Frontline Therapy in Mantle Cell Lymphoma: New Standards in 2017

Morgane Cheminant, MD, and Olivier Hermine, MD, PhD

Abstract

Mantle cell lymphoma (MCL) is a B-cell lymphoma characterized by the t(11;14) translocation and cyclin D1 overexpression that comprises 3% to 6% of non-Hodgkin lymphomas. MCL is an aggressive entity with a median survival of only 3 to 4 years. Several new therapeutic strategies appear to improve the outcome, but it is not yet entirely clear how these results translate into the general population. This review focuses on the new therapeutic standards for untreated patients with MCL. In younger patients, the benefit of an aggressive induction combining rituximab with cytarabine, followed by consolidation with autologous stem cell transplant, has been confirmed. Despite recent advances, MCL remains incurable with a continuous pattern of relapses that led to the incorporation of a maintenance strategy in several studies. In younger as well as in elderly patients, rituximab maintenance has thus become a reasonable standard of care. In addition, MCL is a heterogeneous entity, which requires the precise definition of prognosis factors with the aim of establishing a risk-adapted therapeutic strategy. In this context, the particular cases of indolent and high-risk MCL are discussed. This review also covers the approaches based on the monitoring of minimal residual disease (MRD) that may enable tailored treatment strategies, in particular to select patients who may benefit from targeted therapies, such as BTK inhibitors. Obtaining a complete response with MRD negativity (and/or negative PET scan) by reducing toxicity during induction will become the future therapeutic objective. New therapeutic approaches integrating these novel agents earlier in the disease course or in combination will depend on clinical studies including untreated and relapsed patients with MCL.

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Introduction

Mantle cell lymphoma (MCL) is a B-cell lymphoma characterized by the t(11;14) translocation and cyclin D1 overexpression. MCLs compose 3% to 6% of non-Hodgkin lymphomas, with an annual incidence of 0.5 per 100,000 population in Western countries.[1,2] MCL has been identified as aggressive, with median survival reaching only 3 to 4 years.[3-5] However, while most MCL cases fit a pattern of continuous relapses, the results of several studies indicate that new therapeutic strategies appear to improve outcomes. It is not yet entirely clear how these results will translate into the general population. In addition, MCL is a heterogeneous entity; a significant number of indolent patients with MCL do not require any treatment for months or even years.[6] On the other hand, a minority of patients with MCL, whose disease becomes resistant to standard therapies, has a particularly unfavorable outcome.[7,8]

Prognostic Factors and Mantle Cell International Prognostic Index

With the improvement of treatments and the heterogeneity of responses, it has become evident that prognosis factors should be now defined to help in therapeutic decision making. Classification systems have evolved to predict outcomes in MCL. Blastoid histology, high expression of Ki-67, and *CDKN2A/TP53* deletions have been clearly associated with unfavorable prognosis.[9-12] Additionally, recently developed is an MCL-specific clinical prognostic tool—the Mantle Cell International Prognostic Index (MIPI)—based on 4 independent prognostic factors: age, performance status, lactate dehydrogenase, and leukocyte count.[13,14] The MIPI separates patients with MCL into 3 risk groups: high (including patients relapsing during the year after end of treatment); intermediate (including patients with an incidence of relapse of 10% to 15% per year); and low (including almost 30% of patients with a complete response [CR] lasting 5 years or more).[7,15] The proliferation index Ki-67 was then incorporated into the combined biologic index, or MIPI-c, which allows the identification of 4 risk groups in both younger and elderly patients.[16] These scores have limitations in clinical practice and were not designed to help clinicians decide on treatment strategy. However, researchers should consider some prognostic characteristics to help guide newer MCL therapeutic approaches.

