32)	GALEN	II	R/R aggr. NHL	20 mg, O 1,000 mg; d 8, 15, 22 c 1, d 1 c2–6, 1/8 w during M	13 (85 tot)	–	39% (23%)	md NR	2.5 y	md 5.8 m	NR
R2-bendamustine	(33)	R2-FIL	II	R/R MCL	MTD: 10 mg d 1–14/28 d, c 1–4; 15 mg d 1–14/28 d, c 5–6	42	15 mg d 1–14/28, c 7–18	Of evaluated 4 c: 88% (44%); 6 c: 79% (58%)	–	29 m	md 20 m	2-y OS 67%
	(34)	MCL4 (LENA-BERIT)	I/II	Untreated MCL ≥65 y	MTD: 10 mg, c 1–6; 10 [15] mg, c 7–13	50	M L ×7	ITT 6 c: 80% (64%)	–	45 m	md 42 m	md 69 m

Table 1 (*continued*)

Table 1 (*continued*)

Regimen	Ref	Trial	Phase	Diagnosis	Dose L*	n MCL	Dose L in M	ORR (CRR)	md DOR	md FU time	PFS	OS
R2-bortezomib	(35)	NCT 00633594	I/II	Untreated or R/R MCL	MTD: 10 mg d 1–14//21 d BOR‡	22		Of evaluated 82% (32%)	–	16 m	18 m PFS 61%	18 m OS 79%
	(36)	CALBG 5051	II	R/R MCL	20 mg d 1–14/21 d, BOR, R† ×8	53		40% (15%)	–	46 m	md 7 m	md 26 m
R2-ibrutinib	(37)	MCL6 (PHILEMON)	I + II	R/R MCL	L 15 mg	50	I + R	76% (56%)	–	18 m	12-m PFS 57%	12 m OS 78%

*, d 1–21, cycle duration 28 d; †, R 375 mg/m^2 iv. 1/week c 1; 1/8 w c 2- (d 1 each cycle if with chemotherapy); ‡, BOR 1.3 mg/m^2 iv. d 1, 4, 8, 11. ITT, intention to treat; NR, not reached; NCT, trial number at www.clinicaltrials.gov; M, maintenance; ORR, overall response rate; CRR, complete response rate; DOR, duration of response; FU time, follow-up time; PFS, progression-free survival; OS, overall survival; R/R, relapsed/refractory; m, months; MTD, maximally tolerable dose; L, lenalidomide; R, rituximab; R2, lenalidomide, rituximab; B, bendamustine; I, ibrutinib (560 mg d 1-28); inv.'s, investigator's; tot, in total; O, obinutuzumab.

addition of rituximab, with observed doubling of ORR from 30% to 63%. Of note, in the subgroup of MCL patients (n=11), ORR (55%) after single lenalidomide did not increase by the addition of rituximab, albeit some more patients achieved complete remission (*Table 1*) (42).

R2 has been investigated as an upfront "chemo-free" regimen in one phase II trial reported by Ruan *et al.* (30,31). In the trial cohort, a majority of patients (68%) were scored as low or intermediate-risk according to mantle cell lymphoma prognostic index (MIPI), 79% of the cases were scored with Ki-67 ≤30% and no one were blastoid MCL. Patients with high-risk MIPI were only included in case of ineligibility to tolerate chemotherapy. Of 36 evaluable patients, 61% achieved complete remission and according to a recent update at a median FU time of 64 months, survival analysis demonstrated a 5-year PFS of 64% and 5-year OS of 77%.

Lenalidomide has also been combined with the type II anti-CD20 antibody obinutuzumab within the GALEN trial, by the French LYSA network, to R/R FL and aggressive B cell lymphoma. In the latter cohort, ORR (CRR) was 39% (23%) in the subgroup of 13 MCL patients of which 53% had rituximab-refractory disease (32).

