# Current treatment standards and emerging strategies in mantle cell lymphoma

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**Mantle cell lymphoma (MCL) is a unique subtype of B-cell non-Hodgkin lymphomas characterized by the chromosomal translocation t(11;14)(q13;q32) and nuclear cyclin D1 overexpression in the vast majority of cases. Most patients present with advanced stage disease, often with extranodal dissemination, and pursue an aggressive clinical course in the majority of cases. Recent improvement has been achieved by the successful introduction of monoclonal antibodies and dose-intensified approaches including autologous stem cell transplantation (ASCT) strategies. With the exception of allogeneic hematopoietic stem cell transplantation, current treatment approaches are non-curative and the corresponding survival curves are characterized by a delayed, but continuous decline and a median survival of 4 to 6 years. However, recently a subset (15%) of long-term survivors have been identified with a rather indolent clinical course even after conventional treatment strategies only. Emerging strategies such as proteasome inhibitors, IMIDs, mTOR inhibitors and others are based on the dysregulated control of cell cycle machinery and impaired apoptotic pathways. Monotherapy of these compounds achieves efficacy comparable to conventional chemotherapy in relapsed MCL, and combination strategies are currently being investigated in numerous trials; however, their introduction into clinical practice and current treatment algorithms remains a challenge.**

## Histomorphology

Mantle cell lymphoma (MCL) displays a wide variation of histomorphological appearance including the classical type with typical irregular, cleaved nuclei and diffuse, nodular, or mantle zone growth pattern as well as the chronic lymphocytic leukemia (CLL)-like round cell variant and the blastoid variant with a usually higher cell proliferation.[1,2] The immunophenotype of MCL resembles that of a mature B-lymphocyte ($CD10^-$, $CD19^+$, $CD20^+$, $CD22^+$, $CD43^+$, $CD79a^+$) with coexpression of the T-cell antigen CD5; in contrast to CLL, cells are usually CD23 and CD200 negative. Because of the broad cytological and histological spectrum, detection of the characteristic cyclin D1 overexpression either by immuno-histochemistry or detection of the translocation t(11;14)(q13;q32) by fluorescence in situ hybridization in leukemic cases is essential to confirm the diagnosis.

## Molecular Pathogenesis

In the large majority of cases the genetic hallmark of MCL, the chromosomal translocation t(11;14)(q13;q32), is detectable, resulting in a constitutive overexpression of the cell cycle regulator protein cyclin D1. Rare t(11;14) negative MCL cases have been reported recently that display a similar clinical course.

MCL represents a paradigm of a neoplasm with dysregulated control of cell cycle machinery and impaired apoptotic pathways.[3] Accordingly, in a substantial proportion of MCL cases, inactivation of inhibitors of cyclin-dependent kinases, such as $p16^{INK4a}$, can be detected. Typically those cases are characterized by blastoid morphology and an even more aggressive clinical behavior. Interestingly, the gene locus on 9p21 not only encodes for p16 but also harbors an alternating reading frame ($p16^{ARF}$); its inactivation results in increased MDM2 (mouse double minute 2 homologue)-mediated p53 degradation. Furthermore, the *ATM* (ataxia teleangiectasia mutated) gene on chromosome 11q22-23 is mutated in up to 75% of cases, also resulting in impaired p53-mediated cell cycle arrest, DNA repair and apoptosis. Taken together the pathogenesis of MCL is characterized by simultaneous disruption of cell cycle regulation and DNA damage response. Accordingly, gene expression analysis identified a proliferation signature of genes that identified patient subsets of indolent disease with more than 5 years overall survival.[4]

## Clinical Presentation and Prognostic Factors

The majority of patients present with advanced stage disease (Ann Arbor III/IV) at initial diagnosis. More than 90% of patients display extranodal manifestations, with up to 80% of patients with circulating MCL cells in the peripheral blood smear or even more frequently detected by flow cytometry. GI involvement is frequent, but in advanced stage disease endoscopy is only recommended in symptomatic cases. Central nervous system involvement has been described, especially in relapsed disease, and is usually associated with neurologic symptoms.

