

Treatment of mantle cell lymphomas: recommendations of the Belgian Hematological Society

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Mantle cell lymphoma was recognised in the nineties and is characterised by the t(11;14)(q13;q32) translocation which results in overexpression of cyclin D1.¹ This disease represents approximately 6% of all non-Hodgkin's lymphomas. Mantle cell lymphoma generally affects patients over 60 years-old. Most patients have advanced disease (>70 % Ann Arbor stage IV). Several efforts have been made to predict outcome in mantle cell lymphoma. The cell-proliferation marker Ki-67, the Mantle Cell Lymphoma International Prognostic Index, fluorodeoxyglucose positron emission tomography and minimal residual disease are prognostic tools. For young patients, chemoimmunotherapy followed by high-dose chemotherapy plus stem cell transplantation is the treatment of choice. For the main group of older patients, chemo-immunotherapy followed by maintenance with rituximab is the gold standard. In relapses, temsirolimus is actually registered and new drugs, such as ibrutinib, are currently evaluated with promising preliminary results.²⁻⁵

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Epidemiology

In the United States, during the thirteen-year period between 1992 and 2004, the overall incidence of mantle cell lymphoma (MCL) (per 100,000) was 0.55, which increased with age: 0.07 in patients aged <50 years, 2.97 in patients aged 70-79 years, and 2.78 in those aged >80 years. The median age at diagnosis was 68 years. The incidence of MCL was higher in men (0.84 of 100,000) than in women (0.34 of 100,000) (P < .05). Late-stage (III-IV) MCL was diagnosed in

74.6% of patients.⁶ Incidence trends of mantle cell lymphoma in the United States between 1992 and 2004.

Prognostic factors

Histological characteristics are important, with a more aggressive clinical course for the blastoid and pleomorphic variants. The **cell-proliferation marker Ki-67** has high prognostic relevance: a high index of Ki-67 indicates an aggressive disease.^{7,8} Unfortunately,

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Table 1. MIPI score.

Risk	MIPI	% of patients	5-year OS
HR	≥6.2	21%	29%
IR	≥5.7 <6.2	35%	51%
LR	<5.7	44%	60%

MIPI score is calculated as $[0.03535 \times \text{age (years)}] + 0.6978$ (if ECOG > 1) + $[1.367 \times \log_{10}(\text{LDH/ULN})] + [0.9393 \times \log_{10}(\text{WBC count})]$.

Table 2. Guidelines of the BHS: treatment recommendation for mantle cell lymphoma in Belgium.

Overall recommendations	Category*
<ul style="list-style-type: none"> Inclusion in a clinical trial is advised given the disappointing results of standard management 	
First line	
<ul style="list-style-type: none"> Young patients : R-chemotherapy with high dose cytarabine followed by high dose chemotherapy and ASCT 	
<ul style="list-style-type: none"> Old patients: R-CHOP21 X 8 followed by Rituximab maintenance 	
Salvage	
<ul style="list-style-type: none"> R-chemo (R-Benda, R-DHAP, R-ICE) in second line 	
<ul style="list-style-type: none"> Bortezomib 	
<ul style="list-style-type: none"> Temsirolimus in third line 	
*cfr Table 3	

this tool is not available in daily clinical practice and lacks reproducibility.

The **Mantle Cell Lymphoma International Prognostic Index (MIPI)** is a recently established clinical and biological score for pre-treatment risk assessment in patients with advanced-stage MCL. MIPI is based on four independent prognostic factors: age, performance status, lactate dehydrogenase and leukocyte count. This score, based on data of 455 advanced stage MCL patients, defines three groups of patients with different prognoses: high risk (HR) (MIPI $\geq 6,2$; 21% of patients, 5-year OS 29%), intermediate risk (IR) (MIPI between 5,7 and 6,2; 35% of patients; 5-year OS 51%) and low risk (LR)

(MIPI $<5,7$; 44% patients, 5-year OS 60%) (Table 1). The simplified MIPI (MIPIs) (each variable gives 0 to 3 points, LR if 3 points, IR if 4 or 5 points and HR if more than 5 points) has high concordance with MIPI.⁹

Minimal residual disease (MRD) is probably the most important prognostic factor. The targets for molecular monitoring of MRD by real time quantitative polymerase chain reaction (RQ-PCR) are clonal IGH VH-JH and t(11;14) translocation. Retrospective data showed that quantitative measurement of MRD during and after treatment is an early and strong predictor of clinical outcome and can define subgroups with a significantly different prognosis.¹⁰

A molecular remission is defined by a MRD negativity of at least 10^{-4} . Pott et al reviewed 259 cases of MCL patients treated in two prospective MCL network trials and concluded that achieving a molecular response after induction independently improves remission duration in comparison with patients with residual disease.¹¹ Similar results have been shown in the CAL-BG 559909 study.¹² MRD is also an excellent tool to quantitatively determine the impact of different treatments on tumour clearance, probably better than clinical and morphological complete response.¹¹ However, this interesting tool is not yet routinely available.

