Are Novel Agents Ready to Assume the Mantle in the Frontline Treatment of Mantle Cell Lymphoma?

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Abstract: Although chemotherapy has been a mainstay of the frontline treatment of mantle cell lymphoma (MCL) for many years, novel agents—including Bruton kinase inhibitors, immunomodulatory agents, and BCL2 inhibitors—have shown promise in patients with relapsed and refractory disease, and they are also being studied in the frontline setting. This review summarizes the current clinical data for using these novel agents in untreated MCL, both in combination with chemotherapy and singly, and discusses some of the trials currently under way to assess their future potential.

Introduction

For many years, the combination of chemotherapy plus an anti-CD20 agent has remained the standard frontline treatment of mantle cell lymphoma (MCL). An explosion of therapeutic options has occurred during the past several years, however, with many new agents gaining approval and more being studied. These approved novel therapies, which have varied mechanisms of action, include the proteasome inhibitor bortezomib; the immunomodulatory agent and cereblon/E3 ligase modulator lenalidomide (Revlimid, Celgene); the Bruton kinase (BTK) inhibitors ibrutinib (Imbruvica, Pharmacyclics/Janssen), acalabrutinib (Calquence, AstraZeneca), and zanubrutinib (Brukinsa, BeiGene); and the chimeric antigen receptor (CAR) T-cell product brexucabtagene autoleucel (Tecartus, Kite Pharma). An additional agent of interest is the B-cell leukemia/lymphoma 2 (BCL2) inhibitor venetoclax (Venclexta, AbbVie). The therapeutic indices of these novel agents in the relapsed/refractory setting have fostered interest in moving them into the frontline setting.

The introduction of novel agents in the treatment of chronic lymphocytic leukemia (CLL) offers an illustrative parallel for predicting the path of novel agents in the frontline treatment of MCL. Only a few years ago, fludarabine- and bendamustine-based regimens were the backbone of CLL treatment. Soon after approval in relapsed/refractory disease, ibrutinib showed efficacy in patients with deletion 17p regardless of prior treatment.[1] As a result, the use of ibrutinib was expanded into the relapsed and refractory setting in older/unfit patients, first in combination with chemotherapy in the HELIOS study[2] and subsequently on its own in the RESONATE-2 and

Table 1. Completed Studies of Novel Agents in Untreated MCL

Agents	Study	Phase	N	ORR (CR rate)	PFS	OS
Chemotherapy combined with novel agents						
Younger patients						
Ibrutinib/rituximab induction, R-hyper-CVAD, and R-MTX/cytarabine consolidation	WINDOW-1[14]	2	131	100% (88%)	3-y PFS, 82%	3-y OS, 95%
R-CHOP/R-HDAC induction, autoSCT followed by lenalidomide maintenance	FIL MCL-0208[17]	3	104	NA	3-y PFS, 80%	3-y OS, 93%
Elderly patients						
VR-CAP	LYM-3002[25]	3	243	92% (53%)	24.7 mo	36.5 mo
Chemotherapy-free approaches with novel agents						
Elderly patients						
Ibrutinib + rituximab	IR[29]	2	50	98% (60%)	NR	NR
Elderly and younger patients						
Lenalidomide + rituximab	R2[20]	2	38	92% (64%)	7-y PFS, 60.3%	7-y OS, 73.2%
Ibrutinib + venetoclax + obinutuzumab	OAsIs[21]	1	15	100% (47%)	NA	NA
Indolent MCL						
Ibrutinib + rituximab	IMCL-2015[33]	2	50	82% (75%)	15-mo PFS, 96%	15-mo OS, 100%

autoSCT, autologous stem cell transplant; CR, complete response; FIL, Fondazione Italiana Linfomi; hyper-CVAD, cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine; IR, ibrutinib and rituximab; mo, months; MCL, mantle cell lymphoma; MTX, methotrexate; NA, not available; NR, not reached; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; R2, lenalidomide and rituximab; R-CHOP, rituximab and cyclophosphamide, doxorubicin, vincristine, and prednisone; R-HDAC, rituximab and cytarabine; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone; y, years.

A041202 studies,[3,4] and then in younger patients in the E1912 study from the ECOG-ACRIN Cancer Research Group.[5] Venetoclax-based regimens followed a similar trajectory, with efficacy in the relapsed and refractory setting[6,7] presaging its usefulness in the frontline setting.[8] In less than a decade, novel agents completely shifted the paradigm for the frontline treatment of CLL.

Chemotherapy-free approaches in relapsed/refractory MCL are already the standard of care, but the evidence in the frontline setting continues to evolve. In this review, we discuss the current evidence as well as several ongoing studies of the use of novel agents in the frontline setting.