The clinical course of MCL is characterized by a continuously declining survival curve, but recent reports have observed an improved overall survival of 5 to 6 years and a subset (15%) of long-term survivors with a rather indolent clinical course even after conventional treatment strategies only.[5-7] Clinical features associated with adverse prognosis are advanced stage disease and high tumor burden, occurrence of B symptoms and poor performance status. In contrast, younger age (< 65 years), normal LDH serum levels as well as normal β2-microglobulin seem to be associated with a better outcome. Based on more than 450 patients uniformly treated in prospective trials, a combined clinical and biological score (MIPI) has been recently established and confirmed in numerous studies that implements performance status, age, LDH, and leucocyte counts and allows a more reliable estimation of the individual clinical course.[8] The previously described prognostic role of cell proliferation as determined by Ki67 immunohistochemistry was verified in a large European clinicopathological study.[1] Multivariate analysis confirmed the central prognostic role of cell proliferation and its superiority to other histomorphological criteria and was also confirmed for rituximab-containing regimens.[9]

Although initial data after combined immunochemotherapy were contradictory,[10] recent quantitative analyses confirmed the strong prognostic role of minimal residual disease (MRD).[11] In two prospective studies with 182 evaluable patients, MRD detection was the strongest predictor of clinical outcome superior to remission quality (CR vs PR), with all patients with negative bone marrow after induction still in ongoing remission after 2 years.[11]

## Treatment

Considering the aggressive clinical course in the majority of patients and the limited overall survival prognosis, a watch-and-wait strategy is not generally recommended. However, a small fraction of patients experience a relatively indolent clinical course.[6] To spare those patients highly aggressive treatment strategies, it has been recommended to monitor asymptomatic patients with a low tumor burden very closely and initiate treatment in case of rapid progression or occurrence of disease-related symptoms.[7]

### *Conventional-dose Chemotherapy*

Conventional mono- or polychemotherapy does not provide long-term control of the disease. In two randomized trials, the anthracycline-containing CHOP regimen (cyclophosphamide, vincristine, doxorubicin, and prednisone) showed only a minor advantage over a non-anthracycline combination (COP or MCP).[12,13] In contrast, a retrospective study suggested that anthracycline-containing regimens were superior in patients with low and low-intermediate risk profile according to the IPI.[14] However, because of the aggressive clinical course of MCL many clinicians favor CHOP-like or even more intensive regimens.

While fludarabine monotherapy demonstrated only moderate efficacy in MCL, fludarabine-containing regimens with either alkylating agents or anthracyclines have been successfully applied in first-line or relapsed disease.[15-17] However, hematologic toxicity and even stem cell toxicity have to be considered, especially in patients who are potential candidates for autologous stem cell harvest.

Another highly interesting agent is the nitrogen mustard compound bendamustine, which is chemically related to the alkylating agents chlorambucil and cyclophosphamide.[18] Based on its molecular structure, it has been suggested that bendamustine may also act as a purine analog.

### *Dose-intensified Regimens*

Various study groups reported promising results for high-dose cytarabine (Ara-C)-containing regimens. In a French trial, the DHAP regimen (dexamethasone, high-dose Ara-C, and cisplatin) was given as salvage therapy for patients who failed to achieve a CR after 4 cycles of CHOP. Of 25 patients all but 2 responded, with a CR rate of 84%.[19] Another even more dose-intensified regimen HyperCVAD/MA (fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone; alternated with high-dose methotrexate and cytarabine) was introduced by the M.D. Anderson group and demonstrated a CR rate of 38% and a PR rate of 55.5% after 4 cycles in 45 previously untreated as well as relapsed or refractory MCL patients.

