



Recent advances in the first-line treatment of mantle cell lymphoma

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Abstract: Mantle cell lymphoma (MCL) is a rare B-cell lymphoma, with a median survival of only three to four years. In recent years, the development of new drugs and therapeutic strategies appeared to have improved the outcomes. This review focused on the most important new strategies for untreated MCL patients. Given the heterogeneous clinical evolutions between patients, several prognostic factors have been identified. These factors, as well as the identification of indolent and aggressive MCL, are useful to propose a risk-adapted therapeutic strategy. The prognostic impact and the practical applications of minimal residual disease (MRD) will be addressed. Overall, induction by combining rituximab with cytarabine, followed by consolidation with autologous stem cell transplant had been shown to have benefits for MCL younger patients. However, almost all MCL patients will relapse over time. The addition of rituximab as maintenance therapy for these patients had been shown to improve overall survival. Achievement of complete response with negative MRD and/or negative PET scan while reducing toxicity would be the future therapeutic objective. In this perspective, targeted therapies, alone or in combination as induction or maintenance therapy, are currently being tested earlier in the disease course.

Keywords: Mantle cell lymphoma (MCL); autologous stem cell transplantation; allogeneic stem cell transplantation; minimal residual disease (MRD)

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Introduction

Mantle cell lymphoma (MCL) is a B-cell non-Hodgkin lymphoma with a t(11;14) translocation and cyclin D1 overexpression, that comprises 5.5% of mature B-cell neoplasms (1,2). MCL is a lymphoma of poor prognosis, with median survival of only three to four years and a continuous pattern of relapses (3-5). Several studies showed that new therapeutic approaches could improve the outcomes. In addition, MCL patients have heterogeneous clinical evolutions, with some patients not requiring treatment for months to years (6) while a small proportion

of them are resistant to standard therapies and have very poor outcomes (7,8).

Prognostic factors and mantle cell international prognostic index (MIPI)

Because the therapeutic responses to treatment are heterogeneous, guidance on the therapeutic decisions would need definition of the prognostic factors. Evolving classification systems had been made to predict the outcomes of MCL. Similar to blastoid histology often associated with

high number of Ki-67 positive cells, CDKN2A deletion and TP53 mutations had been identified as poor prognostic factors (9-12). The MIPI, based on four independent factors (e.g., age, performance status, leukocyte count and level of lactate dehydrogenase), had been specifically developed for MCL (13,14). This index separates high-risk MCL, which comprised 15–20% of patients who had response for a duration of less than one year after the end of treatment; the intermediate-risk group, which included patients who had an annual incidence of relapse of 10–15%; and the low-risk group, which comprised nearly 30% of patients who were in complete response (CR) for more than five years (7,15). The combined biologic index, or MIPI-c, incorporated the proliferation index Ki67 has been validated in both younger and elderly patients (16). More recently, in the prospective trials of the European MCL (EMCL) Network, TP53 expression (i.e., >50% positive cells) had been shown to confer relatively short time to treatment failure (TTF) and poor overall survival (OS) among the treated patients, independent of both MIPI score and Ki67 index (17). Moreover, the presence of TP53 mutations identified a unique subset (11%) of chemo-refractory MCL patients (median OS, 1.8 in TP53 mutated cases *vs.* 12.7 years in wild-type cases) (18); 50% of patients in the TP53 mutated group relapsed within one year of diagnosis. It is now accepted that MCL patients should be stratified, according to their prognostic characteristics, which may guide some newer therapeutic strategies.

Indolent mantle cell lymphoma

In selected indolent MCL cases, a watch and wait strategy should be preferred, as shown by the higher rate of survival with observation than with early treatment (6). A non-nodal or localized disease with hyperlymphocytosis and splenomegaly usually characterizes indolent MCL patients. Leukemic non-nodal MCLs showed a classical histology with a low proliferation index, had high levels of somatic mutations in the IGHV locus, a normal karyotype (19) and lacked SOX11 expression (20). However, the prognostic impact of SOX11 expression had been controversial, because some SOX11-negative MCLs can also have genomic alterations, such as TP53 mutations, which leads to poor clinical outcome (21). Moreover, in a recent study of the EMCL Network, SOX11 status, which was assessed by immunohistochemistry, did not show a strong association with OS (17). Therefore, in patients with indolent MCL, initial treatment can be deferred until the development

of symptoms or disease progression. Once decided, the therapeutic strategy will depend on the age and general health of the patient.

