Converging Approaches in the Frontline Treatment of Mantle Cell Lymphoma

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Abstract: Mantle cell lymphoma is a biologically and clinically heterogeneous subtype of non-Hodgkin lymphoma that affects predominantly older patients. The disease remains incurable with modern therapies. The integration of first- and now second-generation Bruton tyrosine kinase inhibitors (BTKis) into earlier-line settings appears to improve outcomes. Remaining questions in the field relate to the need for chemotherapy and the choice and duration of maintenance therapy, given its cost and infectious complications. In this review, we highlight clinical data showing BTKis targeting genetic vulnerabilities within mantle cell lymphoma cells. We then assess the integration of these agents into the first-line setting for all patients with newly diagnosed disease. Special consideration is given to patients with *TP53*-mutated disease, for which non-chemotherapy approaches are preferred.

Overview

Mantle cell lymphoma (MCL) is a moderately aggressive, incurable mature B-cell lymphoma that affects elderly individuals, predominantly men and persons of Northern European ancestry. MCL, characterized by heterogeneous disease biology and clinical outcomes,[1-3] makes up approximately 5% to 8% non-Hodgkin lymphomas (NHLs).[4,5] Although up to 20% of patients present with an indolent form of the disease for which observation is appropriate, most present with advanced-stage disease involving the bone marrow, peripheral blood, and/or gastrointestinal system, and often require treatment upon diagnosis. Owing to the persistence of disease relapse throughout an affected individual's lifetime, therapy is administered in 3 stages: (1) remission induction, (2) consolidation if warranted, and (3) maintenance to attack measurable residual disease (MRD) and increase time to next treatment.[6] The classic paradigm for patients with newly diagnosed disease has been stratification as either fit and transplant-eligible or elderly and presumably transplant-ineligible. This paradigm has influenced the choice of standard induction therapy and consolidation approaches and the decision of whether to employ high-dose chemotherapy followed by autologous hematopoietic stem cell transplant (HDC-AHCT). Most individuals receive multiple lines of therapy, which are associated with progressively shorter remissions if achieved, along with disease that is more resistant to chemoimmunotherapy. These patients are also at risk for treatment-related toxicities such as bone marrow suppression and infectious complications.

MCL variants include classic MCL, which derives from an immunoglobulin heavy chain gene (*IGHV*)-unmutated, antigen-naive, pre-germinal center B cell in the mantle zone of lymph nodes, and less commonly leukemic non-nodal disease, which arises from an antigen-experienced *IGHV*-mutated cell of germinal center origin and is more analogous biologically and clinically to chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).[7-10] The immunophenotype facilitates diagnosis, with aberrant expression seen of CD20, FMC7, and the negative T-cell regulator CD5, along with negativity for CD10 and CD23. Cytomorphologic variants—namely, blastoid and pleomorphic–are distinct from classic MCL. These variants comprise 5% to 10% cases and correlate with worse disease biology and more treatment-refractory disease.[2,11,12] Both conditions are driven by the IGH-CCND1 rearrangement, t(11;14)(q13;q32), which can be detected by either immunohistochemistry or less commonly fluorescence in situ hybridization. The rearrangement juxtaposes the cyclin D1 gene, which promotes the G1-to-S phase transition, and the immunoglobulin heavy chain enhancer and is necessary but not sufficient for pathogenesis and, in classic MCL, SOX11 expression. Sustained proliferative signaling is also driven by 9p21 aberrations, with the *INK4A/CDK4/RB1* and *ARF/MDM2/TP53* alterations, the *CHK2* and *KMT2D* mutations, and—most problematically—the *TP53* mutation associated with loss of genomic integrity and the accumulation of complex chromosomal gains, losses, and rearrangements.[2,9,13-15] These aberrations are collectively summarized and factored into the prognosis with the Ki-67 proliferative index, which confers high-risk biology when greater than 30%.[16] Tonic B-cell receptor signaling through Bruton tyrosine kinase (BTK) contributes to sustained proliferative signaling and apoptosis resistance.[17] The Mantle Cell Lymphoma International Prognostic Index (MIPI) incorporates the Ki-67 index along with age, Eastern Cooperative Oncology Group (ECOG) performance status, serum lactate dehydrogenase (LDH) level, and white blood cell (WBC) count.[18,19] MRD correlates with disease biology and treatment sensitivity and has increasingly been shown to predict survival outcomes.[20-22]

Improved insight into disease biology and response monitoring has informed the development of effective and less toxic targeted therapies that have gradually moved into earlier-line treatment settings. BTK inhibitors (BTKis) block constitutive signaling from the B-cell receptor, which contributes to lymphoma cell efflux from the marrow and lymph nodes, thereby reducing proliferative signaling, tissue infiltration, and tissue destruction. In this article, we critically review recent practice-changing and hypothesis-generating insights into the management of both younger, fitter patients and elderly or unfit patients that have improved outcomes and reduced treatment-related toxicities across all groups. We discuss evolving approaches in the selection of patients for therapies, including MRD-based strategies. We conclude with a discussion of reasonable standard approaches based on the best available data in 2025.

Historical Perspective: What Has Changed, and What Remains Standard?

Historically, the approach to treating MCL was based on categorizing patients as either younger and fitter or elderly and less fit. Part of this paradigm has evolved, whereas the rest has remained standard. Maintenance rituximab has a role in the management of both types of patients.