First-line Therapy in Younger Patients With MCL

Currently, cytarabine-based chemotherapy regimens followed by autologous stem cell transplant (autoSCT) and maintenance with an anti-CD20 antibody are the de facto standard of care in younger, fit patients with newly diagnosed MCL. This approach is based on results from several pivotal clinical trials suggesting a median progression-free survival (PFS) of 7 to 9 years.[9-13] Although the prospect of prolonged remission is enticing, the toxicities of intensive strategies are not trivial.[10,11] In both the MCL Younger and Nordic MCL2 studies, approximately 4% of patients died of complications of autoSCT unrelated to disease relapse. Moreover, many patients choose to avoid intensive treatments for geographic or social/financial reasons.

The WINDOW-1 trial, an early attempt to evaluate novel agents in the frontline setting in younger adults, added up to 12 months of ibrutinib plus rituximab (IR) before 4 cycles of intensive rituximab plus cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine (R-hyper-CVAD) plus R-methotrexate and cytarabine (Table 1). Impressively, the overall response rate (ORR) after induction with IR was 100%, with an 88% complete response (CR) rate. At latest update, the 3-year PFS and overall survival (OS) rates were 82% and 95%, respectively.[14]

Two other key trials in which novel agents are being added to chemotherapy-based frontline regimens in MCL

Table 2. Ongoing Studies of Novel Agents in Untreated MCL

Agents	Study	Phase	N	Principal Outcomes
Chemotherapy combined with novel agents				
R-CHOP/R-DHAP → autoSCT, R-CHOP/R-DHAP + ibrutinib +/- autoSCT	Triangle[15]	3	870	FFS
BR + R-cytarabine, BR + R-cytarabine + acalabrutinib, BR + acalabrutinib	EA4181[16]	3	369	Composite CR rate/MRD rate
BR → maintenance rituximab +/- lenalidomide, BR + bortezomib → maintenance rituximab +/- lenalidomide	E1411[26]	2	332	PFS
BR → maintenance rituximab, BR + ibrutinib → maintenance rituximab + ibrutinib	SHINE (NCT01776840)[27]	3	523	PFS
BR, BR + acalabrutinib	ACE-LY-308 (NCT02972840)[28]	3	546	PFS
BO + venetoclax	NCT03872180	2	27	CR rate
BR + venetoclax	PrE04045 (NCT03834688)	2	56	CR rate
R-BAC → venetoclax maintenance	FIL elderly MCL (NCT03567876)	2	130	PFS
Chemotherapy-free approaches with novel agents				
R-chemotherapy → maintenance rituximab vs IR → maintenance rituximab + ibrutinib	ENRICH (ISRCTN11038174)[30]	3	400	PFS
BR vs zanubrutinib + rituximab	BeiGene (NCT04002297)[31]	3	500	PFS
Acalabrutinib + R2	ALR[43]	2	24	MRD-negative CR rate
Venetoclax + R2	VLR[44]	1	28	ORR

ALR, acalabrutinib, lenalidomide, and rituximab; autoSCT, autologous stem cell transplant; BO, bendamustine and obinutuzumab; BR, bendamustine and rituximab; CR, complete response; FFS, failure-free survival; FIL, Fondazione Italiana Linfomi; MCL, mantle cell lymphoma; MRD, minimal residual disease; ORR, overall response rate; PFS, progression-free survival; R2, lenalidomide plus rituximab; R-BAC, rituximab, bendamustine, and cytarabine; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone; R-DHAP, rituximab plus dexamethasone, cytarabine, and cisplatin; VLR, venetoclax, lenalidomide, and rituximab.

are ongoing: the Triangle study and EA4181 (Table 2). In the Triangle study, patients in a control arm receive rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) alternating with rituximab plus dexamethasone, cytarabine, and cisplatin (R-DHAP), followed by myeloablative consolidation, then autoSCT. Patients in one experimental arm receive ibrutinib in addition to R-CHOP/R-DHAP induction, then maintenance ibrutinib following autoSCT, while those in the other experimental arm receive induction chemotherapy including ibrutinib followed by ibrutinib maintenance, but without high-dose consolidation and autoSCT.[15] In EA4181, patients who are randomly assigned to the control arm receive bendamustine plus rituximab (BR) for 3 cycles, followed by cytarabine and rituximab for 3 cycles. Participants randomly assigned to the experimental arms receive acalabrutinib in addition to either BR for 3 cycles followed by cytarabine and rituximab for 3 cycles or BR for 6 total cycles.[16]