Initial work-up

The initial evaluation should include a clinical examination, laboratory tests (LDH, circulating tumour cells, hepatitis and HIV serologies), contrast-enhanced chest/abdominal/pelvic CT scan and a bone marrow biopsy with cytogenetics. A lymph node biopsy with cyclin D1 evaluation is also warranted. As digestive localisations are frequent, an endoscopic evaluation is recommended in case of symptoms.

Only few small retrospective studies are available about fluorodeoxyglucose positron emission tomography (FDG-PET) in MCL. At initial staging, compared to conventional imaging, FDG-PET allows detection of additional nodal and extranodal sites but is not more sensitive for bone marrow and gastrointestinal tract involvement detection. Usually, it does not upgrade the Ann Arbor staging.^{13,14} The SUV max value at the time of diagnosis seems to be relevant: there is a trend for better outcome in terms of EFS and OS for patients with initial SUV max <5 or 6, depending on studies.^{14,15}

First-line therapy

Localised disease

For the small proportion of patients with limited-stage disease (10% MCL), radiotherapy (RT) is the preferred treatment. A small retrospective study showed an improved progression free survival (PFS) (5 years-PFS 68% versus 11%) and a trend towards improved OS for patients treated with regimens including RT.¹⁶

Advanced disease

Transplant-eligible patients

Conventional R-CHOP-based therapy usually achieves high response rates but with short remission durations. Most patients finally relapse. A different induction chemotherapy and consolidation are thus necessary to improve clinical outcome.

Myeloablative consolidation with autologous stem cell transplantation

In 2005, Dreyling et al demonstrated in a randomised trial that early consolidation by myeloablative radiochemotherapy followed by autologous stem cell transplantation (ASCT) in first remission after an initial CHOP induction significantly prolongs PFS of young and fit patients with advanced stage of MCL (median of 39 months in the ASCT arm versus 17 months in the conventional (IFN alpha maintenance) arm ($p = 0.0108$)).¹⁷

High dose cytarabine (HARA-C)

Growing evidence suggests that HARA-C is probably an important drug in the treatment of MCL. Regimens with HARA-C were recently used with success in young patients: they improved the rate, the quality and the duration of response but at the expense of higher toxicity. In a phase II study with R-HyperCVAD alternated with high dose of methotrexate and cytarabine in first line treatment of 97 patients, the MD Anderson group showed 97% of response with 87% of complete response (CR) or unconfirmed CR (CRu). With a median follow-up time of 40 months, the 3-year event-free survival (EFS) and OS rates were 64% and 82%, respectively.¹⁸

Based on the superiority of ASCT after conventional chemotherapy induction and the efficacy of HARA-C regimens, the GELA trial assessed the potential benefit of the combination of HARA-C containing chemoimmunotherapy followed by ASCT with very good results.¹⁹ In another Nordic trial, 160 untreated young patients were included in a phase II protocol with dose-intensified induction chemoimmunotherapy with R-maxi-CHOP, alternating with R + HARA-C followed by high dose chemotherapy + ASCT. OR and CR was achieved in 96% and 54%, respectively.²⁰ A large prospective, multicentre, randomised phase III study of the European MCL network with 500 young patients (median age 55 years) showed that in comparison with R-CHOP + ASCT, a regimen containing HARA-C alternating with R-CHOP + ASCT increases significantly CR/CRu rates (40 versus 54 %, $p = 0,003$) and TTF (46 versus 88 months, $p = 0.038$) without clinically relevant increase in toxicity.²¹ An induction treatment with four cycles of R-DHAP (dexamethasone, cytarabine and cisplatin) was evaluated in the LyMa trial. Based on preliminary results, induction with R-DHAP is probably better than alternating R-CHOP with R-DHAP (76,3% CR/CRu after four cycles R-DHAP).²²

Table 3. Categories of evidence level.

• Level I: Evidence obtained from at least one properly designed randomised controlled trial.
• Level II-1: Evidence obtained from well-designed controlled trials without randomisation.
• Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.
• Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
• Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

In case of renal impairment, oxaliplatin can be used instead of cisplatin.

