

Current treatment standards and future strategies in mantle cell lymphoma

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molecular genetics

The genetic hallmark of mantle cell lymphoma (MCL) is the translocation t(11;14)(q13;q32), which can be detected by classical cytogenetics or FISH analysis resulting in overexpression of the cell cycle regulator protein cyclin D1, which may be detected by immunostaining in the large majority of cases. It is still under debate whether cases of atypical CLL with t(11;14) represent a different disease entity. On the other hand, t(11;14)-negative MCL cases have been reported recently, which, however, display a clinical course similar to that of classical MCL [1].

In a substantial proportion of MCL cases, decreased levels of inhibitors of CDK4 and CDK6, such as p16^{INK4a}, can be detected. Typically those cases are characterized by blastoid morphology and even more aggressive clinical behavior. Interestingly the gene locus on 9p21 encodes not only p16, but also another protein p16^{ARF}; decreased levels of p16^{ARF} result in increased MDM2 (mouse double minute 2 homolog)-mediated p53 degradation. Furthermore *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. Highly interesting data were obtained by gene expression analysis. Certain proliferation signatures identified patient subsets that differed by >5 years in overall survival [1]. Taken together the pathogenesis of MCL is characterized by simultaneous disruption of cell cycle regulation and DNA damage response [2].

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 present with extranodal manifestations with up to 77% with evidence of circulating MCL cells detected either by peripheral blood smear or flow cytometry. For initial staging of advanced stage disease we usually recommend endoscopy only if clinical symptoms are suggestive of infiltration. Central nervous system involvement has been described especially in

relapsed disease, and is usually associated with advanced, often leukemic disease and neurologic symptoms.

The clinical course of MCL is characterized by a continuously declining survival curve, with a median survival of ~4 years and <15% long-term survivors [3]. Clinical features associated with adverse prognosis are advanced stage, occurrence of B symptoms and poor performance status [4]. In contrast, younger age (<65 years), normal LDH serum levels as well as normal β 2-microglobulin seem to be associated with a better outcome. The prognostic role of cell proliferation was verified by a large clinicopathological study of prospective clinical trials performed by the *European MCL Network*. Multivariate analysis confirmed the central prognostic role of cell proliferation and its superiority to all other histomorphological and clinical criteria [3]. Based on an extensive data set of >450 patients uniformly treated in prospective trials, a combined clinical and biological score (MIPI) has been recently proposed which implements performance status, age, LDH, leucocyte count and Ki 67 immunostaining index and allows a more reliable estimation of the individual clinical course [4].

In addition, minimal residual disease (MRD) seems to be a strong prognostic factor in MCL patients following high-dose therapy and autologous stem cell transplantation (ASCT) [5]. However, data on combined immunochemotherapy are contradictory [6].

treatment

Considering the aggressive clinical course in the majority of patients and the poor overall survival prognosis, a watch-and-wait strategy should not usually be pursued.

conventional dosed chemotherapy

Conventional mono- or polychemotherapy does not provide long-term control of the disease and remains a non-curative approach. In two prospective randomized trials, only minor advantage of the anthracycline-containing CHOP regimen (cyclophosphamide, vincristine, doxorubicin and prednisone) in comparison with a non-anthracycline combination (COP or MCP) was detectable. In contrast, a retrospective study suggested superiority of anthracycline-containing regimens in patients with low and low–intermediate risk profile according to the IPI. However, because of the aggressive clinical course of MCL many clinicians favor CHOP-like or even more intensive regimens.

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While fludarabine monotherapy demonstrated only moderate efficacy in MCL, fludarabine-containing regimens with either alkylating agents or anthracyclines have been successfully applied in the first-line setting or for relapsed disease. However, hematologic toxicity and even stem cell toxicity have to be considered, especially for 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. By replacing the benzene ring in the chlorambucil molecule by a benzimidazole ring, bendamustine may also act as a purine analog. A randomized phase III trial in patients with indolent and mantle cell lymphoma demonstrated, that bendamustine can efficaciously and safely replace cyclophosphamide in combination with vincristine and prednisone (BOP versus COP). In an initial phase II trial bendamustine in combination with rituximab showed a response (OR) rate of 75% with a complete response (CR) rate of 50% in 16 patients with relapsed or refractory MCL [7].