The role of novel agents as maintenance following autoSCT has been examined in younger patients. Lenalidomide maintenance was compared with observation in younger patients following cytarabine induction and autoSCT. Although the study was limited by suboptimal exposure to lenalidomide (28% of the patients received less than 25% of the planned lenalidomide dose), the 3-year PFS favored the lenalidomide arm (80% vs 64%; hazard ratio, 0.51).[17] However, OS did not differ significantly between the 2 arms, and the role for lenalidomide maintenance following autologous transplant in this setting remains unclear. Two trials evaluating the use of bortezomib maintenance following autoSCT came to similar conclusions; the apparently limited efficacy benefit did not appear to justify the toxicity.[18,19]

Fewer studies have evaluated novel agents in the absence of chemotherapy in younger patients. The Weill

Cornell Medicine study of lenalidomide/rituximab enrolled patients with a median age of 65 years and reported 7-year PFS and OS rates of 60% and 73%, respectively.[20] The combination of ibrutinib, venetoclax, and obinutuzumab (Gazyva, Genentech) is currently being studied in the OASIS trial, which includes patients as young as 51 years with newly diagnosed MCL. Initial data have been promising, with a 100% ORR, a 47% CR rate, and a manageable safety profile.[21] Both studies are discussed in further detail below.

First-line Therapy for Older Patients With MCL

The BR combination has become the most common frontline treatment for MCL in elderly patients since the STiL and the BRIGHT studies.[22,23] Although the StiL NHL-2008 MAINTAIN trial did not show a benefit in PFS or OS with the continuation of rituximab following treatment with BR,[24] many trials and clinicians have adopted maintenance rituximab in this setting on the basis of extrapolations from observational data and from trials in younger patients.

As seen in younger patients, one approach to the development of novel agents in the elderly population has been to add them to chemotherapy-based regimens. The combination of bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone (VR-CAP) showed an improvement in both PFS and OS vs R-CHOP in the LYM-3002 trial, and it has emerged as a reasonable option for patients who cannot tolerate more intensive chemotherapy.[25] The combination of bortezomib and BR is currently being examined in older patients with previously untreated MCL in the E1411 study, with study completion expected in May 2021.[26] At least 2 ongoing trials were designed to evaluate the addition of BTK inhibitors to BR in older patients. The SHINE trial (NCT01776840) randomly assigned patients older than 65 years with untreated MCL to receive either a standard BR regimen or BR with the addition of daily ibrutinib until progression of disease, with both arms receiving maintenance rituximab.[27] The study has completed enrollment and we await initial results, with the primary endpoint expected to be reached in June 2021. The ACE-LY-308 study (NCT02972840) is comparing frontline BR vs BR plus acalabrutinib in elderly patients with MCL, with the primary endpoint expected to be reached in October 2022.[28] Several ongoing phase 2 studies are utilizing venetoclax plus chemotherapy. For example, the PrE0405 study (NCT03834688) is enrolling patients older than 60 years with a new diagnosis of MCL and treating them with 6 cycles of bendamustine, rituximab, and venetoclax, with maintenance rituximab left to the discretion of the investigator. NCT03872180, which includes patients as young as 18 years, is using a similar regimen but is replacing rituximab with obinutuzumab and does not utilize maintenance rituximab.

Several studies have evaluated chemotherapy-free approaches to untreated MCL in elderly patients. As noted earlier, the lenalidomide/rituximab (R2) combination showed durable remissions in both younger and elderly patients, with median PFS and OS still not reached after 7 years. The combination also produced significantly less toxicity than chemotherapy.[20] In a single-center study from MD Anderson, patients older than 65 years (median age, 71 years) with Ki-67 expression of less than 50% and non-blastoid histology received continuous ibrutinib and monthly rituximab for the first 8 cycles, and for every other cycle thereafter.[29] The ORR was 98%, with a CR rate of 60% and a minimal residual disease (MRD) negativity rate of 81%. At a median follow-up of 28 months, the disease of 13% of patients had progressed, and 6% had died. Grade 3/4 toxicity was minimal and included new atrial fibrillation in 8% of patients and neutropenia in 8%, although the rate of discontinuation for atrial fibrillation was unexpectedly high. The Spanish GELTAMO-IMCL-2015 study, which evaluated the IR combination in patients with low-risk, indolent MCL, is discussed in more detail below. The OASIS study combined ibrutinib with the BCL2 inhibitor venetoclax and the anti-CD20 antibody obinutuzumab in patients with untreated MCL.[21] The patients were 51 to 77 years of age (median, 65 years). Of note, they had more aggressive disease than did the patients in the IR trials, with 9 of 15 having high-risk scores on the Mantle Cell Lymphoma International Prognostic Index (MIPI). The ORR was 100%, with all 15 patients in response at the end of cycle 2. Grade 3/4 toxicities included lymphocytosis in 7% of patients, neutropenia in 7%, and hepatobiliary toxicity in 27%.