Historical Younger Patient Paradigm

MCL has historically been treated in a paradigm more consistent with that for acute lymphoblastic leukemia (ALL), with induction, consolidation, and maintenance phases. This treatment is quite different from that of other aggressive B-cell lymphomas, such as high-grade B-cell lymphomas, diffuse large B-cell lymphomas, and Burkitt lymphoma, which are managed with standard induction therapy alone for chemoimmunotherapy-sensitive disease.[23,24] ALL-type approaches with rituximab and hyperfractionated cyclophosphamide, doxorubicin, vincristine, and dexamethasone alternating with high-dose methotrexate and high-dose cytarabine (R-hyper-CVAD, modules A and B, respectively) induced high overall response rates (ORRs) and complete response (CR) rates, although with added toxicity, including a higher risk of mobilization failure that precluded stem cell collection for a substantial number of patients.[25-28] Subsequent regimens have been modified to include the high-dose cytarabine component with standard rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP).[25,26,29,30] Examples include the Nordic regimen, which uses dose-enhanced CHOP (“maxi-CHOP") alternating with rituximab and high-dose cytarabine, followed by HDC-AHCT.[31,32] Current data reading out from studies designed in the 2000s and 2010s also include regimens such as R-CHOP alternating with rituximab, dexamethasone, high-dose cytarabine, and cisplatin (R-DHAP). This regimen, developed by the GELA group, improved results vs CHOP-like strategies alone, highlighting the effectiveness of cytarabine in MCL.[33]

The role of high-dose cytarabine in promoting best outcomes in younger individuals was shown in the MCL Younger Trial, which was conducted in 128 centers in Belgium, France, Germany, and Poland and included adults 66 years of age or younger deemed transplant-eligible.[34] The original study was a randomized, open-label, parallel-group phase 3 trial in which patients received either 6 cycles of R-CHOP or alternating R-CHOP and R-DHAP followed by HDC-AHCT.[35,36] Among the 497 patients included, the time to treatment failure (9.1 vs 3.9 years, hazard ratio [HR], 0.56) was longer and the CR rate (55% vs 39%) was higher in the R-DHAP group, as were the rates of hematologic toxicities (grade 3 or 4 anemia, 29% vs 8%; thrombocytopenia, 73% vs 9%) and febrile neutropenia (17% vs 8%). The rate of grade 1 or 2 nephrotoxicity was also higher (43% vs 10%). The number of deaths did not differ between the groups. With longer-term follow-up of 10.6 years, the time to treatment failure was still better with R-DHAP than with R-CHOP (median, 8.4 vs 3.9 years; 5- and 10-year rates, 64%/46% vs 41%/25%; HR, 0.59). In addition, median overall survival (OS) was not reached in the R-DHAP arm vs 11.3 years with R-CHOP. More patients in the R-CHOP arm received a cytarabine-containing therapy in the second line, although with less benefit than with frontline integration. The rate of therapy-related malignancies, however, was higher in the R-DHAP arm than in the R-CHOP arm (4.5% vs 1.4% at 10 years). High-dose cytarabine remains a consideration for young patients, although intermediate doses have shown benefit in elderly individuals also.

Historical Less Fit or Elderly Paradigm

The bialkylating agent bendamustine was first synthesized in East Germany in the 1960s and was further developed in the 1980s as a safer alternative to cyclophosphamide. This agent has proven noninferiority for indolent and moderately aggressive lymphomas, including MCL, from the StiL and BRIGHT studies.[37-39] The noninferiority StiL study, which enrolled 514 patients with NHL, including 94 with MCL, between 2003 to 2008, found that bendamustine/rituximab (BR) improved CR rates (40% vs 30%) and PFS (35.4 vs 22.1 months) in comparison with R-CHOP. No OS benefit was noted, although fewer grade 3 or 4 hematologic and nonhematologic toxicities were found with BR. The similarly designed phase 3 BRIGHT study included 419 patients, 36 of whom had MCL, and found a higher ORR and similar CR rates for BR vs R-CHOP (97% vs 91% and 31% vs 25%, respectively), with similar grade 3 or 4 toxicities.[37] Follow-up analyses showed improved progression-free survival (PFS) and event-free survival (EFS) with BR.[39]

The Fondazione Italiana Linfomi group developed an approach consisting of intermediate-dose cytarabine combined with BR for elderly individuals that was well tolerated and efficacious.[40] This multicenter phase 2 trial enrolled 57 patients, with 95% completing at least 4 cycles and 67% completing all 6 cycles. At a median follow-up of 3 months, the PFS rate was 76%. The 2-year PFS and OS rates were 86% (74%-93%) and 81% (68%-89%), respectively. As expected, the primary toxicity was myelosuppression. Notably, patients did not receive standard maintenance rituximab, although long-term survival outcomes were favorable in that 7-year PFS and OS had not been reached at a median follow-up of 86 months (range, 57-107 months).[41] The 7-year PFS and OS rates were 55% (95% CI, 41%-67%) and 63% (95% CI, 49%-74%), respectively. Blastoid or pleomorphic morphology remained the strongest known predictor for PFS. Updated analyses incorporating MRD showed improved (although the differences were not statistically significant) outcomes for MRD-negative individuals after induction. Importantly, no increases in late toxicities or secondary malignancies were noted. Interestingly, patients did not receive maintenance rituximab, which would seemingly add benefit without any overlapping toxicity, although recurrent sinopulmonary infections in the post–COVID-19 era have limited the use of monoclonal antibodies and bispecific antibodies.