Alternatively to this upfront dose escalation, myeloablative consolidation with autologous stem cells may be added after conventional chemotherapy. Various phase II trials suggested that patient in first remission gained most profit from this approach (**Table 1**). The European MCL Network confirmed the superiority of consolidating myeloablative radiochemotherapy after an initial CHOP-like induction therapy. Patients in the ASCT arm experienced a signifi-

**Table 1. Conventional or dose-intensified induction/consolidation ± rituximab in newly diagnosed mantle cell lymphoma.**

| Author | study | n | Induction | consolidation | Response rate OR (CR) | Median PFS/EFS | Median OS |
|---|---|---|---|---|---|---|---|
| Herold 2008[20] | Phase III | 90 | Conventional (MCP) | IFN | 63% (15%) | 18 mo | 56 mo |
| | | | Conventional (R-MCP) | IFN | 71% (32%) | 20 mo | 50 mo |
| Howard 2002[10] | Phase II | 40 | Conventional (R-CHOP) | — | 96% (CR/Cru: 48 %) | 16.6 mo | n.a. |
| Lenz 2005,[21] Hoster 2008[57] | Phase III | 123 | Conventional (R-CHOP) | IFN maintenance | 94% (34%) | 28 mo (TTF) | 59% (5 y) |
| | | | Conventional (CHOP) | vs ASCT | 75% (7%) | 14 months (TTF) | 46% (5 y) |
| Rummel 2008[23] | Phase III | 88 | Conventional (R-CHOP) | — | 95% (35%) | n.a. | n.a. |
| | | | Conventional (R-bendamustine) | — | 89% (32%) | n.a. | n.a. |
| Dreyling 2008[24] | Phase III | 75 | Conventional (CHOP/MCP) | Intensive (ASCT) | 78% (42%) | 43 months | 90 months |
| Dreger 2007[25] | Phase II | 34 | Conventional (CHOP/ ->R) | Intensive (ASCT) | 88% (24%) | 83% (4 y) | 87% (4 y) |
| LeFrere 2004[19] | Phase II | 28 | Conventional (CHOP/ DHAP) | Intensive (ASCT) | 89% (82%) | 51 months | 81 months |
| de Guibert 2006[26] | Phase II | 24 | Conventional (R-DHAP) | Intensive (ASCT) | 96% (92%) | 65% (3 y) | 69% (3 y) |
| Delarue 2009[27] | Phase II | 60 | Conventional (R-CHOP/R-DHAP) | Intensive (ASCT) | 95% (96%) | 83 mo | 75% (5 y) |
| Dreyling 2008[28] | Phase III | 390 | Conventional (R-CHOP) | Intensive (ASCT) | 91% (51%) | 84% (2 y) | 77% (2 y) |
| | | | Conventional (R-CHOP/R-DHAP) | Intensive (ASCT) | | | |
| Romaguera 2005[29] | Phase II | 97 | Intensive (R-Hyper-CVAD/MA) | — | 97% (CR/CRu: 87%) | 54 mo | 82 % (3 y) |
| Epner 2007[30] | Phase II | 97 | Intensive (R-Hyper-CVAD/MA) | — | 88% (CR/CRu: 58%) | 64% (2 y) | 74% (3 y) |
| Magni 2009[31] | Phase II | 28 | R-High dose Cyclo, Ara-C, Melphalan, Mitoxantrone | Intensive (ASCT) | 96% (96%) | 48% in low risk; 34% in high risk | 76% in low risk; 68% in high risk |
| Tam 2009*[32] | Phase II | 42 7 | Intensive (R-Hyper-CVAD/MA) Conventional (R-CHOP) | Intensive (ASCT) | 96% (CR/Cru: 96%) | 42 mo | 93 mo |
| Ritchie 2007[33] | Phase II | 13 | Intensive (R-Hyper-CVAD/MA) | Intensive (ASCT) | 100% (92%) | 92% (3 y) | 92% (3 y) |
| Till 2008[34] | Phase II | 21 | Intensive (R-Hyper-CVAD/MA) | Intensive (ASCT) | 100% (CR/CRu: 81%) | 81% (3 y) | 94% (3 y) |
| Vose 2006[35] | Phase II | 32 | Intensive (R-Hyper-CVAD/MA) | Intensive (ASCT) | 100% (CR/CRu: 81%) | 78% (3 y) | 97% (3 y) |
| Geissler 2008 [36] | Phase II | 159 | Intensive (R-CHOP-HA) | Intensive (ASCT) | 96% (55%) | 63% (4 y) | 81% (4 y) |