Lenalidomide and immunochemotherapy

Primary treatment of MCL include immunochemotherapy and for young fit patients, consolidation with high dose chemotherapy with autologous stem cell support (HD-ASCT). Elderly patients are recommended rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) followed by maintenance rituximab or R-bendamustine, the latter associated with a preferable toxicity profile compared to R-CHOP as reported from one randomized trial by the German STiL group (43). Consequently, R-B was used to explore lenalidomide in combination with immunochemotherapy in two trials, the Nordic MCL4 (LENA-BERIT) to untreated elderly patients ≥65 years, and the Italian trial FIL-R2-B to R/R MCL patients. In the cohort of 50 patients in MCL4, ORR (CRR) was 80% (64%) after induction with R-B-L ×6 and 56% were negative in evaluation of minimal residual disease (MRD), not increased by maintenance treatment with lenalidomide (34). In FIL-R2-B, reported by Zaja *et al.*, ORR (CRR) was 79% (55%) in 42 patients after induction with R-B-L ×4 followed by consolidation with two cycles of R2 (33). Out of responding patients, 36% achieved MRD negativity in bone marrow (BM). These results suggest that

Table 2 Registered trials with lenalidomide in MCL

Trial/site	NCT number	Phase	Inclusion	Regimen
R2-venetoclax				
NLG-MCL7 (VALERIA)	NCT03505944	I/II	R/R MCL or untreated MCL*	
University of Michigan Cancer Center	NCT03523975	I	Untreated MCL	
R2-ibrutinib				
MD Anderson	NCT03232307	I/II	Untreated MCL	
R2-carfilzomib				
MD Anderson	NCT01729104	I/II	R/R MCL	
L-R-chemo + L-R maintenance				
Memorial Sloan Kettering Cancer Center	NCT02633137	II	Untreated MCL	R2-CHOP ×4 → R-HiDAC → R2 ×6
L maintenance				
European MCL-R2 Elderly	NCT01865110	III, rand	Untreated MCL	R-CHOP/R-HAD ×6 *vs.* R-CHOP ×8; maintenance R2 *vs.* R
MAGNIFY	NCT01996865	III, rand	R/R MCL*	R *vs.* L maintenance
FIL MCL0208	NCT02354313	III, rand	Untreated MCL	R-chemo + ASCT → L *vs.* observation
EOCG randomized	NCT01415752	II, rand, 4-arm	Untreated MCL	R-B *vs.* R-B-BOR followed by maintenance R2 *vs.* R
L + BiTE-ab	NCT02568553	I	CD19 pos R/R lymphoma	L-blinatumomab
Closed trials (cause of termination)				
RENEW (not relevant)	NCT01021423	III, rand	Untreated MCL	R-CHEMO → L maintenance *vs.* observation
R-LEN-idelalisib (DLT)	NCT01088048	I/II		DLT

NCT, trial number at www.clinicaltrials.gov. *, in patients not eligible for chemotherapy. R2, rituximab, lenalidomide; R/R relapsed/refractory; CHOP, doxorubicin, cyclophosphamide, vincristine, prednisone; HiDAC, high-dose cytarabine; HAD, cytarabine, dexamethasone; BOR, bortezomib; BiTE-ab, antibody with bi-specific T-cell engagers; DLT, dose-limiting toxicity.

the addition of lenalidomide to R-B is an active regimen and a substantial portion of the patients may achieve MRD negativity. As discussed in following sections, toxicity was unexpectedly high in the untreated cohort and patients with high-risk profile like *TP53* mutations may not profit from this combination (44).

R-L-CHOP to untreated DLBCL patients has been proved to be more tolerable, possibly due to the corticosteroids included in the regimen (45). Two trials are currently evaluating the addition of lenalidomide to anthracycline-based immunochemotherapy regimens in MCL, the Memorial Sloan Kettering (NCT02633137) including R-L-CHOP followed by R-HiDAC (high-dose cytarabine) and maintenance R2, and the randomized European R2 Elderly trial evaluating the addition of lenalidomide to R-CHOP as well as maintenance R2 compared to rituximab (NCT01865110) (*Table 2*) (46).

