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REVIEW ARTICLE

Mantle cell lymphoma-current literature overview

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Summary

Mantle cell lymphoma (MCL) is a distinct subtype of lymphoma identified as a particular entity in the early 1990s. The prognosis of MCL is generally poor, and is considered one of the worst among all B-cell lymphomas. In general, conventional chemotherapy is only palliative and the median duration of remissions is only 1-2 years. With the exception of allogeneic hematopoietic stem cell transplantation (allo-SCT), current treatment approaches are not curative and the corresponding survival curve is characterized by a relatively steep and continuous decline, with a median survival of about 4 years and <15% long-term survivors. Only a small proportion of patients may be exempted from this disappointing picture, because they have an indolent course of the disease and could be handled with watch and wait strategy. Optimal first-line therapy in MCL is not established yet. Very intensive regimens, including autologous (auto-SCT) and allo-SCT, seem to be required to improve the outcome. Allogeneic stem cell transplantation is the only therapy that can achieve a plateau in the survival curve, but, however, it is not applicable in most of the cases due to the patients' older age when the disease mostly occurs. Molecular knowledge of MCL has progressed and therefore a large number of molecular targeted therapies have been introduced in relapsed and refractory disease.

Key words: *clinical outcome, induction therapy, mantle cell lymphoma, targeted agents*

Introduction

MCL is a distinct subtype of lymphoma, characterized by the chromosomal translocation t(11;14)(q13;q32), resulting in constitutional overexpression of cyclin D1 and cell cycle dysregulation in virtually all cases [1].

The incidence of MCL ranges between 2-10% of all non-Hodgkin lymphomas. The male to female ratio is 2.3-2.5:1 with median age at diagnosis close to 70 years [2]. Moderate associations with MCL risk have been reported for *Borrelia burgdorferi* infection, family history of hematopoietic malignancies, and genetic variation in the interleukin-10 and tumor necrosis factor genes, but these findings remain unconfirmed [2].

MCL, except nodal has very commonly extranodal involvement like bone marrow, spleen, liver, Waldeyer's tonsillar ring and gastrointestinal tract - a form of multiple lymphomatous polyposis (MLP) [3]. Several subtypes of MCL with distinct disease courses have been recognized so far: an indolent subtype, very slow in progress, is found in 10–15% of the patients. This subset of long-term survivors has an indolent course even after conventional treatment only [4]. The most frequent subtype is the classic MCL with a moderate rapid course, and the most aggressive variant is the blastoid subtype that is found in 10% of the patients, with a frequently very dismal course [5].

The MCL international prognostic index (MIPI) was derived by applying the variables included in the international prognostic index (IPI) developed for large cell lymphoma and the variables included in the follicular lymphoma international prognostic index (FLIPI) to the analysis of MCL patients in clinical trials. The resulting index classified patients into a low-risk group comprising 44% of the patients with a median overall survival (OS) not reached, an intermediate-risk group

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comprising 35% of the patients with median OS of 51 months, and a high-risk group with 21% of the patients and median OS of 29 months [6].

In general, conventional chemotherapy is only palliative and the median duration of remissions is only 1-2 years [1]. With the exception of allo-SCT, current treatment approaches are non-curative and corresponding survival curves are characterized by a delayed, but continuous decline and a median survival of 3 to 7 years [1]. During the last decade, the European consortium has successfully initiated the largest phase III trials in MCL worldwide. In the current study generation, the addition of high dose cytarabine to a rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP)-like regimen followed by myeloablative consolidation achieved a significant improvement of progression-free survival (PFS). In younger group of patients the standard of care is the aggressive induction R-HyperCVAD (fractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone) followed by auto-SCT or allo-SCT in high risk group. Similarly, in elderly patients, rituximab maintenance until progression led to a marked prolongation of remission duration [1]. However, with the exception of allo-SCT, current treatment approaches are not curative and the corresponding survival curve is characterized by a relatively steep and continuous decline, with a median survival of about 4 years and <15% long-term survivors [7]. Future management of the MCL in the era of novel agents remains to be determined by wide spectrum of prospective clinical trials.

The basic molecular characteristics of MCL

MCL is one of the B-cell malignancies with the highest degree of genomic instability, and a large number of secondary chromosomal replications during the S phase, leading to double-strand DNA breaks and activation of the ataxia-telangiectasia mutated protein (ATM) pathways [8]. The t(11;14)(q13;q32) translocation, that juxtaposes the proto-oncogene CCND1 at 11q13 to the immunoglobulin heavy chain complex (IGH) at chromosome 14q32, is considered the primary oncogenic mechanism in the development of MCL. This translocation forces the constitutive overexpression of cyclin D1, which is not detected in normal B lymphocytes, and deregulates the cell cycle at the G_1/S phase transition [9]. Overexpression of cyclin D1 is present in about 90% of MCL [10], although in the remaining 10% of lymphomas with typical morphologic features and the characteristic gene expression signature of MCL cyclin D1 messenger RNA is lacking [11]. Those cyclin D1 negative cases often show expression of cyclin D2 and cyclin D3 [11].