*Only relapsed disease.
CHOP indicates cyclophosphamide, doxorubicin, vincristine, and prednisone; FCM, fladarabine, cyclophosphamide, mitoxantrone; HyperCVAD/MA, fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone; alternated with high-dose methotrexate and cytarabine; PR, partial response rate; CR, complete response rate; PFS, progression-free survival; TTF, time to treatment failure; FFS, failure free survival; EFS, event-free survival; OS, overall survival; ASCT, autologous stem cell transplantation.

cantly longer duration of remission with a median of 3.7 years compared with 1.6 years ($P = .0108$) (**Figure 1**). These differences were even more pronounced in the patients who achieved CR (4.5 vs 1.6 years). However, a longer follow-up is needed to exactly determine the effect on OS (median 7.5 vs 5.4 years, $P = .075$).[28] Thus, myeloablative radiochemotherapy followed by ASCT represents one of the standard therapeutic options in the first line treatment of younger patients without significant comorbidity.

### *Monoclonal Antibodies*

Several trials confirmed that single-agent rituximab has only moderate activity in MCL. In the largest trial, overall response rate was only 27%.[37] Other monoclonal antibodies, either chimeric or even fully humanized, targeting a variety of epitopes in addition to CD20, such as CD22, CD74, CD 80, HLA-DR and others, are currently being investigated in preclinical and clinical trials, but data on MCL are still scarce.

Enhanced antibodies either by linkage to radioactive compounds or chemotoxins have shown some higher efficacy in MCL. An interesting approach is the application of a by-specific anti-CD19/anti-CD3 antibody that has shown a high efficacy in an initial phase I/II trial.[38] At doses of 0.015 to 0.030 mg/m$^2$ per day, 4 of 19 heavily pretreated patients with lymphoma, including MCL, responded and all 7 patients at dose 0.06 mg/m$^2$ day.

## *Immunochemotherapy*

*Conventional-dose Regimens and Rituximab*

Based on its favorable toxicity profile, rituximab remains a valuable therapeutic option in combination with chemotherapy and has been investigated in several phase II/III trials (**Table 1**). In a randomized trial the combination of CHOP and rituximab (R-CHOP) was significantly superior to CHOP in terms of OR rate (94% vs 75%; $P = .0054$) and CR rate (34% vs 7%; $P = .0002$), and resulted in an improved progression-free survival (PFS; median, 28 vs 14 months; $P = .0003$ **Figure 2**).[21,57] In another smaller trial (MCP +/- rituximab) initial response rates increased (OR: 71% vs 63%, CR: 32% vs 15%; n.s.), but no significant increment of progression-free survival was observed.[20] In contrast, in relapsed disease a fludarabine-containing regimen FCM (fludarabine, cyclophosphamide, and mitoxantrone) in combination with rituximab (R-FCM) not only improved the OR rate (58% vs 46%) and CR rate (29% vs 0%), but also significantly prolonged overall survival ($P = .0042$).[39] This improvement of overall survival was also suggested by a recent meta-analysis.[40] This analysis was, however, based only on the studies discussed above and detected considerable heterogeneity. Interestingly, in various phase II trials bendamustine in combination with rituximab showed also high response rates in relapsed MCL and first line therapy.[23,41] A preliminary analysis of an ongoing study revealed only slightly lower response rates (OR: 89% vs 95%), but especially better tolerability (grade 3/4 leukocytopenia: 14% vs 38%, infectious complications: 31% vs 41%) in comparison to the standard R-CHOP regimen.[23] These data make this approach especially appealing in elderly patients with potential age-related comorbidities.