Two phase 3 trials that are currently in progress are evaluating BTK inhibition and rituximab without chemotherapy in elderly patients who have untreated MCL. The ENRICH study (ISRCTN11038174) is recruiting patients older than 60 years; the control arm receives standard R-CHOP or BR with rituximab maintenance, while the intervention arm receives rituximab for 6 to 8 cycles followed by rituximab maintenance plus daily oral ibrutinib until disease progression.[30] Similarly, NCT04002297 is comparing oral zanubrutinib vs BR in patients older than 70 years with first-line MCL. Recruitment is currently ongoing.[31] These trials are the first direct comparisons of chemotherapy-free regimens with standard-of-care chemotherapy in elderly patients who have untreated MCL, and they have the potential to change the paradigm for the treatment of older patients with MCL.

Special Settings

Indolent MCL, characterized by a low tumor burden and low levels of Ki-67 expression, is often diagnosed incidentally in patients with no symptoms of disease. Previous data show that outcomes in these patients are not compromised by deferring initial therapy until symptoms develop,[32] and it remains an open question whether they require the same intensity of therapy once they do need to be treated. The GELTAMO-IMCL-2015 trial tested a combination of ibrutinib and rituximab in patients with indolent MCL who did not require treatment in the first 3 months following diagnosis. Patients received 8 total cycles of rituximab without rituximab maintenance and were scheduled to receive oral ibrutinib for 2 years, with an option to stop ibrutinib if they reached MRD negativity.[33] The ORR at the last update was 82%, with a CR rate of 75% and a 15-month PFS rate of 96%. MRD negativity occurred in 87% of patients with a CR. Still, it is unclear how to interpret these data, given that this group of patients with low-risk disease could reasonably have been observed without treatment for a longer period. Longer follow-up is necessary to determine if this regimen has an effect on patient survival.

At the other end of the spectrum are patients who have disease with high-risk characteristics, such as high MIPI scores, *TP53* mutations or 17p deletions, and blastoid histology. In the phase 2 study of R2 in the frontline treatment of MCL, PFS in patients with high-risk MIPI scores was similar to that in patients with low- or intermediate-risk MIPI scores, but OS was inferior.[20] This finding suggests that the R2 regimen may not overcome the poor prognostic factors associated with high-risk MIPI scores. The phase 2 study of IR included a robust cohort of elderly patients with high-risk biological MIPI scores; 28% of the patients in the trial fell into this category, although the endpoints were not stratified by MIPI score.[29]

When they receive chemotherapy, the outcomes of patients with aberrations in the tumor suppressor gene *TP53* are significantly worse than those of other patients with MCL.[34,35] Although no prospective trials have specifically evaluated the first-line use of novel agents in patients who have MCL with *TP53* mutations, one retrospective study reported on the use of R2 in both patients with newly diagnosed disease and those with relapsed/refractory disease.[36] Although the sample size was small, the results suggested that this approach might be preferable to a chemotherapy-based strategy. These results are consistent with those of prospective trials of novel agents in patients with MCL or CLL carrying *TP53* aberrations. Studies of ibrutinib in the relapsed or refractory setting suggest that ibrutinib has significant activity but may not entirely overcome the poor prognostic significance of *TP53* mutations.[37]

Another high-risk group of patients for whom an improvement in outcomes is a significant need is the subset with aggressive histologies—blastoid and pleomorphic MCL, as well as those with hyperproliferative tumors. There is likely significant overlap between these features and *TP53* aberrations, but hyperproliferation is clearly an independent risk factor. In comparison with those who have the classic variant of MCL, patients who have MCL with these histopathologic characteristics have clinically more aggressive courses, inferior responses to intensive chemotherapy, and worse survival,[38,39] even with the addition of cytarabine-based regimens in the frontline setting.[10] In patients with relapsed or refractory MCL, treatment with ibrutinib and rituximab showed a trend toward inferior PFS and OS in those with blastoid histology vs those with the classic variant of MCL.[40] These data from patients with previously treated MCL suggest that BTK inhibitors may not be efficacious in the frontline setting for tumors with aggressive histologic features, although as noted above, evidence does suggest increased efficacy for ibrutinib the earlier it is implemented. Of note, patients with blastoid histology were excluded from the study of ibrutinib and rituximab in newly diagnosed MCL.[29] One ongoing trial, the FIL elderly MCL study (NCT03567876), is enrolling patients older than 65 years with high-risk features, such as blastoid cytology, elevated Ki-67 expression, or *TP53* mutations, and treating them with rituximab, bendamustine, and cytarabine for 6 cycles followed by maintenance venetoclax for a total of 2 years. Although alternatives to intensive chemotherapy are certainly needed for patients with newly diagnosed blastoid MCL, use of the novel agents in the frontline setting has not been promising thus far.