Lenalidomide in chemo-free regimens

Several trials have investigated further development of R2 by addition of a third novel agent such as a small molecule inhibitor. In this overview, we prefer to include reported data from combinations with the proteasome inhibitor

bortezomib, the inhibitor of Bruton's Tyrosine Kinase (BTK) ibrutinib, and the phosphoinositide 3 kinase (PI3K) inhibitor idelalisib. Moreover, registered/ongoing trials evaluate combinations with the novel proteasome inhibitor carfilzomib, the bcl-2 inhibitor venetoclax as well as substituting rituximab with a type II anti-CD20 antibody, obinutuzumab (*Table 2*).

Bortezomib was approved by FDA for treatment of R/R MCL in 2006 and as part of first-line therapy in 2014 based on superiority of addition of bortezomib to anthracycline-based immunochemotherapy (R-CAP *vs.* R-CHOP) (1,47,48). Lenalidomide and bortezomib was explored in a phase I/II trial on 54 R/R MCL patients, showing an ORR (CRR) of 40% (15%) (NCT00553644) (36). One registered trial, SCRI LYM 58, is investigating R-L-bortezomib in R/R or untreated MCL (NCT 00633594). The second-generation proteasome inhibitor carfilzomib, developed to increase response duration and to diminish sensory neuropathy associated with bortezomib, has been combined with L + dexamethasone with acceptable tolerability in MM (49). Although not yet reported as single agent in MCL (phase II trial NCT 02042950 is ongoing), a phase I/II trial conducted by M.D. Anderson Cancer Center, US, will evaluate R2 + carfilzomib to R/R MCL patients (NCT01729104).

Ibrutinib has showed high activity in MCL and has achieved a position of "drug of choice" at first relapse in current guidelines (50). Ibrutinib + R2 (R-L-I) was evaluated within the Nordic MCL6 (PHILEMON) trial in R/R MCL, where patients received twelve months of R-L-I followed by maintenance ibrutinib + rituximab (IR). At median FU time of 17.8 months ORR was 76% and CRR 56% (37). Of note, response was observed even in *TP53* mutated cases, otherwise associated with poor prognosis. Besides another trial in R/R MCL (NCT02446236), potentially confirming the activity of this combination, ibrutinib-R2 will be evaluated in a phase II trial in untreated patients >65 years (NCT03232307).

Less successful outcome was observed when the PI3K inhibitor idelalisib was combined with rituximab and lenalidomide. Two trials have reported unexpected severe toxicity including sepsis, hypotension, rash and impaired liver function when these agents were combined (51,52).

Among recently introduced compounds, the bcl-2 inhibitor venetoclax (ABT-199) may be one of the most promising agents, demonstrating overall response in >70% in R/R MCL patients, previously treated with a median number of 3 [1–7] prior therapies and a potency of durable remission in responding patients (53). Two phase I/II trials are registered for the evaluation of venetoclax in combination with rituximab and lenalidomide, the Nordic MCL7/VALERIA (NCT03505944) in R/R MCL or untreated (not eligible for chemotherapy) and a phase I trial for previously untreated MCL patients (NCT0352975).

Maintenance treatment with lenalidomide

According to reported data, maintenance treatment in MCL may principally have a role for a subset of patients, although further studies are required to identify the specific patient population as well as to define which regimen that should be used. To date, our knowledge is based on single arm trials and a few randomized trials, where rituximab maintenance after immunochemotherapy has been associated with prolonged response duration and superior survival as recently reviewed after meta-analysis by Hilal *et al.* (54). Maintenance lenalidomide has been administered after single agent lenalidomide in an initial R/R MCL trial, in combination with rituximab for maximally three years after upfront R2, and after R-B-L in the MCL4 and FIL-R2B (23,30,34,55).