Targeted therapy approaches in the pre-BTKi era included combining lenalidomide with rituximab and adding the proteasome inhibitor bortezomib to CHOP-based therapy.[42-44] We will not review these studies owing to our focus on the current BTKi era, in which CHOP-based therapy alone—without concurrent high-dose cytarabine and the integration of non-BTKis in frontline therapy—is no longer standard practice.

Role of Maintenance Rituximab, Both Patient Types

In the maintenance setting, the landmark LYMA study proved that maintenance rituximab benefits patients with MCL in terms of both PFS and OS. This finding partially extended to follicular lymphoma, in which only PFS benefit was shown.[45,46] In this randomized, multicenter phase 3 trial, patients received 4 cycles of R-DHAP followed by HDC-AHCT and were then randomized to either maintenance rituximab for 3 years or observation. At a median follow-up of 50.2 months after HDC-AHCT, the 4-year EFS and PFS rates were 70% (99% CI, 70%-86%) vs 61% (95% CI, 51%-70%) and 83% (95% CI, 73%-88%) vs 64% (95% CI, 55%-73%), respectively, when the maintenance rituximab group was compared with the observation group. The OS rate was significantly higher (89%; 95% CI, 81%-94% vs 80%; 95% CI, 72%-88%). No increased toxicities were noted with maintenance rituximab, although the study was completed before the COVID-19 pandemic. Data were replicated in the community practice setting with a heterogeneous population on the basis of a retrospective study of 4216 patients with disease diagnosed between 2011 and 2021 in the United States, the majority of whom received BR induction.[47] The median time to the next treatment with BR followed by maintenance rituximab vs BR alone was 65.3 months (95% CI, 61.6-75.6) vs 37.7 months (95% CI, 33.1-41.2).[47] OS remained improved in the maintenance rituximab group, at 89.5 months (95% CI, 80-108.6) vs 78.1 months (95% CI, 62.9-93.5). These results suggest that maintenance rituximab may drive long-term outcomes more than HDC-AHCT.

Current Younger or Fitter Patient Paradigm

BTKis exploit specific vulnerabilities within MCL cells and exhibit nonoverlapping toxicities with regimens, such as BR, that historically were considered less efficacious than more intensive approaches. However, integrating BTKis into earlier-line settings has deepened the therapeutic responses for transplant-eligible patients, ushering in a new era of less-toxic therapy (Table 1).

Wagner-Johnston and colleagues presented the multicenter EA4181 study at the 2024 American Society of Hematology Annual Meeting.[48] The trial was designed to answer 2 questions: the optimal induction regimen for individuals 70 or younger with newly diagnosed disease and the benefit of adding acalabrutinib (Calquence, AstraZeneca), a second-generation BTKi, to induction. BR with sequential high-dose cytarabine and rituximab achieves high rates of complete metabolic response and undetectable MRD (uMRD) and was selected to serve as an appropriate backbone on which to add a second-generation BTKi.[49-51] Patients were randomized 1:1:1 to receive BR/cytarabine/rituximab (control), BR/cytarabine/rituximab/acalabrutinib (experimental), or BR/acalabrutinib (experimental). Acalabrutinib was administered continuously during BR cycles and on days 1 to 7 and days 22 to 28 during cytarabine/rituximab cycles to avoid toxicities during the chemotherapy nadir. The primary endpoint was a composite endpoint of CR on the basis of positron emission tomography/computed tomography (PET/CT) and uMRD (value of 10^{-5}) in peripheral blood with the clonoSEQ assay (Adaptive Biotechnologies). Secondary objectives included PFS and OS rates at 36 months, ORR, and toxicity rates. A total of 359 patients were enrolled between October 2019 and March 2023 (BR/cytarabine/rituximab, n=128; BR/cytarabine/rituximab/acalabrutinib, n=129; BR/acalabrutinib, n=102). The last arm was closed to accrual on the basis of a Data Safety and Monitoring Committee interim futility analysis. The median age was 61 years (range, 25-70 years), 30% of the patients were aged 65 or older, and the majority were male, Caucasian, and non-Hispanic. MIPI stratification categorized 18% of patients as low-risk, 43% as intermediate-risk, and 39% as high-risk. More than 90% of patients in all arms completed 6 cycles of protocol therapy. The complete metabolic response (CMR)/uMRD rate was 82% for BR/cytarabine/rituximab and BR/cytarabine/rituximab/acalabrutinib and 78% for BR/acalabrutinib. The ORR and CMR rates were 94%/91%, 99%/90%, and 94%/91%, respectively. At a median follow-up of 28 months, the estimated 12-month PFS and OS rates were 86%/94%, 89%/98%, and 87%/95%, respectively. Treatment-related grade 3 or higher adverse events were as expected in the cytarabine/rituximab groups and included neutropenia, anemia, and thrombocytopenia. The BR/cytarabine/rituximab/acalabrutinib arm had the most toxicity, and the BR/acalabrutinib arm had the least toxicity.