The recently recognized SOX11, a neuronal transcription factor, was identified as a very specific marker of MCL [12]. SOX11 is highly expressed in virtually all MCL cases but is not expressed in other mature lymphoid neoplasms and normal lymphocytes at any stage of differentiation. Interestingly, SOX11 is highly expressed in both cyclin D1 negative and positive MCL, suggesting that, in addition to its value as a diagnostic biomarker, it may be an important factor in the pathogenesis of MCL [13].

Almost all of the well known oncogenic pathways have been enrolled in the pathogenesis of MCL. They include proteasome, PI3K/AKT/mTOR, BCR, NF-kB, WNT pathways, antiapoptotic bcl-2 family proteins. The role of tumor microenvironment in MCL has been demonstrated in *in vitro* and *in vivo* models, especially in studies with immunomodulatory drugs such as thalidomide and lenalidomide. Finally, epigenetic regulation has been studied very recently in MCL cell lines and demonstrated the probable future targets, including HDAC inhibitors, chaperon inhibitors and others.

Induction treatment

The prognosis of a patient with MCL is generally poor, and is considered one of the worst among all B-cell lymphomas. Conventional chemotherapy is not curative but achieves frequent remissions (60-90%) which are usually shorter (1-2 years) compared with other lymphoma types [14]. Only a small proportion of patients may be exempted from this rather disappointing picture, because they have an indolent course of the disease and they could be handled by watch and wait strategy. Optimal first-line therapy in MCL is not established yet. This is due to the heterogeneity of the disease and according to risk-adopted (MIPI index) and age-adjusted stratification of the therapeutic approach. In that order we will consider current review of induction treatment to MCL in elderly patients (aged ≥65 years) and younger patients (aged < 65 years).

First-line therapy in elderly MCL patients (≥ 65 years)

Historically, data shows that the "gold standard" cyclophosphamide, doxorubicin, vincristin,

prednisone (CHOP) or CHOP-like protocols for induction treatment were the most commonly used therapeutic approach to MCL. This is due to patient age when the disease most usually appears. The study of Lenz et al. demonstrated that combined immunochemotherapy of R-CHOP vs CHOP alone significantly improved the complete remission (CR) rate (34 vs 7%; p=0.00024), the overall response rate (ORR) (94 vs 75%; p=0.0054), and the time to treatment failure (TTF) (median 21 vs 14 months; p=0.0131) in patients with advanced-stage MCL [15]. This study did not show any difference in PFS and OS in the two compared arms. The favorable clinical and molecular response rates associated with R-CHOP immunochemotherapy do not translate into prolonged PFS in MCL [16]. On the other hand, the results of a meta-analysis of randomized controlled trials, including 260 MCL patients, indicated an overall survival benefit in patients treated with immunochemotherapy compared with chemotherapy alone [17]. The latter conclusion is statistically invalid because the study did not have sufficient statistical power to detect clinically statistical significant differences in OS.

The R-CHOP regimen seems to benefit elderly patients, who are not fit enough for an aggressive therapeutic approach. The recently published study with rituximab maintenance [18] found that elderly patients with MCL benefit from rituximab maintenance. The study design included double-randomization with two objectives: first to compare response to induction treatment of two different arms [rituximab, fludarabine, cyclophosphamide (R-FC) vs R-CHOP], and second to randomize responsive patients to maintenance therapy (rituximab vs interferon alpha). The results showed that the achieved CRs were not statistically different in both induction regimens (40% for R-FC vs 34% for R-CHOP), ORR was better for R-CHOP, although not statistically different (86 vs 76%, respectively). The rate of progression was significantly higher in the R-FC arm than during R-CHOP (14 vs 5%). The remission duration and time to failure (TTF) were similar (only one month difference better for R-FC). OS was much better for R-CHOP arm (survival rate at 4 years 62 vs 47%). Maintenance therapy with rituximab showed not only a significantly better PFS benefit but also a significant survival advantage among patients who were successfully pretreated with R-CHOP, but not for those pretreated with R-FC. Cytarabine-containing regimens in MCL seem to be the most effective ones in younger patients the, but in the elderly who are not fit for high dose cytarabine, dose modifications of cytarabine appear to be feasible for the elderly with relapsed MCL [19].

