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Lymphoma and Chronic Lymphocytic Leukemias

Mantle Cell Lymphoma: Individualizing Therapy

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ABSTRACT: Despite substantial improvements in the management and treatment of mantle cell lymphoma (MCL), the disease is still considered incurable. While high-dose cytarabine followed by autologous stem cell transplantation (ASCT) is considered as the gold standard in younger patients, the Rituximab, Cyclophosphomide, Doxorubicin, Oncovin, Prednisone (R-CHOP) regimen followed by rituximab maintenance is the recommended treatment for the elderly. Our better understanding of the pathogenesis of the disease through the identification of different altered signaling pathways has contributed to the development of new-targeted therapies offering a new era in the management of MCL. Early results achieved with these therapies are promising. However, new questions are arising regarding how and when to use these agents. This paper reviews these different approaches in patients with MCL.

KEYWORDS: mantle cell lymphoma, therapeutic agents, stem-cell transplantation

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Introduction

Mantle cell lymphoma (MCL) is a phenotypically and genetically distinct B-cell lymphoma, accounting for approximately 6–8% of adult non-Hodgkin lymphomas (NHLs).[1] The median age at diagnosis is around 68 years, and the prevalence is higher in men.[2,3]

Despite significant improvements in the management and treatment, the prognosis remains poor with a median overall survival (OS) of less than five years.[4] However, the promising results of novels agents with innovative mechanisms of action are progressively changing our approach to manage these patients.

Diagnosis and Pitfalls

Minimum diagnosis criteria. Minimum diagnosis criteria are based on morphologic, phenotypic, and genetic features. The tumor proliferation is characterized by a diffuse pattern of small- to medium-sized non-cleaved cells with irregular nuclei. The tumor cells usually exhibit CD5, CD20, and FMC7 antigens and are negative for CD23, BCL6, and CD10 antigens.[5] Importantly, these cells are cyclin D1-positive, which is the consequence of the reciprocal translocation between chromosomes 11 and 14, resulting in the juxtaposition of loci 14q32 on chromosome 14 encoding for the immunoglobulin heavy chain variable region gene (IGVH) and loci 11q13 on chromosome 11 encoding for the proto-oncogene BCL-1 (or CCND1).[6] This chromosomal aberration is detected either by conventional cytogenetic examination or by fluorescence in situ hybridization (FISH) technique detecting the BCL-1–IgH rearrangement.[7]

Pitfalls and traps. Besides the classical diffuse pattern discussed above, some MCL cases will present with a more aggressive form characterized by blastic cells. These blastoïd variant forms carry the morphologic pattern of large cells with prominent nuclei and a high mitotic rate mimicking some aspects of diffuse large B-cell proliferation. They usually have a poorer prognosis with a short duration of response and a reduced OS.[8,9]

Less than 5% of MCL lack CD5 expression or are CD10 positive.[10] These cases have all the morphologic and

immunophenotypic characteristics of MCL except the expression of CD5. The diagnosis relies on the expression of cyclin D1 and/or the t(11;14) abnormality.

In a very few cases (<5%), MCL cells do not express the pathognomonic cyclin D1 protein, making the diagnosis more difficult. The neural transcription factor SOX11 that is expressed in almost all MCL cases but not in other B-cell malignancies will be helpful for the diagnosis as well as the presence of the specific chromosomal aberration.[11] In addition, these cases often exhibit high expression of cyclin D2 or cyclin D3.[12,13]

Prognostic Markers in MCL

Several factors are useful to predict the outcome. Some are related to the patient's characteristics, and some reflect the tumor burden and/or the cell proliferation.

Clinical and biological markers. The performance status at diagnosis is one of the most important predicting factors. In the study reported by Bosch et al,[14] patients with an Eastern Cooperative Oncology Group (ECOG) ≥2 had a poorer prognosis ($P = 0.002$). This was confirmed in a recent study of van de Schans et al where the authors highlighted that men as well as the presence of B-symptoms have a negative impact on survival.[15]

Age, LDH levels, and white blood cell counts are also considered important. This led to the construction of a prognostic score called the mantle cell lymphoma international prognosis index (MIPI) in its simplified version.[16] As for the IPI score, this index separates patients into high-, intermediate-, or low-risk groups depending on the number of adverse prognostic factors (see Table 1).