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 four cycles of CHOP. Of 25 patients all but two responded, CR rate was 84% [8]. Another even more dose-intensified regimen, HyperCVAD/MA (fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone; alternated with high-dose methotrexate and cytarabine) was introduced by the MD Anderson group and demonstrated a CR rate of 38% and a partial response (PR) rate of 55.5% after four

cycles in 45 previously untreated as well as relapsed or refractory MCL patients. Alternatively to this upfront dose escalation, myeloablative consolidation with ASCT may be added after conventional chemotherapy. Various rescue small phase II trials suggested that patients in first remission gained most profit from this approach.

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 significantly longer progression-free survival (PFS) with a median of 39 months compared with 17 months ($P = 0.0108$) (Figure 1). However, a longer follow-up is needed to determine the effect on overall survival (OS) (3 year OS was 83% versus 77%) [9]. 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 a relatively large trial, OR rate was only 27%. Other monoclonal antibodies, either chimeric or even fully humanized, targeting a variety of epitopes in addition to CD20, such as CD22, CD80 or HLA-DR, are currently being investigated in preclinical and clinical trials, but data for MCL are still premature.

immunochemotherapy

After promising results of phase II trials [6], rituximab in combination with polychemotherapy has been investigated in several phase II and III clinical 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%

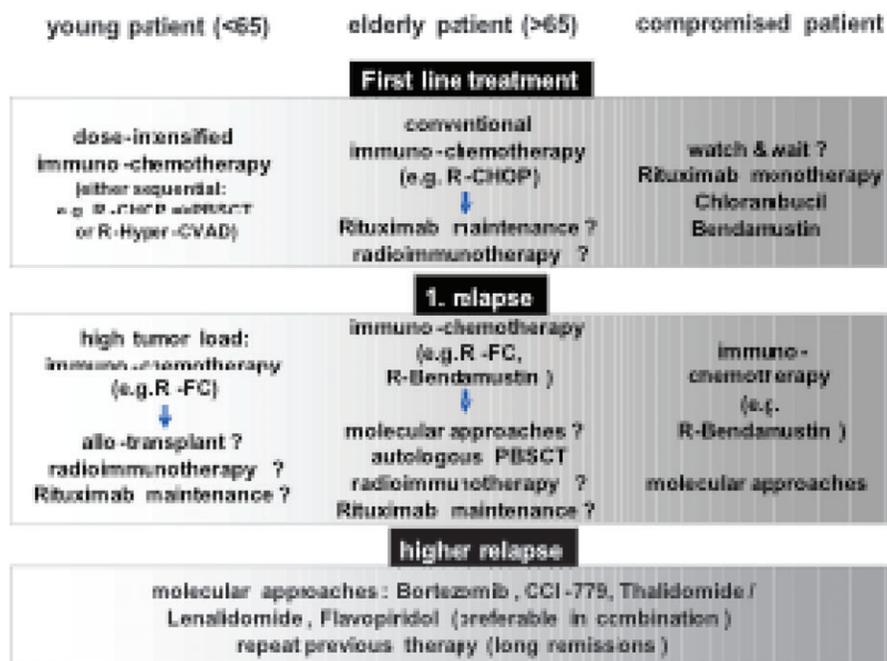


Figure 1. Current therapeutic recommendations outside of clinical studies (Dreyling, ASCO Educational 2006).

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versus 75%; $P = 0.0054$) and CR rate (34% versus 7%; $P = 0.00024$), but showed only moderate impact on time to treatment failure (TTF; median 21 versus 14 months; $P = 0.0131$) [10]. Importantly, there was no clinically significant additional toxicity. A similar trend has been reported in a smaller phase III trial applying a similar regimen (MCP \pm rituximab). In relapsed disease, a fludarabine-containing regimen FCM (fludarabine, cyclophosphamide, and mitoxantrone) in combination with rituximab (R-FCM) not only improved OR rate (58% versus 46%) and CR rate (29% versus 0%), but also significantly prolonged OS ($P = 0.0042$). This benefit on OS was also suggested by a recent meta-analysis [11].

Rituximab in addition to the dose-intensified regimen HyperCVAD/MA 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 failure-free survival and OS rates were 64% and 82%, respectively [12]. However, these excellent results could not be replicated in a recently published multicenter trial. Overall response rate was 88% resulting in a PFS of 60% at 2 years only (Table 1).

maintenance therapy

Analysis of phase III trials suggested a tendency towards a prolonged PFS after interferon- α maintenance (IFN α). However, the number of patients was too low to exactly define the benefit of IFN α . More interestingly, the addition of rituximab maintenance therapy also improved the 3-year PFS from 9% to 45% in relapsed disease. However, these data are based on a limited number of patients only.