In spite of different protocol length of induction and maintenance phase in these trials, the results indicate that maintenance lenalidomide may increase CRR in responding patients, albeit to a limited extent. Ruan *et al.* reported a CRR of almost 60% at 24 months after start of treatment, compared to 45% at 12 months in evaluated patients who received maintenance with R2. Still, the majority of complete remissions were found during the early treatment phase as demonstrated by a reported median time [range] to response and complete remission of 3 [2–13] and 11 [3–22] months respectively (30). In the Italian trial FIL-R2B, CRR increased from 44% to 55% after consolidation with 2 cycles of R2 after R-B-L ×4, although MRD negativity in BM did not increase. Moreover, subsequent single agent lenalidomide up to 18 months after R-B-L as in FIL-R2B did not maintain disease control and the PFS curve did not show a plateau (33). A similar pattern was observed after R-B-L in MCL4, where molecular remission in BM was achieved in 42% of all patients, not improved by maintenance treatment with lenalidomide (34).

A relevant point in evaluating a maintenance regimen, besides response and survival, is the toxicity profile with respect to duration of the treatment and quality of life. According to reported data, the risk of grade ≥3 adverse events is not eradicated by lowering of lenalidomide dose

from 20 mg to 15 mg and several trials report a sustained BM suppression during maintenance with lenalidomide after induction with regimens including anti-CD20 antibody with or without chemotherapy, as demonstrated in the R-B-L trials FIL-R2B and MCL4.

In summary, prolonged treatment with lenalidomide ± rituximab may be relevant in a small portion of patients but available data is not sufficient to conclude whether the benefit is explained by lenalidomide or by the anti-CD20 component. Current randomized trials will hopefully lead to a better understanding of its potency to consolidate and sustain remission, either as single agent as in the phase III trial MAGNIFY (NCT01996865) to R/R MCL or in combination with rituximab in the EU Network trial MCL R2 Elderly to untreated MCL (NCT01865110) (*Table 2*).

Toxicity profile of lenalidomide in MCL patients

Myelosuppression and risk of infection

Witzig *et al*. performed a pooled analysis of grade 3/4 adverse events in the initial trials, NHL-001, -002-003, MCL-001 and a UK phase II trial including all patients and not only MCL (56). Grade 3/4 neutropenia, thrombocytopenia and anemia were the most common side effects, reported in 42%, 28% and 11% respectively. Similar frequencies could be observed when lenalidomide was combined with rituximab or dexamethasone (29,30,55). Of note, in spite of a high frequency of grade 3 neutropenia among the patients, grade 3/4 febrile neutropenia or infection were reported in less than 10% of the study population.

However, when lenalidomide is combined with chemotherapy, the safety profile is markedly different, especially in previously untreated patients. The MCL4 trial reported grade 3/4 neutropenia in 76% at any time during induction with R-B-L or maintenance L. Grade ≥3 infection was reported in 42 % of the patients, significantly higher compared to the R-B-L in R/R patients in the SAKK and FIL-R2B trials respectively, in spite of comparable rate of high grade neutropenia in the three trials (33,34,57). The mechanism behind the observed higher risk of infection in untreated patients remains to be clarified but might be explained by difference in immune activity compared to when being previously exposed for immunochemotherapy. Moreover, in the trial of untreated patients in MCL4, three patients were diagnosed with opportunistic infections, two with pneumocystis pneumonia (PCP) and one patient with CMV-retinitis, reflecting a more profound immunosuppression when lenalidomide is combined with a T-cell suppressive agent such as bendamustine and a CD20 ab.

In MCL6, grade 3/4 neutropenia and infection were observed in 38% and 22% respectively in patients treated with R-L-I, indicating that the risk of myelosuppression is not eradicated by chemo-free strategies (37).

In summary, lenalidomide is associated with hematologic toxicity and an elevated risk for severe infections has been observed in treatment-naïve patients or when lenalidomide is combined with other cytostatic compounds or small molecule inhibitors.