Indolent Mantle Cell Lymphoma

The first question when managing MCL is when to initiate treatment. In selected asymptomatic patients, a watch-and-wait strategy is acceptable, as demonstrated by the superior survival profile of the observation group compared with the early treatment group in

a retrospective analysis of the outcome of deferred initial therapy.[6] In these patients, MCL is nonnodal or localized, usually characterized by hyperlymphocytosis and splenomegaly. Leukemic nonnodal MCLs show a very low proliferation index with no blastoid histology, have high levels of somatic mutations in the immunoglobulin heavy-chain variable (IGHV) locus, a normal karyotype,[17] and lack *SOX11* expression.[18] Some SOX11-negative MCLs can acquire oncogenic mutations, such as *TP53* mutations, and progress toward a fatal clinical outcome.[19] Nonetheless, initial treatment can be deferred until symptoms or other treatment indications develop. At that point, treatment strategy will depend on the age and general condition of the patient.

Autologous Stem Cell Transplantation

The benefit of autologous stem cell transplantation (ASCT) in younger and fit patients was confirmed by the results of a prospective randomized study that demonstrated better progression-free survival (PFS) with ASCT compared with alpha-interferon (IFN) maintenance therapy.[20] This was also suggested by results of several nonrandomized studies that showed PFS improvement in previously untreated and relapsed patients who had not previously undergone transplantation.[21-23] Results of the randomized study showed that ASCT as first-line therapy improved PFS significantly, but the 3-year overall survival (OS) was similar in both treatment arms (83% ASCT vs 77% IFN, $P = .18$). This can be explained by the fact that a significant number of patients in the IFN arm who experienced relapse were subsequently transplanted.[20] It is currently unclear which conditioning regimen is superior. Across Europe, commonly used conditioning regimens include total body irradiation (TBI) with high-dose cyclophosphamide and a combination of high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM). Based on a comparative retrospective analysis of European MCL (with TBI) and MCL Nordic group (no TBI), studies that used a similar induction chemotherapy containing high-dose cytarabine (Ara-C), TBI seems to improve PFS only in the group of patients who are in partial response before ASCT.[24] Because the goal of most new induction regimens is CR, TBI is no longer used in Europe, and the BEAM regimen is the new standard.[15]

Response Assessment

The use of rituximab during induction therapy before ASCT was associated with an increase of overall response rate (ORR) and CR, which translated into an improvement of PFS.[25] Based on these results, reaching the best response before ASCT has been the therapeutic goal in subsequent trials. The response before ASCT can be assessed both at the molecular and metabolic levels. Monitoring minimal residual disease (MRD) has proved relevant in MCL to evaluate the quality of remission and predict clinical relapse.[26,27] In the 2 randomized trials of the European MCL Network (MCL Younger and MCL Elderly trials), multivariate analysis showed that the MRD status at the end of induction before ASCT or maintenance is among the strongest independent prognostic factors.[27] Therefore, MRD negativity should become the therapeutic goal in MCL and guide the choice of induction regimen. The role of PET scans is not yet defined in MCL, although the scans may have prognostic value both at diagnosis and after induction therapy.[15] The final results of the LyMa trial (testing the efficacy of rituximab maintenance after ASCT in MCL) will help answer these questions.

Induction Regimen in Younger Patients

Although adding rituximab to conventional chemotherapy improves OS, the CR rate and time to treatment failure (TTF) of patients after treatment with rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) remain below 50% and less than 2 years, respectively.[28] The most active induction regimens have included Ara-C. Results of a single-center study testing a regimen combining rituximab-hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (RHyper-CVAD), alternating with high-dose methotrexate plus cytarabine, indicated that the regimen was effective and safe, but the results of other multicenter studies indicate that it should be used cautiously, because it was associated with substantial toxicity and a high rate of stem cell collection failures.[29-32] In younger patients (median age 55 years), the results of the randomized study of the European Mantle Cell Lymphoma Network (EMCL) established the superiority of an Ara-C–containing induction regimen over R-CHOP alone,[7] confirming the promising results obtained with various phase II studies.[33-36] Ara-C treatment significantly increased the CR rate compared with R-CHOP (from 39% in the R-CHOP arm to 55% in the Ara-C arm; $P = .0005$) and molecular response rates in the peripheral blood (from 47% in the R-CHOP arm to 79% in the Ara-C arm), which translated into better TTF at 5 years (65% in the Ara-C arm vs 40% in the R-CHOP arm; $P = .038$). The LyMa study, which used R-DHAP (rituximab, dexamethasone, cytarabine, and cisplatin) without R-CHOP during induction, led to results of similar response rates at both the clinical and molecular levels.[15] Therefore, the addition of Ara-C to induction treatment followed by ASCT has become a new standard in younger patients.