Therapeutic goal and response assessment

In the early studies that assessed the role of ASCT, the use of the anti-CD20 monoclonal antibody rituximab combined with chemotherapy before ASCT was associated with a higher rate of overall response rate (ORR) and CR, which led to longer progression-free survival (PFS) (22). It is therefore commonly accepted that achievement of the best response before ASCT should be an important goal in the therapeutic strategy. The monitoring of minimal residual disease (MRD) is a valuable biomarker of quality of response (23,24). Indeed, the two randomized younger and elderly trials of the EMCL Network showed that molecular remission at the end of induction (before ASCT) was a strong independent prognostic factor (response duration, 87% *vs.* 61% patients in remission at two years, $P=0.004$) (24). Therefore, increasing the proportion of patients who achieve negative MRD should become the therapeutic objective of the induction therapy. The role of PET scan has not been defined, although it may have a prognostic value, both upon diagnosis and by assessing the response (15). The final analysis of the LyMa trial, which tested the efficacy of rituximab maintenance in MCL (see below), will provide answers to these questions.

Induction regimen in younger and fit patients

Although the addition of rituximab to chemotherapy improved the OS, the CR rate remained below 50% and the TTF was shorter, compared with the outcomes at two years after rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (25). The most active induction regimens included high-dose cytarabine (Ara-C). A regimen that combined rituximab-hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, alternating with high-dose methotrexate plus cytarabine, was shown to be active and safe in a single-center experience, but was highly toxic with a non-negligible rate of stem cell collection failure in multicenter studies (26-29). In younger patients, the randomized study of the EMCL Network for Younger patients showed that Ara-C-containing induction regimen was superior to R-CHOP alone (7), confirming the previous results obtained in several phase II studies (30-33). Compared

with R-CHOP alone, Ara-C treatment significantly increased the CR (39% to 55%, $P=0.0005$) and molecular response rates (47% to 79% in the peripheral blood), which led to a better TTF at five years (65% *vs.* 40%, $P=0.038$). The Nordic MCL2 trial, which have included six alternating courses of R-CHOP and R-Ara-C followed by an ASCT, showed impressive results of 96% ORR and 54% CR rates after induction, which led to a median OS of 12.7 years and PFS of 8.5 years (25). The LyMa study, based on four courses of rituximab, dexamethasone, cytarabine and cisplatin (R-DHAP), reported ORR and CR rates of 89% and 77% respectively (26). Of the 299 enrolled patients, 20 who were having a partial response (PR) received rescue induction therapy with four courses of R-CHOP, which improved the response in nine cases (26). Therefore, the ASCT after an induction combining rituximab and Ara-C chemotherapy has become a validated therapeutic approach in younger patients.

Autologous stem cell transplantation

In younger and fit patients, the benefit of ASCT was confirmed by a randomized study, which demonstrated better PFS with ASCT than with interferon- α (IFN) maintenance therapy (27), as suggested by several non-randomized studies on patients who received first-line treatment and those in relapse (28-30). In the only randomized study available, ASCT performed as first-line therapy, compared with IFN therapy, significantly improved the PFS but had similar three-year OS (83% *vs.* 77%, $P=0.18$) (27), a fact that can be explained by the use of ASCT as a salvage therapy in the IFN arm. Moreover, a recent large retrospective study demonstrated improved PFS (hazard ratio 0.54; 95% CI, 0.44 to 0.66; $P<0.01$) and a trend toward improved OS in patients who underwent consolidative ASCT (31). Certain subgroups of patients, such as those with high-risk MIPI scores, a blastoid or pleomorphic morphology or who were treated with CHOP-like induction *w/o* Ara-C, achieved the largest improvement in OS. Currently, the superior conditioning regimen remains unclear. The commonly used conditioning regimens included high-dose cyclophosphamide and total body irradiation (TBI) or high-dose carmustine, etoposide, cytarabine, and melphalan (BEAM). TBI only improved the PFS only in the group of patients in PR before ASCT, as shown by a retrospective comparison of the EMCL (with TBI) and the MCL Nordic group (no TBI) trials, which used similar induction with Ara-C (32). Because it

is becoming clear that most of the new induction regimens intend to reach CR, TBI is not currently being used and BEAM regimen is now the new standard in Europe (15). Because the status of MRD can predict the outcome, it could be postulated that patients with negative MRD after induction may not benefit as well as that after ASCT. Therefore, the role of ASCT is currently being investigated in patients with MRD-negative MCL in the first CR (ClinicalTrials.gov identifier: NCT03267433).