Immune-related side effects include rash and allergic reactions

Among non-hematologic side effects of lenalidomide, the immune-related toxicity including cutaneous and allergic reactions should be emphasized. Rash grade ≥3 was reported in less than 10% of patients with R/R disease receiving lenalidomide as monotherapy or in combination with rituximab or dexamethasone (56). Severe cutaneous reactions, are more frequent in treatment-naïve patients, as reported in 23% with R2, 32% with R2-bortezomib and 18% in the R-B-L compared to <10% in previously treated patients or patients receiving lenalidomide monotherapy (30,34,35,56). R-CHOP + lenalidomide was investigated as first line treatment to patients with diffuse large B cell lymphoma (DLBCL) but did almost not report any rash (2%). The low frequency could be explained by a prophylactic or hampering effect by the administration of corticosteroids within the regimen, similarly to the reduction of early reactions after protocol amendment in MCL4 phase I portion by adding corticosteroids to first cycles of L-R-B (34,45).

Lenalidomide and thalidomide are associated with increased risk of venous thromboembolic events (VTE). Although previous studied is mostly based on MM as reviewed by Carrier in 2011, a recent systemic meta-analysis has stated that NHL patients are at the same risk as myeloma patients upon treatment with these agents, although possibly lower by combination of L with biologics compared to L + chemotherapy (58,59). To date, there is no consensus whether all patients should receive VTE prophylaxis during treatment but should be carefully evaluated in each individual case (2).

Altogether, these data indicate that the toxicity profile of lenalidomide, either as monotherapy or in combination with dexamethasone or rituximab, is acceptable, especially in previously treated patients. However, treatment-naïve patients may be more susceptible to severe toxicity upon treatment with lenalidomide in combination with rituximab and the addition of a third partner, such as bendamustine and bortezomib, is associated with a higher risk of dose-limiting toxicity.

Second primary malignancy (SPM) is a late onset complication of immunomodulatory agents

Lenalidomide is associated with increased risk of SPM. A higher frequency of SPMs was demonstrated in a pooled analysis of patients with MM treated with lenalidomide within randomized trials and a higher incidence of SPMs was reported in MM patients treated with lenalidomide compared to a population-based age-adjusted incidence (60-63).

MCL patients have been suggested to be at a higher risk of developing SPMs, compared to the general population, as demonstrated from a large population-based analysis by Shah *et al.* (64). Concerning the incidence of SPMs in MCL after treatment with lenalidomide upfront, Ruan *et al.* reported SPMs in 6 of 38 (16%) patients receiving R-lenalidomide at 5 years median FU time in SPM was reported in 18% of the patients at a median FU of 4 years (31,44).

There is no established theory to explain the increased risk of a SPM. Binding of lenalidomide to cereblon have been associated with deregulated cell cycle regulation via p21, CDK/cyclin complex and p53 as well as via IKZF1+3 ubiquitination mechanisms (6,8). With that in mind, one could speculate whether the cellular repair systems for DNA damage induced by an alkylating agent such as bendamustine are inhibited by concomitant use of lenalidomide and thereby put the cell less resistant to stress and genetic alterations.

However, as Demopoulos discussed in MM patients, the risk of SPMs in MCL patients should be weighed towards the potential benefit of lenalidomide treatment. We recommend that patients with a history of a prior malignancy should be carefully evaluated for active/pre-stage malignancy before and during treatment of lenalidomide.

Who will respond to lenalidomide based on tumor characteristics?

Although several prognostic factors have been described in MCL, such as morphologic subtype, proliferation rate of the tumor cells as well as presence of specific genetic alterations, few trials incorporate analysis of outcome in relation to a broad panel of base-line prognostic markers.

The proliferation marker Ki-67 is one of the most established prognostic factors in MCL and evaluation of Ki-67 is recommended to be included in routine diagnostic (50). In patients treated with single agent lenalidomide within the MCL-001 trial, Ki-67 >30% or >50% respectively was associated with inferior PFS and OS, leading to the conclusion that single agent lenalidomide is not active in previously bortezomib-treated R/R MCL with high Ki-67% (25).