Induction Regimen in Elderly Patients

However, two-thirds of patients with MCL are elderly or unfit for a regimen of high-dose induction and ASCT. Effective, well-tolerated first-line therapeutic options have been evaluated for this group of patients with MCL. In the EMCL network study of elderly individuals (66 years of age or older), R-CHOP resulted in superior OS compared with rituximab, fludarabine, and cyclophosphamide (4-year survival rate, 47% vs 62%; $P = .005$) although CR rates were similar (34% and 40%, respectively; $P = .10$).[37] Therefore, many practitioner groups accept combination chemoimmunotherapy regimens, such as R-CHOP, as standard treatment for elderly patients. However, in this setting, bendamustine is also an active monotherapy, and is

well tolerated by older or frail patients. Bendamustine combined with rituximab (BR) has shown improved efficiency in comparison with R-CHOP in a randomized trial including patients with MCL.[38] Moreover, the synergistic action of rituximab, bendamustine, and cytarabine demonstrated in preclinical studies[39] led to the use of this combination in trials with patients with MCL who were not eligible for intensive regimens. In a phase II study, the addition of cytarabine 800 mg/m^2 intravenously during day 2 and day 4 to BR (R-BAC) was active against MCL, with a 2-year PFS rate of 95% in previously untreated patients, but its use was restricted by high hematological toxicity.[40] However, the same regimen with low-dose cytarabine (RBAC500) was an effective treatment for elderly patients (median age 71 years) with MCL.[41] The proteasome inhibitor bortezomib has modest single-agent activity in MCL, with an ORR of 30%,[42,43] but appears useful in combination with chemoimmunotherapy. A regimen replacing vincristine with bortezomib in R-CHOP (VR-CAP) improved the CR rate compared with R-CHOP in newly diagnosed patients with MCL (42% vs 53%) but showed disappointing results in terms of PFS (median PFS, 24.7 months with VR-CAP compared with 14.4 months with R-CHOP) in previously published data.[44] Finally, although it is generally agreed that rituximab should be included, the standard induction regimen in these elderly patients is yet to be completely defined.

Maintenance Therapy

The constant risk of MCL relapse throughout a patient's lifetime led to the incorporation of maintenance treatment into various trials. In the EMCL elderly trial, patients who had a response underwent a second randomization for maintenance therapy with rituximab or IFN for 2 years. Maintenance rituximab improved duration of response (DOR) compared with IFN (hazard ratio, 0.55; 95% CI, 0.36-0.87). Moreover, maintenance rituximab showed impressive results in terms of OS among patients who received R-CHOP induction (4-year OS, 87% with maintenance rituximab vs 63% in observation arm; $P = .005$).[37]

Recent data provided by the phase III LyMA study confirmed the benefit of rituximab maintenance in younger patients with newly diagnosed MCL, even after receiving ASCT. Patients received R-DHAP as induction, followed by ASCT, and were then randomized for rituximab maintenance or observation. Rituximab maintenance after ASCT prolonged both PFS and OS compared with the observation arm (4-year PFS, 82.2% vs 64.6%; $P = .0005$, and 4-year OS, 88.7% vs 81.4%; $P = .0413$).[15] Thus, rituximab maintenance represents a reasonable standard of care in treating both younger and elderly patients with MCL.