Continuous relapse risk has necessitated consolidation approaches for younger individuals, followed by standard-of-care maintenance rituximab. Gerson and colleagues conducted a multicenter retrospective study of 1254 patients treated between 2000 and 2015 with various induction regimens and found a PFS benefit, although not an OS benefit, following HDC-AHCT (post-propensity score weight analysis: PFS HR, 0.70; 95% CI, 0.59-0.84; OS HR, 0.87; 95% CI, 0.69-1.1).[52] The EA4151 study from the US Intergroup, which was conducted through the National Cancer Institute's National Clinical Trials Network and the Blood and Marrow Transplant Clinical Trials Network (BMT CTN), was designed to assess the role of MRD in predicting benefit from HDC-AHCT followed by maintenance rituximab vs maintenance rituximab alone. It was hypothesized that outcomes would be similar in patients with MRD-negative CR after induction and either 3 years of maintenance rituximab alone or HDC-AHCT followed by maintenance rituximab. Inclusion criteria included transplant-eligible patients aged 65 years or younger who completed induction therapy and were tested for MRD with PET/CT, bone marrow biopsy, and a peripheral blood clonoSEQ MRD assay. MRD-negative individuals were randomized 1:1 to Arm A (HDC-AHCT and 3 years of maintenance rituximab) or Arm B (3 years of maintenance rituximab alone); MRD-positive (Arm C) and MRD-indeterminate (Arm D) patients were randomized to HDC-AHCT and 3 years of maintenance rituximab. The primary endpoint was OS in Arms A and B. PFS was a secondary endpoint. A total of 650 patients were enrolled (257, 259, 49, and 85 on Arms A, B, C, and D, respectively). The median age was 60 years (range, 27-70). A high or high-intermediate MIPI score was noted in 37% of individuals. Intensive, cytarabine-containing induction was used in 73% of individuals. A BTKi was administered to 7% of patients. The 3-year OS rates for Arms A and B were 82.1% and 82.7% in randomized patients and 86.2% and 84.8% in patients treated as assigned. The 3-year PFS rates for Arms A and B were 76.6% and 77.4% in all randomized patients

Table 1. Mantle Cell Lymphoma in Younger Patients

Study Name	Key Clinical Questions	Key Eligibility Criteria	Protocol Details	Outcomes	What Is Added to the Literature?
EA4181, US Intergroup, Wagner-Johnston et al, presented at ASH 2024[48]	(1) Does addition of BTKi improve CR rate when added to HiDAC regimen? (2) If BTKi is added to BR, can HiDAC be eliminated?	• Patients aged ≤70 y • Composite PET/CT CMR and PB uMRD rate (1×10^{-5}) • Secondary: PFS and OS at 36 mo, ORR, toxicity	• 1:1:1 randomized, stratified by MIPI • BR/Ara-C-R (control) vs BR/Ara-C-R-acala vs BR-acala • Enrolled 10/2019-3/2023 • Median age 61 y (25-70), baseline clonal sequence in 95% • n=128 BR/Ara-C-R • n=129 BR/Ara-C-R-acala • n=102 BR-acala	• CMR/uMRD 82%, 82%, 78%; in sensitivity analysis, 74%, 76%, 74% • ORR 94%, 99%, 94% • Median follow-up 27.9 mo, 12-mo PFS/OS rates 86%/94%, 89%/98%, 87%/95%	(1) BTKi added to HiDAC regimen increased toxicity without improving outcomes (2) BTKi added to BR was least toxic option and produced outcomes comparable with those of regimens with HiDAC *Future directions:* Who should receive HiDAC in the era of BTKi?
ECOG-ACRIN EA4151[67]	(1) Does auto benefit patients who achieve a deep first remission, as measured by highly sensitive Ig high-throughput sequencing MRD assay?	• Ages 18-70 y in first CR • 4-arm trial	• PET/CT, marrow biopsy, and clonoSEQ MRD assay from PB after induction • If CR at 1×10^{-6}, then randomized 1:1 to Arm A (auto + MR × 3 y) or Arm B (3 y MR alone) • If MRD-positive or MRD-indeterminate (Arms C and D, respectively), then auto + MR × 3 y, repeat MRD day +100	• 3-y OS: 82.1% vs 82.7% in randomized, 86.25% vs 84.8% in assigned • 3-y PFS: 76.6% vs 77.4% in randomized, 81.5% vs 80.4% in assigned • Arms C and D 3-y OS and PFS: 81.9% and 76.9%, 85.1% and 73.4%, respectively	(1) Patients achieving uMRD in response to induction can be spared auto (2) MRD remains a powerful predictor of post-auto outcomes
TRIANGLE[54]	(1) Does BTKi improve outcomes when added to auto? (2) Does addition of BTKi eliminate need for auto?	• Ages 18-65 y included • Open-label, randomized, 3-arm, parallel-group design, superiority, 165 centers in Europe and Israel • Primary: FFS • Secondary: OS and toxicity	• Control group A (auto in CR1) vs auto + ibrutinib (A + I) or ibrutinib without auto (I) • Induction regimen A alternating R-CHOP and R-DHAP or D-DHAX	• 7/29/16-12/28/20, 870 patients randomized, 228 group A, 292 group A + I, 290 group I • 31-mo median follow-up, A + I > A with 3-y FFS 88% vs 72%, no superiority A vs I with 3-y FFS 72% vs 86%	Addition of BTKi appears to eliminate need for auto *Future directions:* (1) Contribution of BTKi during induction vs maintenance? (2) If BTKi is used, can HiDAC be eliminated during induction?