Maintenance

The interest of R maintenance after immunochemotherapy (4x R-DHAP) followed by ASCT for young patients is currently under investigation in the randomised phase III LyMa trial.²²

Lenalidomide in maintenance therapy is also being studied in an ongoing Italian randomised phase III study (MCL 0208).²³

Non transplant-eligible patients

MCL typically affects patients over 60 years of age and more than half of them are elderly. The prognosis of elderly patients with MCL is very poor with low rates of CR and high rates of rapid recurrences. Clinical trials attempt to establish more effective induction therapy to improve CR rates, and better post-induction strategies to prolong duration of remission.

Fit

Chemo-immunotherapy

Results of a first large randomised study in elderly MCL patients (560 patients) were recently presented by the European MCL network. In comparison with R-FC (six cycles, R-FC/28 days), induction therapy R-CHOP (eight cycles R-CHOP/21days) is superior in terms of ORR (86% versus 78% $p=0.059$) and OS (4-years OS 62% versus 47%, $p=0.005$). Furthermore, additional toxicities and lower compliance were more frequently observed in the R-FC arm.²⁴

Maintenance

Historically, maintenance consisted of interferon alpha treatment (improvement of PFS and OS).²⁵ The recent

study of the European MCL network demonstrated the superiority of R (one dose every two months until progression) compared to IFN alpha in maintenance, not only in terms of PFS benefit (doubling of duration remission for patients who had responded upon induction therapy), but also in terms of survival for patients pre-treated with R-CHOP.²⁴ For elderly untreated patients, a modified fractioned hyper-CVAD regimen followed by R maintenance improves PFS and OS: the proportion of patients surviving at five years is 62%, comparable to trials using intensive strategies in similar patient populations.²⁶

The efficacy of R maintenance depends nevertheless on the type of induction regimen. After single agent monoclonal antibody therapy, R maintenance does not demonstrate a significant benefit in comparison with the observational arm.²⁷

Unfit

A palliative or reduced-intensity chemotherapy +/-R is indicated if the patient is unable to tolerate aggressive treatment. In this setting, chlorambucil could be a valuable option with few side effects.²⁸

Salvage therapy

Despite the advances in front-line regimen (both for induction and consolidation/ maintenance), relapses still occur. Treatment of relapsed/refractory MCL is currently not standardised and a wide variety of salvage strategies are available. Chemotherapies are often used in combination with immunotherapy and eventually followed by R maintenance or consolidation by allogeneic stem cell transplantation in highly selected cases. We discuss here the use of fludarabine and bendamustine because these drugs are predominantly

used in relapses. Neither are licensed nor reimbursed in Belgium for this indication.

Fludarabine

Fludarabine plus rituximab (F-R) is an established treatment option in relapsed/refractory MCL. As reported above, the GLSG explored the combined use of R and F-containing regimen in the treatment of recurrent and refractory MCL and found that the combination of R-FCM (compared with chemotherapy alone) significantly improved ORR (58% versus 46%), CR rates (29% versus 0.0%) and also OS.²⁹

However, in the setting of relapsed disease, recently published results showed that the combination bendamustine-rituximab (B-R) is superior to F-R in terms of PFS.³⁰

As for the other molecules, the future for fludarabine could be in combination with new drugs. In a small phase I study, a response was achieved in 8 of 10 MCL patients with R-F-Flavopiridol (CDK inhibitor leading to downregulation of cyclin D1).³¹

Bendamustine

Based on results of two small phase-II studies, B-R is potentially a good option for patients with relapsed/refractory indolent or mantle cell lymphoma.^{32,33}

A recent large multicentre randomised phase III study (StiL) compared the efficacy and safety of B-R versus F-R for relapsed follicular, indolent and mantle cell lymphomas. Results confirmed the superiority of B-R in terms of PFS (30 versus 11 months; $p < 0.0001$), OR (83.5% versus 52.5%, $p < 0.0001$) and CR (38.5% versus 16.2%; $p = 0.0004$) but not in terms of OS.³⁰

Targeted approaches

R-chemotherapy is not very satisfactory after relapse. This emphasises the need for novel therapies. Based on a better knowledge of the MCL pathogenesis, new targeted approaches are being developed.

Ibrutinib

Of particular interest in this situation, the Burton's Tyrosine Kinase-inhibitor (PCI32765-ibrutinib) is actually extensively evaluated.³⁴ Good results were recently published in a phase II study on 115 relapsed MCL patients. The overall response rate was 68% with 21% of CR and the median duration of response was 17.5 months.³⁵ This molecule has recently been approved by the Food and Drug Administration (FDA) for relapsing mantle cell lymphoma. However, not all targeted drugs

are currently licensed nor reimbursed in Belgium, except temsirolimus for second relapse.