Study results have also indicated that MRD-based pre-emptive rituximab treatment converts patients to MRD negativity and likely postpones clinical relapse.[45,46] Molecular monitoring could thus select patients who may benefit from therapeutic intervention, while avoiding unnecessary treatment of other patients. However, the best way to achieve MRD negativity, whether by blood, bone, marrow, or biological techniques, is currently not fully defined. Based on these studies, a phase II trial (LyMA101) includes treatment-naïve patients with MCL and proposes obinutuzumab (GA101) combined with DHAP as induction, then ASCT followed by obinutuzumab maintenance for 3 years, then random assignment for preemptive treatment or observation.

Allogeneic Stem Cell Transplantation

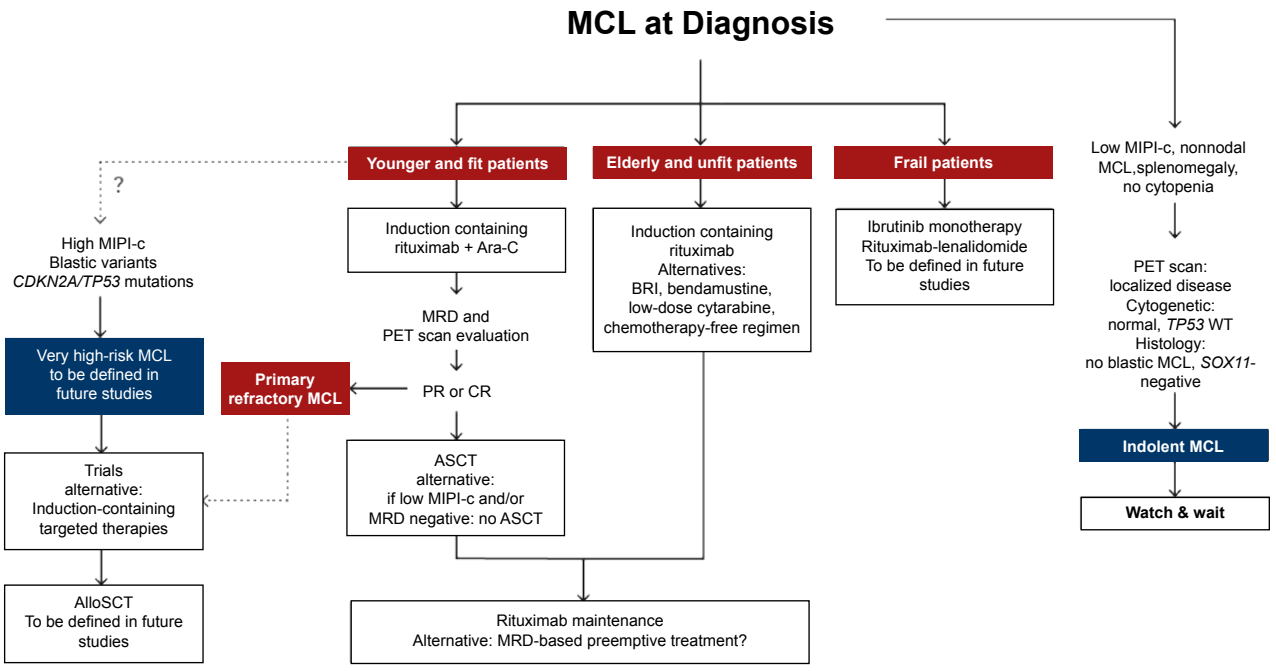
Despite these advances, about 5% to 10% of patients with MCL who are primary refractory to chemotherapy have an extremely dismal prognosis, even after optimal salvage chemotherapy.[47] This outcome is only partially recovered by allogeneic stem cell transplantation (alloSCT) that could be a benefit to chemosensitive patients with MCL.[8] Based on the high toxicity in the first 2 years after alloSCT, it has been suggested that it should be reserved for fit patients for whom risk of relapse without this treatment is very high.[48] Blastoid variants, high expression of Ki-67, and *CDKN2A/TP53* deletions, as well as suboptimal response after induction, may all help identify these very high-risk patients. However, the prognostic stratification of newly diagnosed patients with MCL is not efficient enough to predict clinical behavior and to guide a targeted treatment approach for an individual patient. At this time, for that reason, alloSCT is not recommended as first-line therapy.[49] Future studies should aim to identify prognostic markers so that early risk-adapted strategies may be employed.