acala, acalabrutinib; Ara-C, cytarabine; ASH, American Society of Hematology; auto, high-dose chemotherapy and autologous hematopoietic stem cell transplant; BR, bendamustine and rituximab; BTKi, Bruton tyrosine kinase inhibitor/inhibition; CMR, complete metabolic response; CR, complete response; CR1, first complete remission; FFS, failure-free survival; HiDAC, high-dose cytarabine; Ig, immunoglobulin; mo, months; MIPI, Mantle Cell International Prognostic Index; MR, maintenance rituximab; MRD, measurable residual disease; ORR, overall response rate; OS, overall survival; PB, peripheral blood; PET/CT, positron emission tomography/computed tomography; PFS, progression-free survival; R, rituximab; R-CHOP, rituximab, cyclophosphamide, vincristine, and prednisone; R-DHAP, rituximab, dexamethasone, cytarabine, and cisplatin; R-DHAX, rituximab, dexamethasone, cytarabine, and oxaliplatin; uMRD, undetectable MRD; y, years.

and 81.5% and 80.4% in those treated as assigned. MRD-positive individuals had a 3-year OS rate of 81.9% (95% CI, 69.6%-96.5%) and a 3-year PFS rate of 76.9% (95% CI, 64.4%-91.7%), which were comparable with the rates of Arm D: 85.1% (95% CI, 76%-95.4%) and 73.4% (95% CI, 62.7%-85.9%), respectively. Intensive induction improved the 3-year OS rates in Arms A and B vs nonintensive induction (83% vs 79.5% and 86.2% vs 72.8%, respectively). MRD conversion correlated closely with outcomes; Arm C patients with MRD conversion to negative after HDC-AHCT achieved 3-year OS and PFS rates of 100%; the corresponding rates were 63.6% and 48.8% without such conversion. MRD status after induction may be an effective biomarker to stratify patients for HDC-AHCT.

The European TRIANGLE study hypothesized that immunotherapy with high-dose cytarabine (R-CHOP alternating with R-DHAP; GELA regimen) combined with the first-generation BTKi ibrutinib (Imbruvica, Pharmacyclics/Janssen) would obviate the need of benefit from HDC-AHCT in first CR.[53,54] To test this hypothesis, Dreyling and colleagues conducted a 3-arm, randomized, open-label, phase 3 superiority trial that enrolled 870 patients aged 17 to 65 years at 165 sites in 13 European countries. Patients were randomized 1:1:1 to HDC-AHCT alone (control, group A) vs HDC-AHCT and ibrutinib (experimental, group A+I) vs ibrutinib alone (experimental, group I). Study participants received maintenance rituximab per standard guidelines, which were altered during the study. At 31 months of follow-up, group A+I was superior to group A in terms of the 3-year failure-free survival rate: 88% (95% CI, 84%-92%) vs 72% (95% CI, 67%-79%; HR, 0.52; 1-sided 98.3% CI, 0-0.86). Group A was not superior to group I: 72% (95% CI, 67%-79%) vs 86% (95% CI, 82%-91%; HR, 1.77, 1-sided 98.3% CI, 0-3.76). The numbers of grade 3 to 5 adverse events were similar with or without ibrutinib during induction and consolidation, but not during maintenance. Updated survival analyses have shown both improved OS and manageable safety in the ibrutinib-only group in comparison with the control arms. Questions remain regarding the choice and duration of BTKi in combination with maintenance rituximab, although the study remains practice-changing given the novel approach, long-term follow-up across multiple centers, and favorable benefit-to-toxicity ratio for individuals in whom HDC-AHCT had been the standard of care for longer than decades. Subsequent iterations may include the addition of second-generation BTKis, which are more potent and less toxic, to less-intense non–anthracycline-containing backbones, such as BR with or without cytarabine/rituximab.

Our approach to younger, traditionally transplant-eligible patients is a modified version of the TRIANGLE regimen in which BR is combined with continuous, time-limited second-generation BTKi administration followed by 3 years of maintenance rituximab. A secondary approach that is more logistically cumbersome includes integrating 3 high-dose cytarabine and rituximab cycles, during which second-generation BTKis are held during the chemotherapy nadir, along with 3 cycles of BR followed by standard maintenance rituximab. Neither R-CHOP nor an alternating platinum-containing regimen has shown superior outcomes in comparison with the BR backbone.

Current Management, Elderly and/or Unfit

BR-based therapy has long been considered a standard of care for older patients with MCL (Table 2) who are unfit for high-dose cytarabine or HDC-AHCT. Given the promising activity of BTKis in setting of the relapsed or refractory MCL, it was natural to move these agents into the frontline setting for testing.[55,56] The SHINE study enrolled non–transplant-eligible patients aged 65 and older and randomized them to 6 cycles of BR with or without ibrutinib (Imbruvica, Pharmacyclics), which was administered during induction and until disease progression or lack of tolerability, in addition to maintenance rituximab every 2 months for 12 additional doses.[57] The primary endpoint was PFS. A total of 523 patients were included. At a median follow-up of 84.7 months, the median PFS was significantly higher in the ibrutinib group (80.6 vs 52.9 months; HR, 0.75; 95% CI, 0.59-0.96). CR rates also were higher (65.5% vs 57.6%), although OS was similar. Although the primary endpoint was met, competing toxicity from indefinite first-generation BTK inhibition has prevented this regimen from being adopted as the standard of care. Subsequent iterations have included second-generation drugs administered in a time-limited fashion; this approach has been hypothesized to enhance the depth of initial remission without adding survival-limiting toxicity.