A phase II study [20] used R-CHOP$_{21}$+bortezomib as induction therapy for DLBCL and MCL (N=36, median age 66 years, MIPI intermediate 28%, and high 39%). Bortezomib was administered on day 1, 4-dose schedule (from 1.3 mg/m^2 to 0.7 mg/m^2). For all 36 patients the ORR was 81%, with CR/unconfirmed CR (CRu) in 64%. For the evaluable patients (N=32), the ORR was 91%, and CR/CRu 72%, PFS was 44% at 2 years, and OS 86% again at 2 years. Median PFS was 23 months, while median OS was not reached and MIPI was the only significant predictor of survival.

In a phase III study of Rummel et al., which compared R-CHOP vs. R-Bendamustin (R-B) in indolent non-Hodgkin lymphomas and MCL as a first-line therapy, significantly better PFS (69.5 months vs 31.2 months) for the R-B arm was found [21]. Bendamustin showed non-inferiority and better tolerability over R-CHOP in first-line approach, and therefore it can be considered as a new standard of care in elderly patients, the authors concluded. However, the study included much more patients with follicular lymphoma (FL). Hence, this could be an option for MCL patients with underlying heart problems or elderly who are not candidates for anthracycline-based regimens.

A most recent published phase II study compared R-CHOP vs R-CHOP+bevacizumab in 11 patients. No significant improvement in efficacy was found in the bevacizumab arm [22].

Treatment of the unfit patients who, either because of age or comorbidities, are unable to tolerate aggressive treatment, are treated with palliative chemotherapy or reduced intensity usually with single agents [14].

First-line therapy in younger MCL patients (< 65 years)

Treatment of MCL in younger patients remains a challenge. The primary goal is to develop long-term remissions with prolongation of survival or cure of disease. The standard of care in younger patients who are transplant-eligible is the up-front induction therapy followed by auto-SCT consolidation in first remission, especially in the intermediate risk group according to MIPI, whereas in the high risk group such an approach remains suboptimal. Randomized studies are needed to clarify the significance of allo-SCT in first remission, which seems to be the best known

option to this time point.

A French group of authors published their results of phase II study with CHOP and DHAP + rituximab followed by auto-SCT in MCL [23]. Included were patients aged < 66 years with stage 3 or 4 MCL. As induction treatment they used 3 cycles of $CHOP_{21}$ (the third one was with the addition of rituximab) and 3 cycles of R-DHAP sequentially. Responding patients were eligible for auto-SCT with conditional regimens (TAM6 or BEAM). The ORR was 93% after (R)-CHOP and 95% after R-DHAP. With a median follow-up of 67 months, the median event-free survival was 83 months, and the median OS had not been reached. Five-year OS was 75%. This study confirmed that induction with rituximab and cytarabine-based regimen is safe and effective in MCL patients.

An Italian group of authors published their study with R-HyperCVAD-AM (R-HCVAD alternating with high dose cytarabine and methotrexate) [24]. Patients aged ≤ 70 years received 4 alternating cycles each of R-HCVAD and AM. Patients who obtained a partial response proceeded to auto-SCT. ORR and CR rates were 83 and 72%, respectively. After a median follow-up of 46 months (range 1-72) the estimated 5-year OS and PFS rates were 73 and 61%, respectively. MIPI maintained the prognostic value with an estimated 5-year OS of 89, 80 and 24% for low, intermediate, and high risk groups, respectively ($p<0.001$). This multicentre study confirmed that R-HCVAD-AM is an active regimen for the initial treatment of patients with MCL, but it is associated with significant toxicity.

The GELTAMO group published their results in 2013, showing that induction with R-HCVAD-AM and consolidation with ^{90}Y-ibritumumab tiuxetan is effective, although less feasible than expected. The substantial toxicity advised against the use of this strategy [25].

The authors of the SWOG 0213 trial concluded that R-HCVAD-AM regimen is toxic but active in patients < 65 years of age, with median OS of 6.8 years [26].

In an updated review of the Nordic MCL2 trial at 6.5 years median observation, the authors reported median OS and response duration longer than 10 years, and median event-free survival of 7.4 years. The MIPI and Ki-67 expression were the only independent prognostic factors for event free survival (EFS) and OS. Subdivided by the MIPI-Biological Index (MIPI+Ki-67, MIPI-B), more than 70% of the patients with low-intermediate MIPI-B were alive at 10 years, in contrast to 23% of the patients with high MIPI-B. The conclusion was that risk-adopted treatment strategy is required [27].