*Dose-intensified Regimens and Rituximab*

In younger patients, dose-intensified schemes in combination with rituximab represent the current standard of care. Hyper CVAD/MA with rituximab was investigated in a large, monocenter trial in patients with previously untreated MCL. Of 97 assessable patients, 97% responded, and 87% achieved a CR or unconfirmed CR. With a median follow-up time of 40 months, the 3-year FFS and overall survival rates were 64% and 82%, respectively.[29] These results are comparable to an ASCT approach, considering efficacy but also toxicity (8% treatment-related deaths). However, these excellent results could not be replicated in a recently published multicenter trial. Overall response rate was 88%, resulting in a progression-free survival of 60% at 2 years[30] (**Table 1**).

Based on the promising results of regimens containing Ara-C and the superior outcome after autologous transplantation, recent trials have investigated the combination of all of these promising approaches in combination, namely high-dose Ara-containing immunochemotherapy followed by ASCT (**Table 1**). The Nordic group investigated an induction containing high-dose Ara-C followed by autolo-

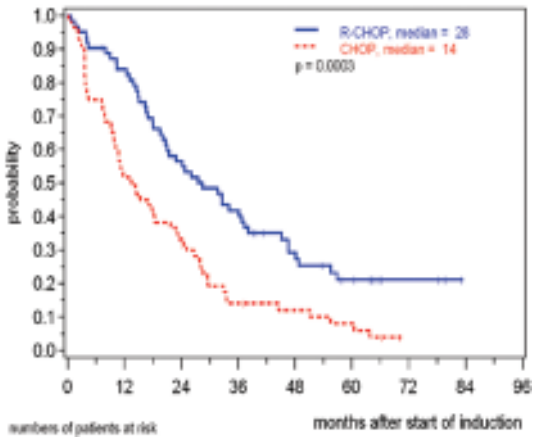


**Figure 1. Progression-free survival after a CHOP-like induction followed either by autologous stem cell transplantation (ASCT) or interferon (IFNα) maintenance.[24]**

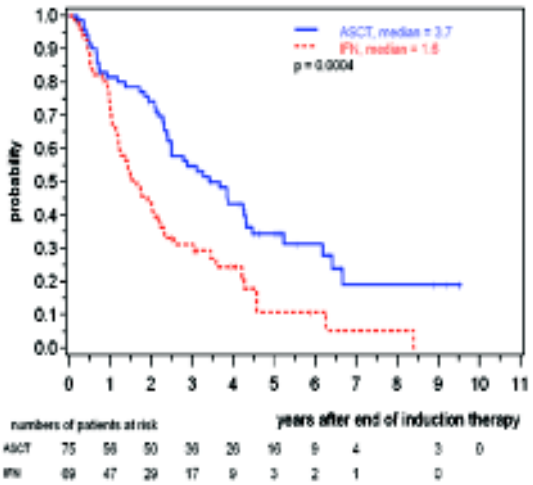


**Figure 2. Progression-free survival after CHOP induction ± rituximab (with optional consolidation).[57]**

gous transplantation with excellent results so far.[36] Event-free and overall survival were 63% and 81%, respectively, at 4 years, with a suggested long-term survival plateau. Similar results were recently reported for a French phase II trial with a median event-free survival of 83 months and an overall survival rate of 75% at 5 years.[27] The European MCL Network investigates the impact of high-dose Ara-C in addition to an R-CHOP induction followed by ASCT in an international phase III trial. After inclusion of almost 400 patients, no significant differences were observed so far with a progression-free and overall survival of 84% and 77% after 2 years, respectively.[24] However, the benefit of this strategy remains reserved for younger patients without significant comorbidity.

### *Consolidation Strategies*

As conventional-dose immunochemotherapy achieves rather high response rates but only moderate remission durations, various concepts investigate different consolidation strategies to further improve the clinical outcome of MCL.