Targeted Therapies

Because of drug resistance observed at relapse, some new strategies, such as the use of novel therapeutic agents, have emerged and are now being evaluated in various studies. A recently published phase II study incorporating a combination of lenalidomide and rituximab for unfit and untreated patients with MCL showed encouraging results, with a CR rate of 61%.[50] The TRIANGLE study, designed by the EMCL network for younger patients, will randomize patients to a combination of chemotherapy with or without the Bruton tyrosine kinase inhibitor ibrutinib as induction, followed by a second randomization evaluating the role of ibrutinib maintenance. A treatment combining rituximab and ibrutinib followed by chemotherapy according to the response rate is currently being tested, and preliminary results indicate that ORR is excellent.[51]

The results of an open-label, multicenter, industry-sponsored phase III study, SHINE, comparing ibrutinib or placebo given in combination with bendamustine and rituximab in elderly untreated patients with MCL, are expected this year. Moreover, although they show relatively modest single-agent activity, cyclin-dependent kinase 4/6 (CDK) selective inhibitors may lead to durable responses in relapsed/refractory MCL. It would thus be interesting to test these compounds in first-line therapy, as monotherapy or in combination.[52-54] These new strategies may prolong the PFS in unfit patients or those with a very poor prognosis,

FIGURE. Algorithm for Mantle Cell Lymphoma Management



AlloSCT indicates allogeneic stem cell transplantation; Ara-C, high-dose cytarabine; ASCT, autologous stem cell transplantation; BRI, bendamustine, rituximab, and ibrutinib; CR, complete response; MIPI-c, Mantle Cell International Prognostic Index; MRD, minimal residual disease; PR, partial response; WT, wild type.

but they should also demonstrate improvements in OS, given the dismal outcomes of relapsing patients after ibrutinib treatment.

Conclusions

Past clinical trials have demonstrated the role of rituximab combined with Ara-C, followed by ASCT, for younger and fit patients with MCL; the benefits of rituximab maintenance in both young and elderly patients have also been shown. Future research should integrate risk-adapted therapeutic strategies that include new agents that could overcome resistance in high-risk MCL. The stratification of patients at diagnosis implies a better understanding than we currently have of MCL pathogenesis, and of the identification of biomarkers that can be specifically targeted with novel agents. MRD negativity (and/or negative PET scan) will probably be the therapeutic goal to achieve following the induction regimen.

In the future, a risk-adapted approach as well as postinduction MRD analysis may enable tailored treatment strategies, in particular to select patients who may benefit from targeted agents (alone or in combination with chemotherapy) during induction, from intensification with ASCT, and/or from maintenance therapy. The ultimate objective will be to obtain complete responses by reducing toxicity during induction with regimens based on targeted therapy alone. However, careful analysis of both benefits and risks, and the economic burden of such strategies, will be required before proposing new standards of care. Molecular monitoring could be a tool assisting in both the selection of patients for maintenance or pre-emptive treatment, and the follow-up strategies (**Figure**).

Author affiliations: Both Morgane Cheminant, MD, and Olivier Hermine, MD, PhD, are with Clinical Hematology, Necker University Hospital, AP-HP; Imagine Institute; INSERM U1163, CNRS ERL8654, and Paris Descartes University-Sorbonne Paris Cité. All are in Paris, France.
Address correspondence to: Olivier Hermine, MD, PhD, Department of Clinical Hematology, Necker Hospital, 149 rue de Sèvres, 75015 Paris, France. Telephone: +33(0)144495368; E-mail: ohermine@gmail.com.
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