Temsirolimus

MCL is characterised by a t(11;14) resulting in overexpression of cyclin D1 messenger RNA. Temsirolimus (Tem) selectively inhibits the mammalian target of rapamycin (mTOR) kinase that regulates cyclin D1 translation. With this molecule as a single agent therapy (250mg IV every week) for relapsed MCL, RR was 38 %, median time-to-progression 6.5 months and the duration of response 6.9 months.³⁶ A randomised phase III study confirms the superiority in terms of PFS of Tem (dose 175 mg once weekly for three weeks followed by 75 mg once weekly) to standard options (investigator's choice) in relapsed/refractory MCL.³⁷

RAD 001 (everolimus), another mTOR antagonist, seems to have a better effect in vitro. Its clinical efficacy in relapsed MCL is now evaluated (ORR was 20% in a multicentre phase II trial with over 35 patients with a maximum of three prior lines of chemotherapy).³⁸ Results are promising for Tem in combination with immunotherapy or immunochemotherapy. In a phase II study of 71 patients, Tem with R allows 59% ORR, with interestingly good results for prior R-refractory patients (52% ORR).³⁹ The Tem-B-R association is currently being studied.^{23,40}

Bortezomib

According to the Pinnacle study, bortezomib represents a valuable treatment option for patients with relapsed/refractory MCL (32% RR), including those who have relapsed following high-intensity therapy. Moreover, toxicity profile is manageable.⁴¹ This drug is approved for MCL treatment in the US but not in Europe.

Some recent data from a small German multicentre observational study suggest synergistic efficacy of bortezomib in combination with cytarabine: responses were observed in four patients (two CR) of eight heavily pre-treated patients who received bortezomib, dexamethasone, and HAra-C + R if they were not refractory to prior R-containing regimens. Median PFS and OS were five and 15.5 months, respectively.⁴² To confirm these preliminary results, a randomised, multicentre phase III study of the European MCL network was launched to compare efficacy and safety of R, HAra-C and dexamethasone alone or in combination with bortezomib in patients with relapsed or refractory mantle cell lymphoma (MCL 2005-01). Synergistic effect is also described between proteasome and

Key messages for clinical practice

1. In young patients: R-chemotherapy including high dose cytarabine followed by high dose chemotherapy with autologous stem cell transplantation is standard of care.
2. In old patients: R-chemotherapy with R maintenance is standard of care.
3. New targeted therapies, such as ibrutinib, are promising in relapse.

histone deacetylase (HDAC) inhibitors. Results of a small phase II trial presented at the 2011 ASH meeting suggest the activity of bortezomib in association with the HDAC inhibitor vorinostat in MCL (RR 47 %).⁴³

Lenalidomide

Single-agent

Some phase II trials investigated the efficacy and safety of single-agent Lenalidomide (Len) (25 mg once a day d1-d21 of a 28 days cycle) in patients with relapsed or refractory MCL: it was well tolerated and active (ORR: 28-53%).⁴⁴⁻⁴⁷

Based on synergistic effects of in vitro observation and positive results in myeloma, the combination Len + dexamethasone were studied. Results were comparable to Len alone but with a possible detrimental effect of dexamethasone on the immune activation generated by Len.⁴⁸

In combination

R directly targets CD20 positive lymphoma cells while Len targets the microenvironment. Both have single-agent activity in MCL. This combination is active with an ORR of 57 % and a median duration of response of 18,9 months in the study of Wang.⁴⁹ The interest of treatment with R-Len and bendamustine for refractory/relapsed MCL is being studied in an ongoing prospective phase II.²³

Allogeneic stem cell transplantation

In second-line consolidation, alloSCT is an option in selected patients with MCL. There are few data about the role of alloSCT but good results are obtained for relapsed MCL in small studies.^{50,51} In fact, this approach is currently the only potentially curative treatment, based on graft versus host disease effect. Its application is limited by the important age-dependent mortality and co-morbidities. A full-intensity conditioning regimen appears too toxic and dose-reduced intensity conditioning (RIC-allo) is probably the best option.^{52,53}

Conclusion

Despite recent advances, MCL remains a challenging disease. More effective and new management strategies are currently being studied in order to optimise treatment and improve clinical outcome. In this setting, precisely defined subgroups of MCL with reliable prognostic tools will be necessary to predict the individual course of the disease and to propose the most appropriate therapeutic approach.

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