Some very new statements [28] are questioning the role of SCT consolidation approach in first remission, especially in the era of an improved survival and higher response rates with immunochemotherapy. This might be due to the heterogeneity of some clinical factors that have to be considered (patient age, MIPI or comorbidity index scores) before making a decision on SCT. In younger transplant-eligible patients first line induction with R-HCVAD followed by auto-SCT consolidation is now the standard of care with documented survival benefits. The problem with R-HCVAD is connected with the frequent stem cell mobilization failure. This implies the need for new front-line treatment strategy or consideration of an early stem cell collection, when this induction regimen is to be used.

However, aggressive approaches to MCL may have shifted the survival curve to the right, but it still remains unclear if long-term remission is possible.

Relapsed/refractory MCL

Despite better understanding of MCL pathophysiology and improved OS this disease remains incurable and most patients will experience relapse which is almost inevitable. Selection of chemoresistant malignant clones after multiple chemotherapy regimens may explain relapse. Therefore, it is of paramount importance to find an optimal management for relapsed disease. A huge number of phase I and II clinical trials has been conducted to demonstrate ORR or PFS with the use of new targeted agents in order to introduce them or not in the treatment of relapsed and refractory MCL. Some selected prospective studies of new molecular approaches to MCL are shown in Table 1. A large number of ongoing clinical phase III trials will define the real clinical benefit of new targeted agents.

Molecular approaches in relapsed MCL

The role of proteasome inhibitors

The results of the phase II multicenter PINNACLE study led to the inclusion of the proteasome inhibitor bortezomib in the treatment of relapsed/refractory MCL. In this study bortezomib was administered to patients who progressed after a minimum of 1 prior treatment (range 1-3)

Table 1. Selected prospective studies of new molecular approaches to MCL

Drug/Agent	*Clinical development phase*	*Mechanism of action/Drug class*	*First author [Reference]*
Bortezomib	Phase II	Proteasome inhibitor	Fischer RI, et al. (2006) [27]
Temsirolimus	Phase II	mTOR inhibitor	Hess G, et al. (2009) [32]
Everolimus (RAD001)	Phase II	mTOR inhibitor	Renner C, et al. (2012) [35]
Thalidomide	Phase III	Immunomodulator	Hess G, et al. (2009) [33]
Lenalidomide	Phase II	Immunomodulator	Zinzani PL, et al. (2013) [38]
Ibrutinib	Phase II	Bryton's kinase inhibitor (BTK)	Wang ML, et al. (2013) [40]

for MCL with anthracycline, cyclophosphamide or mitoxantrone+rituximab. Doses were the same as in the treatment of multiple myeloma (1.3mg/m^2 on days 1, 4, 11 and 12, on a 21-day cycle). The ORR was 33%, including CR+CRu plus partial response (PR); median response duration was 9.2 months. The CR+CRu response rate was 8% with a median response duration of 13.4 months and median OS not reached [29]. Updated time-to-event data of the PINNACLE study with an extended median follow-up of 26.4 months confirmed the high activity of bortezomib in relapsed or refractory MCL patients. The median OS was 23.5 months, and the median TTP 6.7 months. In responding patients, the median TTP was 12.4 months, the median duration of response 9.2 months, the median OS 35.4 months, and the one-year OS rate were 69% and 91% in responders. The median OS from diagnosis was 61.1 months after a median follow-up of 63.7 months [30]. The phase II study of the combined therapy bortezomib+rituximab in MCL and FL demonstrated activity (ORR for MCL was 29%) in relapsed/refractory MCL. It could be an effective salvage for the debulking of disease prior to auto or allo-SCT [31]. However, grade 3 neurotoxicity (in > 50% of patients) was a serious limiting factor.

The role of mTOR inhibitor targeted agents

Temsirolimus is an inhibitor of the mammalian target of rapamycin (mTOR). It has been investigated in relapsed/refractory MCL and is confirmed to be an effective agent in this condition. When single-agent temsirolimus was investigated in two phase II studies for the treatment of patients with relapsed or refractory MCL, it showed considerable antitumor activity, with ORR of 38% and 41% [32]. A phase III study investigated the dose schedule of temsirolimus+rituximab in relapsed/refractory MCL and the authors concluded that the 175/75mg schedule significantly improved PFS and objective response rate compared with 175/25 schedule and investigator's choice [33]. The median duration of PFS was 4.8 months in the 175/75 arm. A most recently published review on single-agent temsirolimus in relapsed/refractory MCL confirmed previous findings [34].