Maintenance therapy

The constant risk of MCL relapses led to propose a maintenance therapy in several trials. Responding patients included in the EMCL elderly trial underwent a second randomization to receive IFN or rituximab maintenance for two years. Compared to IFN, rituximab improved the duration of response (hazard ratio 0.55; 95% CI, 0.36 to 0.87), particularly in the subgroup of patients who received R-CHOP as induction (four-year OS of 87% in the maintenance group *vs.* 63%, $P=0.005$), a beneficial effect that has not been found with RFC (R-fludarabine and cyclophosphamide, $P=0.48$) (33). The phase III LyMA study confirmed the interest of rituximab maintenance compared to observation in younger MCL patients who received four courses of R-DHAP followed by ASCT as first line therapy. As a result, rituximab maintenance after ASCT is associated with higher rates of both 4-year PFS (82.2% *vs.* 64.6%, $P=0.0005$) and four-year OS (88.7% *vs.* 81.4%, $P=0.0413$) (26). In patients treated with the Nordic MCL2 protocol, rituximab maintenance was shown to significantly improve PFS, but not OS (34). However, in patients with previously untreated MCL, maintenance rituximab did not have benefits after 6 courses of rituximab and bendamustine (35). Therefore, rituximab maintenance may be a reasonable standard of care in responding younger and elderly MCL patients, at least after induction treatment including R-CHOP and/or R-DHAP. These differences among the studies are not clear but might have been due to the immunosuppression induced by purine analogs, which can reduce the antibody-dependent cellular cytotoxicity effect of rituximab. Moreover, MRD-based preemptive rituximab treatment had been shown to convert patients to MRD negativity and can probably postpone MCL relapses (36,37). Therefore, MRD monitoring may guide therapeutic interventions during the follow-up of MCL patients. These results led to a phase II trial (LyMA101) randomizing assignment for observation or MRD-based preemptive treatment after induction, ASCT and

obinutuzumab maintenance (ClinicalTrials.gov identifier: NCT02896582).

Allogeneic stem cell transplantation

Around 5% to 10% of MCL were primary refractory to chemotherapy with an extremely poor prognosis and there is no consensus about salvage therapy (38). Moreover, progression within two years of diagnosis had been shown to lead to poor outcomes, with median OS of 2–12 months (versus not reached), regardless of the prognostic information obtained upon diagnosis or the induction regimen administered (39). Allogeneic hematopoietic stem cell transplantation (alloSCT), which may benefit chemosensitive MCL patients, is a salvage option in some patients. In an Italian retrospective study, alloSCT had a favorable significant impact on survival in relapsed MCL patients (39). Moreover, frontline alloSCT appeared to be feasible, with a PFS at two years of 68%, although regimen-related mortality and morbidity remained significant (40). Because alloSCT can lead to high toxicity in the first two years after administration, it may only benefit high-risk fit patients (41). These very high-risk patients may be identified, based on the presence of blastoid variants, high Ki-67 expression, CDKN2A/TP53 deletions, TP53 mutations, KMT2D mutations (42) and suboptimal response after induction. However, the prognostic stratification of untreated MCL patients has to be adapted to guide an individualized targeted therapeutic strategy. Future studies should aim to develop early and risk-adapted strategies that may include frontline alloSCT, based on already identified and new biomarkers (43). However, the ability of alloSCT to overcome these putative poor prognostic parameters remains to be determined.

Unfit MCL patients

In patients ineligible for transplantation, the benefits of chemotherapy should be weighed against its potential toxicity. Treatment with R-CHOP, R-bendamustine or targeted therapy alone can be discussed. Purine analogs had been used for the treatment of elderly MCL patients. However, a large randomized trial on the older MCL patient population showed a better outcome with R-CHOP compared to R-FC, with a four-year OS of 62% for R-CHOP and 47% for R-FC ($P=0.005$) (33). A recent update confirmed the better OS in the R-CHOP arm (median, 6.4 *vs.* 3.9 years after RFC, $P=0.0054$) (44).

Several trials have assessed the efficacy and safety of R-bendamustine as first-line treatment. Compared with R-CHOP, R-bendamustine had a significant longer median PFS (22 *vs.* 35 months, $P=0.004$) and fewer toxic effects, in a phase 3 non-inferiority trial (45). The BRIGHT study showed that the CR rate for first-line R-bendamustine was statistically non-inferior to that for R-CHOP or R-CVP in MCL (46). The combination of R-bendamustine and lenalidomide, followed by lenalidomide maintenance, was shown to have a poor safety profile (47). The phase 3 MCL-R2 elderly trial is currently evaluating the role of cytarabine-containing induction using R-CHOP alone or alternating with the combination of rituximab, cytarabine, dexamethasone (R-HAD), followed by lenalidomide-containing maintenance in older patients (ClinicalTrials.gov identifier: NCT01865110). For frail patients who are not candidates for intensive chemotherapy, a combination of rituximab with targeted therapy should be considered. This point is discussed below in the targeted therapies section.