One treatment modality that may be beneficial for patients who have MCL with both blastoid histology and *TP53* mutations in the relapsed and refractory setting is the CAR T-cell therapy brexucabtagene autoleucel. In subgroup analyses, PFS in patients with high-risk features (*TP53* mutations, blastoid histology, elevated Ki-67 expression) was similar to that seen in patients with lower-risk features, albeit at only 6 months of follow-up.[41] A trial that is currently enrolling patients is attempting to improve the efficacy of CAR T-cell therapy in MCL by adding oral acalabrutinib therapy 5 days before CAR T-cell infusion (but following lymphodepletion chemotherapy) and continuing acalabrutinib treatment for 6 total cycles.[42] Although CAR T-cell therapy is currently approved only for patients who have MCL refractory to multiple treatments, its promising efficacy in those with very high-risk features suggests that it could eventually make its way to the frontline setting, possibly in combination with a novel

oral agent. Still, CAR T-cell therapy for MCL in the frontline setting, either singly or in combination with novel therapies, remains several steps away from clinical use.

Future Directions

Until recently, most of the studies of novel agents in untreated MCL have targeted specific subpopulations, including patients with indolent or aggressive disease and elderly persons. With the notable exception of the phase 2 trial of R2, few studies in the frontline setting have employed broad inclusion criteria to assess the efficacy of novel regimens in MCL. Two current studies with broad inclusion criteria are recruiting younger and elderly patients alike, as well as populations with high- and low-risk features of disease. Following the promising results of the lenalidomide and rituximab regimen, both studies are building on the R2 backbone with the addition of another targeted agent. One trial adds the BTK inhibitor acalabrutinib to the lenalidomide and rituximab regimen (ALR),[43] whereas the other includes the BCL2 inhibitor venetoclax (VLR).[44] Notably, the plan is for patients on the VLR regimen to stop treatment after 12 cycles, whereas patients on the ALR regimen will continue maintenance with all 3 agents until disease progression or unacceptable toxicity. It is hoped that the results of these studies will be a large step forward in determining whether novel agents can be used more broadly in the frontline treatment of MCL.

Conclusions

Many studies have demonstrated the efficacy of lenalidomide, BTK inhibitors, and venetoclax in relapsed and refractory MCL, leading to their approval in this setting. The appeal of being able to use these agents in untreated MCL is clear; they offer the possibility of increasing efficacy by combining them with chemotherapy, or the ability to decrease the toxicity of frontline treatment by eliminating chemotherapy entirely. Still, demonstrating the utility of novel agents in the frontline setting, whether in combination with chemotherapy or as a chemotherapy-free approach, remains a work in progress.

Although the toxicity profile of the novel agents differs from that of chemotherapy, they are not without side effects of their own. Lenalidomide may be associated with secondary primary malignancies and thrombosis, although the rates of secondary malignancies in studies of follicular lymphoma were similar to those following chemotherapy[45] and the risk for thrombosis may be lower when lenalidomide is combined with other therapies.[46] Patients taking ibrutinib have an increased risk for bleeding and high rates of arrhythmias, such as atrial fibrillation, although this latter risk appears to be reduced with the newer BTK inhibitors acalabrutinib and zanubrutinib.[47] Venetoclax has been implicated in tumor lysis syndrome, which has been largely manageable with prophylaxis, as well as in cytopenia.[48] Still, regimens with these agents would offer another option for patients, with a different toxicity profile.

If the experience with CLL is a prelude to that with lymphomas in general, we are likely to see chemotherapy-free regimens move forward quickly. These regimens will initially be used in patients with higher-risk disease or those who are frailer, and then more broadly. The treatment of MCL, with its heterogeneous biology and populations, will likely lead the way.

Disclosures

Dr Yamshon has no relevant disclosures. Dr Martin has served as a consultant for ADC Therapeutics, Bayer, BeiGene, BMS, Cellectar, Epizyme, Gilead, Incyte, Janssen, Karyopharm, Merck, Regeneron, Teneobio, and Verastem, and has received research funding from Karyopharm.

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