Everolimus as a single agent is well tolerated and has antilymphoma activity in relapsed/refractory MCL [34]. A multicenter phase II trial with single-agent everolimus demonstrated an ORR in 20% of the patients (2 CRs of 35 patients totally enrolled in the trial). Median PFS was 5.5 months in 6 months follow up. Further investigations are warranted.

The role of immunomodulatory targeted agents (thalidomide and lenalidomide)

A phase II study published in 2004 [35] (N=16 patients) with relapsed/refractory MCL used a combination of rituximab+thalidomide (rituximab 375 mg/m^2 for 4 weekly doses concomitantly with thalidomide 200 mg for 2 weeks and after that 400 mg on day 15 and continuously until disease progression. ORR was 81%, and CR 31% (5 patients including one who was primary CHOP resistant and one after auto-SCT) with median PFS of 20.4 months and estimated 3-year OS of 75%. The authors concluded that thalidomide has marked anti-lymphoma activity in relapsed/refractory MCL [36]. No follow-up results were reported.

Lenalidomide has proven tumoricidal and antiproliferative activity in MCL [36]. The MCL-001 EMERGE phase II trial investigated the role of single-agent lenalidomide in MCL. Lenalidomide was administered at a dose of 25 mg for 21 days every 28 days until disease progression. The ORR was 28% (CR/CRu in 7.5%) with a fast time to response. Median PFS was 4 months and median OS 19 months [37]. The results of the NHL-003 study published just recently, after long-term follow up of single-agent lenalidomide showed very similar results in ORR (35%) and demonstrated activity of lenalidomide in heavily pretreated relapsed/refractory MCL. Responders had a durable response with manageable side effects [38].

A recently published phase II trial with lenalidomide (10 mg daily), low-dose dexamethasone

(8 mg once weekly) in cycles 1 and 2 for a 28-day schedule and rituximab (375 mg/m^2 weekly in cycles 3 and 4) in patients with rituximab-resistant, relapsed/refractory, indolent B-cell lymphoma or MCL showed that this combination could achieve high and durable responses. ORR increased from 29% after two 28-day cycles of lenalidomide and low-dose dexamethasone to 58% after the addition of rituximab, suggesting that lenalidomide can overcome resistance to rituximab. The median follow up was 12.2 months and the median PFS 23.7 months [39].

The role of Bryton's kinase inhibitor

Ibrutinib has shown durable single-agent efficacy in relapsed or refractory MCL. Single-agent ibrutinib gave 68% response rates, with 47% of the patients having partial response and 21% having CR. The remission was durable, given the relatively short period of follow up (estimated median duration of response about 17.5 months) and the estimated median PFS was 13.9 months. The median OS was not reached (estimated OS was 58% at 18 months) [40]. Therefore, ibrutinib, as a potent Bryton's tyrosine kinase (BTK) inhibitor was approved by FDA in November 2013 for the treatment of refractory/relapsed MCL.

Most recent findings demonstrate that B-cell receptor signaling pathway appears to be critical in the pathogenesis of MCL. Ibrutinib and idelalisib (PIK3 inhibitor) that target this signaling pathway are highly active in relapsed/refractory MCL [40]. In very early preclinical studies, epigenetic drugs such as romidepsin and belinostat (HDAC inhibitors) showed promising results, especially in the study of MCL cell lines where synergistic action with bortezomib was strongly documented [41]. The purine analog cladribine has been shown to have hypomethylating properties and has activity as a single agent or in combination with other therapies in MCL [42]. Epigenetic therapy with the DNA hypomethylating agent 5-aza-2-deoxycytidine can also cause restoration of cell surface expression of the CD20 protein and increase rituximab sensitivity *in vitro*. Combinations of epigenetic agents may act synergistically to further potentiate the efficacy of monoclonal antibodies like rituximab and ofatumumab and improve the treatment outcome in MCL [43].

Conclusion

No gold standard therapy for MCL exists today. Front-line therapies do not lead to cure but have mostly palliative character. Initial high ORR (even including CR), does not translate into prolonged OS, and prolongation of PFS is questionable. Very intensive front-line regimens, including consolidation with auto-SCT, seem to be required to improve the outcome, but with a median age at diagnosis being 60 years or more, such approaches are feasible only in a limited number of patients. Even then, late relapse does occur. Allo-SCT is the only approach that can make a plateau on the survival curve, but, however, is not applicable in most of the cases. In relapsed/refractory disease many novel agents are introduced with some benefit in ORR, but without defined improvement in survival. These new drugs target a wide spectrum of pathogenetic pathways and indeed are promising, but at this time point more prospective trials are warranted to define whether they are accompanied with real clinical benefit. Unfortunately, the story of MCL is still in grey-black color.

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