The phase 3 ECHO study improved upon the design of SHINE in that the less-toxic second-generation BTKi acalabrutinib was assessed in combination with BR induction in individuals aged 65 years and older. Patients were randomized 1:1 to either acalabrutinib/BR or placebo/BR, with the BTKi administered in indefinite fashion until either disease progression or lack of tolerability.[58] Maintenance rituximab was administered for the standard 3 years in individuals who achieved a complete or partial response to induction therapy. Crossover was allowed per protocol. The primary endpoint was PFS. MRD was assessed in peripheral blood every 24 weeks, at CR, and at disease progression; it was also assessed in bone marrow at CR with the next-generation sequencing (NGS)–based clonoSEQ assay. A total of 598 patients were randomized, with 299 in each arm. The study population in the experimental and

Table 2. Mantle Cell Lymphoma in Elderly Patients

Study Name	Key Clinical Questions	Key Eligibility Criteria	Regimen Details	Outcomes	What Is Added to the Literature?
SHINE[57]	Does the combination of ibrutinib + BR improve outcomes in comparison with BR alone?	• Age >65 y • Primary endpoint: PFS • Secondary endpoint: OS and safety	• BR + BTKi followed by MR × 2 y plus indefinite BTKi vs BR + placebo followed by MR × 2 y plus indefinite placebo • Median follow-up 84.7 mo	• 261 ibrutinib and 262 placebo • PFS 80.6 vs 52.9 mo, HR 0.75 • OS and toxicity similar	(1) Ibrutinib addition improves PFS but not OS (2) Ibrutinib toxicity is clinically meaningful, limits benefit from well-tolerated BR backbone (3) Toxicity trade-off with prolonged exposure to first-generation BTKi
ECHO[58]	Does the combination of acala + BR improve outcomes in comparison with BR alone?	• Age ≥65 y • 195 global sites	• Phase 3 • BR + BTKi followed by MR × 2 y plus indefinite BTKi vs BR + placebo followed by MR × 2 y plus indefinite placebo • Crossover at PD allowed	• Median follow-up 45 mo • 299 each arm • Median PFS 66.4 vs 49.6 mo • 51 patients crossed over • No OS difference	Acala addition improves PFS but not OS *Future directions:* (1) Should SOC in older adults be BR or BR + acala on the basis of this study? (2) Consider cost, toxicity, and duration of maintenance therapy
ENRICH[66,69]	Are frontline chemotherapy-free regimens superior to SOC?	• Age ≥60 y, considered non-auto candidates • 65 UK and Nordic sites	• 1:1 randomized to ibrutinib-R induction vs either BR or R-CHOP × 6 cycles • Indefinite BTKi maintenance therapy	• 397 patients randomized, 199 to IR and 198 to R-chemo (R-CHOP 53, BR 145) • Median follow-up 47.9 mo • PFS IR vs R-chemo 65.3 vs 42.4 mo but IR benefit limited to R-CHOP comparison • No OS difference	(1) IR better than R-CHOP for PFS but comparable to BR (2) Ibrutinib known for higher toxicity, which may decrease some of the benefit

acala, acalabrutinib; auto, high-dose chemotherapy and autologous hematopoietic cell transplant; BR, bendamustine and rituximab; BTKi, Bruton tyrosine kinase inhibitor; HR, hazard ratio; IR, ibrutinib and rituximab; mo, months; MR, maintenance rituximab; OS, overall survival; PD, progression of disease; PFS, progression-free survival; R, rituximab; R-CHOP, rituximab, cyclophosphamide, vincristine, and prednisone; SOC, standard of care; y, years.

control groups included patients with high-risk biology, evidenced by high-risk simplified MIPI scores in 24.1% and 24.4%, blastoid histology in 8.7% and 6.7%, pleomorphic histology in 5% and 6%, a Ki-67 level above 30% in 46.5% and 49.2%, and known *TP53* alterations in 7.4% and 9.7%, respectively. Median PFS was higher with acalabrutinib/BR than with placebo (66.4 vs 49.6 months; HR, 0.73; 95% CI, 0.65-1.13), a difference that was statistically significant after COVID-19 deaths were censored (not reached vs 61.6 months; HR, 0.65, 95% CI, 0.49-0.86).