Recent studies on prognostic factors in MCL have demonstrated a correlation of prognosis and presence of specific genetic alterations of the tumor cells, of which deletions and/or mutations of *CDKN2A* and/or *TP53* have been associated with inferior outcome after standard treatment with immune chemotherapy (65-67). In untreated patients within the MCL4 trial, patients harboring *TP53* mutations were associated with inferior PFS and OS compared to non-mutated cases and none of these patients achieved MRD (44). However, when lenalidomide was combined with rituximab and ibrutinib in the MCL6 trial, response was observed in *TP53*-mutated cases, which is similar as observed from a trial in CLL patients where lenalidomide was associated with activity in *TP53*-aberrated patients (37,68). Still, it remains to be clarified if and in which combination lenalidomide is capable of eradicating MCL clones with non-functional p53.

In summary, studies on activity of IMiDs in relation to molecular profile are few. So far, data suggests that single agent lenalidomide is not sufficient in patients with highly proliferative MCL and probably not in cases with poor molecular profile, although an approach using lenalidomide in combination with multiple agents may be more active.

Discussion

Although historically associated with its teratogenic effect, causing one of the worst tragedies in pharmacology history,

thalidomide has been re-explored based on its immune modulating and anti-tumoral activity. Thalidomide and further development of the molecule, referred to as immunomodulatory agents, IMiDs, have demonstrated activity in both solid tumors and hematologic malignancies. Lenalidomide is the most studied immunomodulatory agent in MCL and is thus the focus of this review. In this section we aim to discuss and give our perspectives on how to use IMiDs in MCL based on reported data and personal experience.

One of the most interesting properties of IMiDs is the potency of enhancing the immune response to monoclonal antibody treatment, including anti-CD20 antibody, which today constitutes the backbone of MCL treatment. Based on reported data from a few single arm trials in R/R MCL, one could argue that R-L is preferable, as demonstrated by higher CRR compared to L monotherapy. In patients with rituximab-refractory disease, there is not enough support of a re-sensitizing effect of L in MCL as reported from other NHL. In these patients, L + obinutuzumab might be a better option, although reported data needs to be confirmed from larger cohorts.

According to population-based analyses of MCL, one group in need of improved treatment outcome is the aged patient population, partly due to limited treatment options with respect to efficacy and tolerability (16). Given the limited toxicity when L is combined with anti-CD20 antibody and the results from the trial on R2 in first-line reported by Ruan *et al.*, this combination might be a preferable option in elderly patients with low/intermediate risk disease according to MIPI, alternatively in frail patients non-eligible for chemotherapy (31). A randomized trial would possibly confirm whether lenalidomide is superior to established regimens in these patients.

The efforts to reinforce induction with immunochemotherapy by addition of lenalidomide have reported somewhat conflicting results. Although a deep remission may be achieved with R-B + lenalidomide, toxicity has been dose-limiting, especially in the untreated patient population. Lenalidomide + R-CHOP may be more tolerable but there is not sufficient data to evaluate this regimen in MCL (69). Future trials, such as the randomized MCL R2 Elderly will bring further insight whether patients do benefit from the addition of lenalidomide to standard immunochemotherapy.

Out of experiences from lenalidomide in chemo-free regimens, R-L-I is an active and tolerable combination with potency of achieving deep remissions with undetectable MRD in R/R MCL patients (37). One can speculate whether L contributes to a deeper remission, based on the observed higher CRR in R-L-I (MCL6 trial) compared to R-I (37,70). Notably, ORR does not seem to be higher by R-L-I, suggesting that lenalidomide may only have an additive effect in responding patients. Evaluation of MRD after treatment with these agents on an intention-to treat basis is needed to confirm an additive effect of lenalidomide. Moreover, trials reported on R + I and R + L in R/R or untreated MCL do not report outcome in relation to poor prognostic markers such as persisting MRD positivity or *TP53* alterations why it is still unclear about whether lenalidomide has any additive affect in these cases.

As described in previous sections, toxicity may be an issue in patients receiving IMiDs. With lenalidomide, the most relevant side effects include immune mediated reactions, rash, neutropenia with increased risk of infection, venous thromboembolism and SPM which should be carefully evaluated by the responsible clinician before and during treatment with lenalidomide.