## Maintenance Therapy

While rituximab maintenance failed to demonstrate a significant benefit compared to observation only after antibody monotherapy,[37] an improved 3-year progression-free survival (45% vs 9%) was detected after a more effective induction regimen (FCM +/- R) in another randomized trial.[39] However, these data are based on a limited number of patients only (n = 50). A recent phase II trial trial also reported a remarkable progression-free survival of 37 months after a modified hyper-fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone regimen followed by a similar rituximab maintenance therapy.[42]

## Radioimmunotherapy

Radioimmunotherapy (RIT) represents a novel therapeutic approach that combines the tumor-targeting attributes of lymphocyte-specific monoclonal antibodies with therapeutic radioisotopes. The most extensively studied, Yttrium-90 ($^{90}$Y)-ibritumomab tiuxetan (Zevalin®) and Iodine-131 ($^{131}$I)-tositumomab (Bexxar®) are both directed against CD20. Although no comparative clinical trial has been performed between $^{90}$Y-ibritumomab tiuxetan and $^{131}$I-tositumomab, published results suggest that the two compounds achieve similar response rates and response durations.

Single-agent RIT with $^{90}$Y-ibritumomab tiuxetan has been investigated in phase II trials in relapsed and refractory MCL. Overall response rates were about 30%, but with only moderate event-free survival of 6 months (median) in relapsed MCL.[43] However, RIT might be more efficient as part of multimodal strategies. RIT may be applied as part of the induction therapy, consolidation therapy or part of high-dose regimen followed by autologous transplantation.[44] Accordingly, preliminary data of a phase II study suggest that consolidating radioimmunotherapy results in impressively improved CR rates (from 13% to 55%) and a prolonged progression-free survival of 31 months in first line therapy.[45]

## Molecular Targeted Approaches

The growing insights into the underlying biology and pathogenesis of MCL form the basis for the introduction of molecularly targeted therapeutic approaches. Gene-profiling studies demonstrated a constitutive activation of the NFκB-signalling pathway. NFκB has been implicated in blocking apoptosis, promoting cell proliferation and mediating resistance to treatment. Activation of NFκB requires phosphorylation of its inhibitor IκB leading to poly-ubiquitinylation and degradation by the proteasome. Thus, the ubiquitin-proteasome pathway is essential for maintaining intracellular protein homeostasis and represents a valid target for the treatment of malignant disease. Apart from IκB various other regulatory proteins for cell cycle progression and apoptosis as well as oncogenes are processed by this pathway, which are of particular importance in MCL, including p53, p27, p21, CDKs and cyclins, members of the Bcl-2 family, Mcl-1, BH3 only protein Noxa, and ROS.

### *Bortezomib*

Bortezomib is a potent, selective and reversible inhibitor of the 26S proteasome with especially encouraging results in relapsed or refractory MCL. Objective response is achieved in up to 45% of MCL patients; however, CR rates are low and median response durations are relatively short; in the largest two trials enrolling 141 and 40 relapsed or refractory MCL patients a median progression-free survival of 5.3 and 6.7 months, respectively, was observed.[46,47] Considering the abundant presence and requirement of proteasome activity in eukaryotic cells, bortezomib displays surprisingly little toxicity in clinical practice with mild thrombocytopenia, neuropathy and diarrhea being most common. Thus combination therapy of bortezomib with conventional chemotherapy is a highly attractive option. Preliminary preclinical and clinical data suggest synergistic efficacy of a combination with cytarabine representing the rationale of currently ongoing trials.[48]

### *Thalidomide and Lenalidomide*

Thalidomide is known to interfere with angiogenesis and the microenvironment. In a small phase II trial the combination with rituximab yielded an response rate of 81% (CR: 31%) in favorable-risk patients.[49] Even more interestingly, recent studies confirmed the high efficacy of IMIDs. The second-generation compound lenalidomide achieved response rates of up to 50% in relapsed MCL (**Table 2**).[50,51]