Therefore, modern approaches have used CLL/SLL as an example, assessing whether chemotherapy-free regimens may improve outcomes by reducing toxicity. The phase 3 ENRICH study, led by Lewis and colleagues, hypothesized that ibrutinib and rituximab (IR) would be superior to BR in individuals 60 years and older with newly diagnosed disease.[59] Patients were randomized to receive either IR induction followed by indefinite maintenance therapy or prerandomization BR or R-CHOP for 6 to 8 cycles. Patients in both arms received 2 years of maintenance rituximab. The primary outcome was PFS stratified by chemoimmunotherapy choice. A total of 397 patients were enrolled between December 2015 and June 2021, of whom 199 received IR, 53 R-CHOP, and 145 BR at 65 sites in the United Kingdom and Nordic regions. The median age was 74 years. A total of 57% of patients were categorized as high-risk by MIPI score, and 6.4% had blastoid cytomorphology. At a median follow-up time of 48 months, median PFS was superior with IR vs R-CHOP (not reached vs 26.6 months; HR, 0.37; 95% CI, 0.22-0.62), although not with IR vs BR (65.3 months vs 42.4 months; HR, 0.91; 95% CI, 0.66-1.25). The 5-year OS did not significantly differ between the groups. The rate of grade 3 or higher nonhematologic toxicities was higher with IR than with R-CHOP or BR (61.1% vs 51.9% and 51.7%), although the rate of grade 3 or higher hematologic toxicities was higher with R-CHOP (50%) than with either IR or BR (16.7% vs 33.6%). Quality-of-life metrics, assessed by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), were higher with IR than with chemotherapy (median interquartile range, 91 [95% CI, 84-95] vs 85 [95% CI, 76-92]). Mortality related to COVID-19 was higher with IR than with chemotherapy (19 vs 14).

The combination of acalabrutinib, venetoclax (Venclexta, Abbvie), and rituximab (AVR) induction followed by indefinite acalabrutinib and maintenance rituximab has been assessed in a phase 1b study of 21 patients, 57% of whom were older than 65 years.[60] The Ki-67 level was above 30% in 50% of patients. The ORR was 100% (95% CI, 83.9%-100%), including a CR rate of 74%. Median PFS and OS were not reached at median follow-up of 27.8 months. In addition, 88% of patients with MRD data achieved MRD negativity according to NGS. Grade 3 or 4 adverse events occurred in 62% of patients, including 5 deaths due to COVID-19; none of these deaths were in patients who were vaccinated early during the pandemic. Fewer deaths related to COVID-19 would be predicted at present. No other idiosyncratic or unexpected toxicities were noted with this novel combination. A larger, phase 2 trial is underway (TrAVeRse study). Future approaches may consider toxicity mitigation with time-limited BTK inhibition.

Whereas induction and consolidation approaches have been changing rapidly, maintenance rituximab administration has a proven survival benefit in both clinical trial and real-world settings, as evidenced by multiple retrospective studies and a landmark phase 3 randomized trial.[45,47] Therefore, the results of MANGROVE, in which zanubrutinib (Brukinsa, BeiGene) and rituximab are compared with BR without maintenance rituximab, must be interpreted with caution, as other similar study designs have included maintenance rituximab. Ongoing studies, including the phase 3 randomized ALLIANCE study (AO52101), are designed to assess whether intermittent BTKi therapy after induction for individuals who achieve CR may have outcomes similar to those of continuous therapy, but with fewer toxicities. Our approach for elderly patients is first to consider clinical trial enrollment with a nonchemotherapy backbone—namely, second-generation BTK inhibition and rituximab followed by maintenance rituximab. For individuals not eligible for trials, we then consider time-limited BR with up to 2 years of maintenance rituximab, which remains essential regardless of the induction approach. Financial toxicity analyses are being conducted as well.

Special Considerations

Special considerations may apply to patients with *TP53*-mutated disease (Table 3) and to younger individuals with highly proliferative disease.

Individuals With **TP53***-Mutated Disease*

TP53 alterations occur more commonly after repeated exposure to chemoimmunotherapy, with selective pressure promoting malignant clonal expansion. In addition, *TP53*-mutated disease is diagnosed in some individuals, for which the efficacy of DNA-damaging chemotherapeutics is known to be poor.[61] In response, Kumar and colleagues at Memorial Sloan Kettering Cancer Center and Massachusetts General Hospital conducted a phase 2 study of the combination of zanubrutinib, obinutuzumab (Gazyva, Genentech), and venetoclax (BOVen), which was administered as first-line therapy to 25 patients with *TP53*-mutated MCL.[62] At a median follow-up of 28.2 months, the 2-year PFS, disease-specific survival, and OS rates were 72%, 91%, and 76%, respectively. Individuals in CR on the basis of uMRD after 24 months discontinued treatment. The ORR and the CR rate were 96% (24/25) and 88% (22/25), respectively, with high rates of uMRD at sensitivity levels 1E-5 (95%, 18/19) and 1E-6 (84%, 16/19), respectively. The regimen was well tolerated, with primary toxicities including diarrhea, neutropenia, and infusion-related reactions. This study improves the existing paradigm in which patients must fail short-course frontline chemoimmunotherapy before progressing to standard-of-care second-generation BTKi