Our experience from the Nordic phase II trials MCL4 and MCL6 is that immune-mediated reactions are more likely to appear in treatment-naïve patients, and when IMiDs are combined with other agents, which should be taken into account when designing trial protocols involving novel regimens. Adverse reactions could be minimized by stepwise introduction of L, eventually with concomitant use of corticosteroids during the first [1–2] cycles, as used in an MD Anderson trial (NCT03232307) on R-L-I to untreated MCL. When using single agent L in R/R MCL, the risk is negligible and patients can generally start at the recommended dose of L 25 mg.

Grade 1–2 rash could generally be managed with local corticosteroids, without treatment discontinuation whereas grade 3 rash requires temporarily stopped administration of L and 1–2 weeks of systemic corticosteroids and anti-histamine before L could be re-started. Rash is not diminished or prevented by a lower dose of L, although it may be appropriate to re-start at a lower dose in patients with a history of grade 3 rash with subsequent dose-escalation if tolerated.

Mild neutropenia could generally be managed by dose reduction, but in case of neutrophil count below 10^3/μL, L should be temporarily stopped until recovering.

In patients receiving single agent L, we do not routinely prescribe VTE-prophylaxis. However, when combined with other agents, or in patients with a history of VTE, prophylaxis is used.

Similarly, prophylactic antibiotics cannot generally be recommended. As discussed in the previous section, PCP-prophylaxis and G-CSF should be used routinely in case of persisting myelosuppression, recurrent use of corticosteroids and when L is combined with other myelosuppressive agents.

Finally, we would like to advise against using IMiDs in patients that have previously received allogenic stem cell transplant, as this may provoke a severe and potentially fatal graft-versus-host reaction (71).

In R/R MCL, the BTK-inhibitor ibrutinib has shown high response rates, and besides being recommended at first relapse in current guidelines, ibrutinib is evaluated as part of first line treatment within several ongoing trials in elderly and young patients with MCL (50). Concerning the activity of lenalidomide in relation to ibrutinib, it should be noted that the SPRINT trial comparing L to investigator's choice was performed prior to the introduction of ibrutinib. Moreover, resistance to ibrutinib, either primary or acquired is a well-described phenomenon and has been associated with short overall survival in pooled retrospective analysis (72). One study has investigated outcome of lenalidomide-regimens in patients with R/R MCL post-ibrutinib, demonstrating an ORR of 28%, the majority of responding cases in patients receiving lenalidomide in combinatory regimens.

Consequently, as future patients will have received a BTK inhibitor, either at first relapse or upfront within any of the ongoing clinical trials, patients may be treated with R + L at relapse, preferably in combination with a third agent.

Given that IMiDs have a place in treatment of MCL, there are two main points that should be considered in designing future trials to provide a more economic use of these compounds; to whom and for how long time IMiDs should be administered. To date, trial protocols have included IMiDs with or without rituximab for long time periods, such as three years or until progression. Individual evaluation of discontinuous administration, i.e., at CR or MRD negativity, would not only reduce long-term toxicity but also the economic burden in public health systems. Similarly, outcome in relation to specific patient or disease characteristics, such as p53 expression and/or *TP53* alterations, Ki-67% as well as MIPI should be integrated into trial design in order to identify which patients that do benefit from immunomodulatory agents.

In summary, lenalidomide may have a place in MCL upfront, in combination with anti-CD20 ab in low-risk elderly patients. Likewise, R/R MCL patients may benefit from lenalidomide, preferably in combination with multiple agents. The outcome of several ongoing trials will reveal if lenalidomide should be added upfront to immunochemotherapy regimens or be a part of a chemo-free strategy. Similarly, exploration of novel regimens including IMiDs in combination with novel small molecule inhibitors such as BTK-inhibitors, venetoclax, second generation anti-CD20 antibodies, bi-specific antibodies or chimeric antigen receptor (CAR) T cells, will hopefully lead to a better understanding of how these agents optimally could be used and how to improve outcome in patients with MCL.

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Footnote

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