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 two ongoing phase II trials in relapsed and refractory MCL. Overall response rates were ~ 30 – 40% , but with disappointingly short durations of remission. Hence there might be a more potent effect of RIT in multimodal approaches. RIT may be applied as part of induction therapy, as consolidation therapy or as part of a high-dose regimen followed by ASCT. Preliminary data in first-line therapy suggest that consolidating RIT not only results in impressively increasing CR rates, but also suggests a significant prolongation of PFS.

molecular targeted approaches

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 duration of response (DR) relatively short; in the largest trial enrolling 141 patients a median DR of 9.2 months and a median TTP of 6.2 months was observed [13].

Table 1. Clinical trials evaluating chemotherapy combined with rituximab in mantle cell lymphoma

| Author, year | Phase and disease status | Regimen | <i>n</i> | Results |
|-----------------------------|---------------------------------------|--|----------|--|
| Howard et al., 2002 [6] | Phase II, newly diagnosed MCL | CHOP + rituximab | 40 | CR/CRu: 40%; PR: 48%; median PFS: 16.6 months |
| Lenz et al., 2005 [10] | Phase III, newly diagnosed MCL | CHOP \pm rituximab (followed by IFN maintenance versus ASCT) | 122 | CR: 34% versus 7%; PR: 60% versus 68%; no significant difference in PFS; median TTF: 21 versus 14 months |
| Forstpointner et al., 2004 | Phase III, relapsed or refractory MCL | FCM \pm rituximab (followed by observation versus rituximab maintenance) | 40 | CR: 29% versus 0%; PR: 29% versus 46%; median PFS: 8 versus 4 months; median OS: NR versus 11 months |
| Romaguera et al., 2005 [12] | Phase II, newly diagnosed MCL | HyperCVAD/MA + rituximab | 97 | CR/CRu: 87%; PR: 10%; 3-year FFS: 64%; 3-year OS: 82% |
| Epner et al., 2007 | Phase II, newly diagnosed MCL | HyperCVAD/MA + rituximab | 97 | CR/CRu: 58%; PR: 30%; 2-year PFS: 64%; 2-year OS: 76% |

Abbreviations: ASCT, autologous stem cell transplantation; CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone); CR, complete response rate; EFS, event-free survival; FCM (fludarabine, cyclophosphamide, mitoxantrone); FFS, failure-free survival; HyperCVAD/MA (fractionated cyclophosphamide, doxorubicin, vincristine, dexamethasone, alternated with high-dose methotrexate and cytarabine); IFN, interferon; MCL, mantle cell lymphoma; NR, no response; PFS, progression free survival; PR, partial response rate; OS, overall survival; TTF, time to treatment failure.

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 [14] suggest synergic efficacy of a combination with cytarabine representing the rationale of currently ongoing randomized trials.

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 OR rate of 81% and a CR rate of 31% [15]. 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.

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 DR of 6.5 and 6.9 months, respectively [16]. Rad001, a similar compound with much higher *in vitro* efficacy, is being tested in current phase II trials.

Flavopiridol. Flavopiridol directly inhibits CDK4 and CDK6, leading to down-regulation of cyclin D1. Recently, after pharmacokinetic improvement of the application schedule significant activity and even tumor lysis syndrome has been observed.

allogeneic stem cell transplantation

Allogeneic stem cell transplantation still 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 in a small phase II trial for relapsed, mostly chemosensitive MCL patients. The CR rate was impressively high at 94%, and no patient died during the first 100 days. While no severe acute graft-versus-host disease (GVHD) was observed, every third patient suffered from significant chronic GVHD. After a follow-up of 28 months, estimated 3-year progression free and overall survival were 82% and 85%, respectively. In contrast, results in chemorefractory disease is still sobering with an OS of <2 years.

In summary, the current standard therapeutic approaches to patients with MCL may be summarized as follows (Figure 1).

- Younger patients without significant comorbidity should be treated aggressively, either with 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 either anthracyclin- or fludarabine-containing regimens plus rituximab; however, it is crucial to implement additional consolidation concepts to maintain remission.

- Clinical trials investigating innovative approaches including RIT, molecular targeted therapeutic options or allogeneic transplantation should be considered in all patients.
- Finally, allogeneic transplantation should be applied only in suitable patients with relapsed disease after appropriate first-line therapy.

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