Table 3. Mantle Cell Lymphoma With *TP53* Mutation

Study Name	Key Clinical Questions	Key Eligibility Criteria	Protocol Details	Outcomes	What Is Added to the Literature?
BOVen[62]	Patients with high-risk, blastoid variant or *TP53*-mutation perform poorly, and disease is refractory to treatment with DNA-damaging chemotherapies Noncytotoxic agents may provide benefit in patients with otherwise chemotherapy-refractory disease without adding unnecessary toxicity	• Multicenter phase 2 study • Primary endpoint was PFS at 2 y	• Zanubrutinib 160 mg BID and obinutuzumab lead-in therapy (1000 mg days 1, 8, and 15 on cycle 1 followed by day 1 on cycles 2-8) • Venetoclax added with ramp-up to 400 mg daily on third cycle • If uMRD after 24 cycles (with sequencing assay), then treatment can be discontinued	• 25 patients included • ORR 96% (24/25), CR 88% (22/25) • uMRD at 1×10^{-5} 95% (18/19) and at 1×10^{-6} 84% (16/19) • 2-y PFS, disease-specific survival, and OS were 72%, 91%, and 76%, respectively • Toxicities included diarrhea 64% (56% grade 1, transient), neutropenia 32% (16% grade 3, reversible with growth factor support, no cases of febrile neutropenia), and infusion-related toxicity from obinutuzumab 24%	(1) Builds on OAsis study (ibrutinib, obinutuzumab, and venetoclax, phase 1/2)[68] (2) First approach to our knowledge of non-chemotherapy treatment for *TP53*-mutated classic MCL (3) Small patient numbers, 2 institutions, short follow-up, although changes prior paradigm in which individuals with known *TP53* alterations challenged first with short-course chemoimmunotherapy before proceeding to second-line BTKi and then third-line CART19 *Future directions:* Because these patients experience relapse, consider how these agents influence proceeding to CART, how to consolidate once in remission

BID, twice a day; BTKi, Bruton tyrosine kinase inhibitor; CART19, CD19-directed chimeric antigen receptor T-cell therapy; CR, complete response; MCL, Mantle cell lymphoma; ORR, overall response rate; PFS, progression-free survival; uMRD, undetectable MRD; y, years.

therapy, and often autologous CD19-directed chimeric antigen receptor (CAR) T-cell therapy thereafter. The omission of bendamustine with the BOVen approach may enhance the effectiveness of CD19-directed CAR T-cell therapy by preserving autologous T-cell function and cytolytic capacity.[63]

Younger Individuals With Highly Proliferative Disease

Approximately one-third of individuals in each arm of the TRIANGLE study had a Ki-67 level above 30%, although individuals with more proliferative disease and no *TP53* mutations may require induction based on high-dose cytarabine rather than R-CHOP alternating with R-DHAP or BR. This uncommon, unique scenario is challenging in terms of short-term management in that BTKi overlapping toxicity obviates concurrent administration and long-term consolidation for individuals who achieve remission, given the now-conflicting data about the benefit of HDC-AHCT in first CR. Our approach in these scenarios is to consider alternating BR and CR, which facilitates continuous BTKi administration with the former and intermittent administration with the latter.[34,35,49,50] Although the regimen is more logistically nuanced and sometimes confusing for patients and providers, it may be warranted for these high-risk individuals. Continuous BTKi maintenance may reduce loss of MRD negativity for individuals inCR according to the clonoSEQ assay and improve conversion of positivity to negativity over time. A BOVen-type regimen may also be effective in this scenario, although it has not yet been studied in part because patients with *TP53*-mutated disease experience the worst induction outcomes and progress to CD19-directed CAR T-cell therapy faster than patients in other disease subgroups, including those with a high Ki-67 level without *TP53* aberrations.[64] Although bendamustine exposure during induction has a known deleterious effect on T-cell number and function within the first year of exposure, endogenous immunity improves after 1 year, so that CD19-directed CAR T-cell therapy is an appropriate consideration at this time.[65] European and North American practice patterns differ in that R-CHOP is omitted in the latter, given its equivocal effect. Both approaches include high-dose cytarabine, which has unique efficacy in MCL.[29,34,35,50]

Future Directions

Our current, evidence-guided practice pattern for transplant-eligible and -ineligible individuals with newly diagnosed classic MCL is a "TRIANGLE-type" approach,"in which BR is combined with a second-generation BTKi or BR alternates with continuous BTKi. CR with interrupted therapy accounts for the chemotherapy nadir in individuals with relatively proliferative disease, defined as a Ki-67 level above 50% and/or the presence of additional high-risk features, such as blastoid or pleomorphic cytomorphology or complex cytogenetics. Individuals 65 years and older who are less fit but have relatively proliferative disease may be considered for regimens such as R-BAC500, which induces a more balanced approached between MCL killing and its known dependence on cytarabine, although with toxicities that include transfusion dependence and increased infectious complications. An MRD-guided approach can facilitate the selection of individuals with high-risk disease who may still benefit from HDC-AHCT.[40,54] We recommend approaching patients with newly diagnosed *TP53*-altered MCL with a BOVen-type regimen that includes agents with synergistic, non-*TP53* mechanisms of tumor cell apoptosis.[62]

Unanswered questions include the optimal chemoimmunotherapy backbone, including regimens often used in Europe, such as the GELA and Nordic regimens, and the regimens preferred in North America, such as BR or BR alternating with CR. Determining the patients for whom high-dose cytarabine is worthwhile is still unclear, especially after consideration of the long-term follow-up data from the MCL Younger trial, which appears to show a survival plateau.[34] Although a randomized trial comparing these approaches would provide a higher level of evidence for practitioners, MCL strategies are converging with those for CLL/SLL, in which chemotherapy-free regimens including second-generation BTKis—and in the case of *TP53*-mutated disease, BCL2 inhibitors—are more appealing owing to their favorable toxicity profiles. A greater number of treatment-related toxicities no longer necessarily correlates with the ability to achieve and maintain remission.

Disclosures

The authors do not have any financial interests to disclose.

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