Targeted therapies

Some new therapeutic agents have recently emerged and are now incorporated in clinical trials. In the R-CHOP combination, vincristine has been replaced by bortezomib (i.e., VR-CAP), a regimen that significantly improved median OS in newly diagnosed MCL patients (91 versus 56 months, $P=0.001$) with a manageable safety profile (48). A phase II study combining lenalidomide and rituximab as first-line in unfit MCL patients was promising with a CR rate of 61% (49). The Triangle study (EMCL network) randomized the Bruton's Tyrosine Kinase (BTK) inhibitor ibrutinib with a combination of chemotherapy (R-CHOP alone or alternating with R-DHAP) as induction, and will discuss the role of ibrutinib maintenance for younger patients (ClinicalTrials.gov identifier: NCT02858258). The use of ibrutinib and venetoclax for dual targeting of BTK and BCL2 showed promising results in relapsing patients with poor risk markers, such as a high-risk MIPI score or TP53 aberrations (50). A chemotherapy-free treatment with rituximab and ibrutinib until best response, followed by a minimum of four intensive chemotherapy courses, is currently being tested, but the preliminary ORR after induction had been excellent (ClinicalTrials.gov identifier: NCT02427620) (51). The results of the industry-sponsored phase III Shine study comparing ibrutinib and placebo in combination with bendamustine and rituximab, in elderly untreated MCL patients, are still expected. Moreover, selective

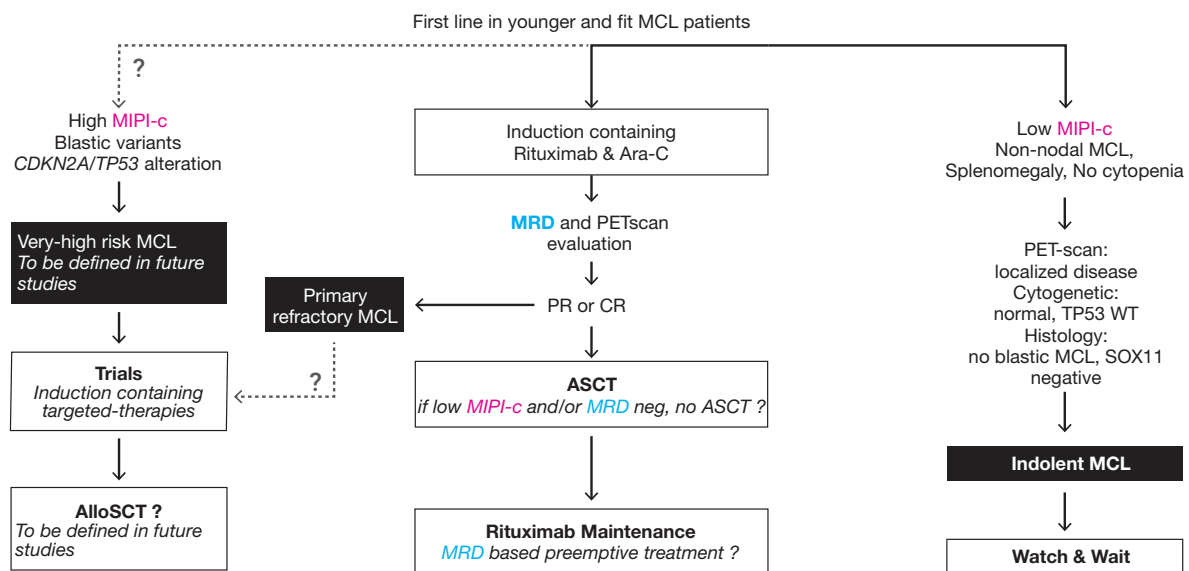


Figure 1 Algorithm for MCL management in younger and fit patients.

inhibitors of cyclin-dependent kinases 4/6 (CDK) may allow good responses in relapsed/refractory MCL, despite the relatively modest single-agent activity (52). Therefore, these compounds could be of interest as first-line therapy, alone or in combination (53-55). These new strategies may improve the outcomes in high-risk MCL or unfit/frail patients.

Conclusions

In younger MCL patients, the role of rituximab combined with Ara-C as induction, followed by ASCT has been demonstrated. In both young and elderly patients, the rituximab maintenance, at least after Ara-C containing induction, is also a promising approach. Future directions should integrate a risk-adapted therapeutic approach that includes new agents alone or in combination with chemotherapy, which could overcome resistance in high-risk MCL. Obtaining a negative MRD and/or negative PET scan at the end of induction is a major goal of the treatment (Figure 1). A better understanding of the lymphoma pathogenesis is necessary to identify biomarkers, which can be specifically targeted with less toxic agents. Finally, analysis of the benefits and risks, as well as the economic burden, of such strategies will be required before proposing new standard of care.

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Footnote

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