**Table 2. Efficacy of selected targeted strategies in relapsed or refractory mantle cell lymphoma (MCL).**

| Author, year | Regimen | n | Response rates, OR | Median PFS | Median OS |
|---|---|---|---|---|---|
| Wang 2009[43] | Ibritumomab d 8<br>Rituximab 375 mg/m$^2$ | 34 | 31% | 6 mo | 21 mo |
| O'Connor 2009[47] | Bortezomib 1.5 mg/m$^2$ d 1, 4, 8, 11 | 40 | 47% (CR/CRu: 13%) | 5.3 mo | n.a. |
| Goy 2009[46] | Bortezomib 1.3 mg/m$^2$ d 1, 4, 8, 11 | 141 | 33% (CR/CRu: 8%) | 6.5 mo | 23.5 mo |
| Kaufmann 2004[49] | Thalidomide 200 mg<br>Rituximab 375 mg/m$^2$ | 16 | 81% (CR/CRu: 31%) | 20.4 mo | 75% (3 y) |
| Habermann 2009[50] | Lenalidomide 25 mg d 1-21 | 15 | 53% (CR/CRu: 20%) | 5.6 mo | n.a. |
| Zinzani 2008[51] | Lenalidomide 25 mg d 1-21 | 39 | 43% (CR/CRu: 8%) | 7.2 mo | n.a. |
| Witzig 2005[52] | Temsirolimus 250 mg weekly | 35 | 38% (CR/CRu: 3%) | 6.5 mo | 12 mo |
| Hess 2008[53] | Temsirolimus 175 mg/75mg weekly | 54 | 22% | 4.8 mo | 13.6 mo |
| | Temsirolimus 175 mg/25mg weekly | 54 | 6% | 3.4 mo | 10 mo |
| Lin 2008[54] | 40-60 mg d 1 (-3) Fludarabine 25 mg/m$^2$ d 1-5<br>Rituximab 375 mg/m$^2$ d 1 | 10 | 80% (CR/Cru: 70%) | 32.3 mo (only responders) | n.a. |

PFS indicates progression-free survival; OS, overall survival; ORR, overall response rate; CR(u), complete response (unconfirmed) rate; N.a., not available.

### *Temsirolimus*

The mechanism of action of temsirolimus is complex: translation of cyclin D1 mRNA is inhibited by interfering with the mammalian target of rapamycin. In a phase II trial single-agent treatment yielded response rates of 38% comparable to proteasome inhibitors and median time to progression and duration of response of 6.5 and 6.9 months, respectively.[52] Furthermore hematologic toxicity was considerable, so lower dose levels (25 mg) were evaluated and showed comparable efficacy. In a randomized phase III trial, this compound was shown to be superior to standard monotherapy in heavily pretreated patients.[53] Rad001, a similar compound with much higher in vitro efficiacy, appears to be well tolerated in a phase I trial and is now evaluated in relapsed MCL.

### *Flavopiridol*

Flavopiridol directly inhibits CDK 4 and 6, leading to downregulation of cyclin D1. Recently, after pharmacokinetic improvement of the application schedule significant activity and even tumorlysis syndrome has been observed. In combination with fludarabine and rituximab, responses were achieved in 8 of 10 patients.[54]

### *Othe Therapeutic Options*

Other interesting therapeutic options in early clinical development include inhibitors of members of the Bcl-2 family, antisense approaches (eg, oblimersen), and directly targeting apoptosis via in the extrinsic pathway (eg, TRAIL) or further downstream (IAPs, XIAPs, nutlins).

## Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation remains the only curative therapeutic option for advanced stage MCL based on a graft-versus-lymphoma effect. Recent improvement has been made with the introduction of reduced intensity conditioning pioneered by Khouri and colleagues[55] in relapsed, mostly chemosensitive MCL patients.[32] CR rate was impressively high with 97%, and only 3 patients (9%) died within the first year. While only grade I/II acute graft-versus-host disease (GVHD) was observed in 37% or patients, about 60% of patients suffered from significant chronic GVHD (limited: 23%, extensive: 37%). After a follow-up of 56 months, estimated 6-year progression-free and overall survival were 46% and 53%, respectively. Interestingly, in a non-randomized comparison, this approach resulted in a significant superior clinical outcome in comparison with autologous transplantation. In another multicenter survey of 60 patients, allogeneic transplantation after dose-reduced intensity conditioning achieved a 3-year event-free survival of 69% and 45% in CR and PR patients, respectively,[56] but results in chemorefractory disease are still sobering with an overall survival of less than 2 years.

Current therapeutic recommendations are based on following considerations (**Figure 3**):

- Treatment strategies should depend on the individual risk profile and patient's comorbidities, as discussed.
- Younger patients without significant comorbidity should be treated aggressively, either with

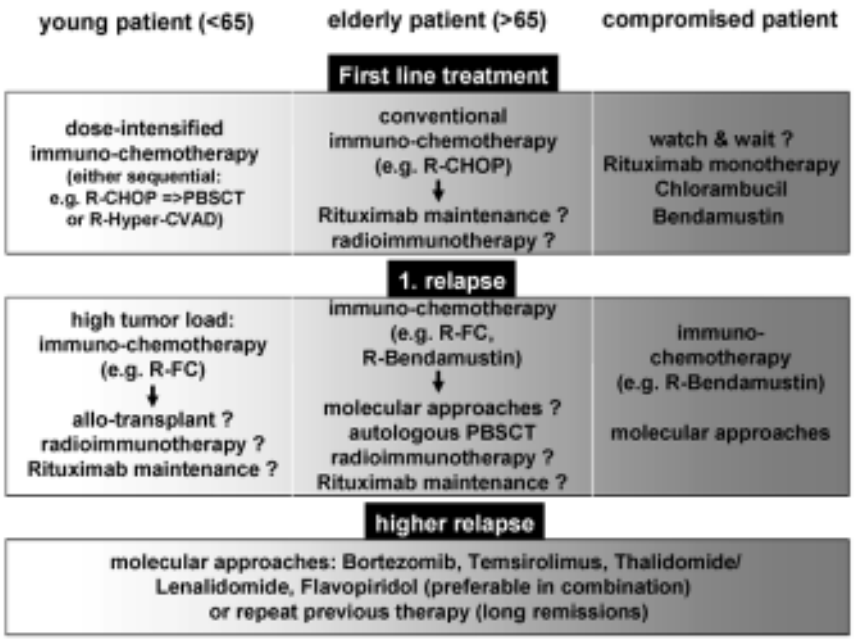


**Figure 3. Therapeutic considerations in mantle cell lymphoma (MCL).**

myeloablative regimens followed by ASCT after initial CHOP- or DHAP-like induction therapy or with up-front dose intensification (HyperCVAD plus rituximab).

- Patients who are not considered candidates for aggressive regimens may be treated with conventional chemotherapy (either anthracycline-, bendamustine- or fludarabine-containing regimens plus rituximab); however, it is crucial to implement additional consolidation concepts (eg, rituximab maintenance, radioimmunotherapy consolidation within studies) to maintain remission.
- Clinical trials investigating molecularly targeted therapeutic options, preferably either in combination or sequential, should be considered in all patients. So far, the most mature data have been presented for bortezomib, lenalidomide, and temsirolimus.
- Allogeneic transplantation should be considered in all patients with relapsed disease after appropriate first-line therapy.

## Disclosures

Conflict-of-interest disclosure: MHD receives research funding from Sanofi, Janssen Cilag, Mundipharma, Celgene, Bayer, Roche and Lilly and honoraria from Mundipharma, Bayer and Roche. He is a consultant for Celgene. WH receives research funding from Roche Germany and Roche International.

Off-label drug use: Rituximab, Yttrium Ibritumomab Tiuxetan, Lenalidomide, Thalidomide, Bortezomib in combination with chemotherapy, temsirolimus, Rad 001 (all in MCL)

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