Tumor markers. As discussed previously, the blastoid cytological variant is an aggressive subtype with a poor outcome as compared to the classical variant. In a retrospective study reported by Bernard and colleagues,[9] patients with blastic variant of MCL had a poorer median OS (14.5 vs. 53 months, $P < 0.0001$). These results were confirmed in another study showing that patients with the blastoid cytological subtype were more resistant to initial chemotherapy with a short response duration (11 vs. 28 months) together with a shorter OS (20 vs. 42 months).[8]

The blastoid cytological variant is characterized by a high tumor proliferation rate with an excessive mitotic activity as measured by the MIB-1 (Ki-67) immunostaining.[17,18] This mitotic index has been shown to be correlated with a sorter OS[19] and has been added as a prognostic marker to the variables included in the MIPI score to define a biological MPI (MIPIb).[16]

Cytogenetic events and particularly *TP53* gene mutations or del(17p13) have also been associated with shorter survival and poor outcome.[20,21] These oncogenic alterations are not surprisingly often displayed in blastoid variants of MCL.

Table 1. MIPI score.

POINTS	AGE (YEARS)	ECOG SCORE	LDH (ULN)	WBC (mL)
0	<50	0–1	<0.67	<6700
1	50–59	–	0.67–0.99	6700–9999
2	60–69	2–4	1.0–1.49	10000–14999
3	≥70	–	≥1.5	≥15000

Treatment Options in MCL

Except for the wait and watch strategy that concerns a small proportion of patients with no risk factors,[22] the majority of patients with MCL have to be treated. This indolent form often presents with a very low proliferation activity, a low tumor burden, and a limited stage, and is characterized by a better prognosis with prolonged survival.[6,19] Furthermore, these patients have a characteristic clinical and biological presentation with isolated splenomegaly and circulating leukemic cells expressing SOX11.[6,11–23]

Treatment for young patients (≤65 years).

First-line strategy. For patients ≤65 years and fit enough to undergo intensive treatments, rituximab in association with high-dose cytarabine-based regimen, followed by intensive chemotherapy and supported by autologous stem cell transplantation (ASCT), is considered as the optimal treatment.[24] As in other B-cell malignancies, rituximab in association with chemotherapy has been shown to improve responses rates and progression-free survivals (PFSs).[25] In a randomized, controlled trial comparing CHOP to R-CHOP, Lenz and colleagues demonstrated that the addition of rituximab to the chemotherapy regimen resulted in better survival.[26] These results as well as the improvement of survival were subsequently confirmed in randomized trials as summarized in a meta-analysis.[27]

High-dose cytarabine has become a major drug in the treatment of MCL. Several phase II studies have suggested its importance to achieve high complete response (CR) rates and prolonged PFS.[28–31] A recent phase III study conducted by the European MCL network has evaluated the role of cytarabine in first-line therapy. In this study, six cycles of R-CHOP (control arm) were compared to three cycles of R-CHOP alternating with three cycles of R-DHAP (dexamethasone, high-dose cytarabine and cisplatin, experimental arm), followed by ASCT in both arms.[32] The results showed a significantly higher CR and CR/uCR (unconfirmed CR) in the experimental arm (25 vs. 36%, $P = 0.012$ and 40 vs. 54%, $P = 0.0003$, respectively). In addition, patients in the investigational arm experienced longer response duration (46 vs. 48 months, $P = 0.0382$) and median OS (82 months vs. not reached, $P = 0.045$).

ASCT is now considered as the standard consolidation treatment in young patients. A single randomized trial published to date evaluated a strategy based on myeloablative radiochemotherapy followed by ASCT compared to maintenance with interferon-α in 122 patients under 65 years of age who achieved at least a partial response after CHOP or

CHOP-like regimen. After a median follow-up of 2.5 years, patients assigned to the ASCT arm had a longer median PFS (39 vs. 17 months, respectively, $P = 0.01$) without significant difference in three-year OS (83 vs. 77%, respectively, $P = 0.18$).[33] In the Nordic MCL-2 phase II trial, 160 MCL patients younger than 66 years were given six cycles of rituximab and high-dose cytarabine containing induction regimen followed by carmustine, etoposide, cytarabine, and melphalan (BEAM) conditioning regimen and ASCT. The CR rate rose from 56 to 90% after myeloablative chemotherapy, stressing the role of intensive consolidation therapy to improve the response rate.[28] In the European MCL Network phase III trial, the response rate after ASCT was 97% in the two arms, but the rate of molecular remission that is a powerful and independent prognostic factor for the duration of the response rose from 55 to 72% after ASCT ($P = 0.0116$).[32,34] The BEAM regimen is the most common conditioning regimen used before ASCT, mainly because of its convenience. Total body irradiation (TBI) is not recommended, although some data suggest its beneficial role in patients who are in partial response.[35] The role of rituximab in association with BEAM for in vivo purging is still unclear and has not been demonstrated yet.[33,36] However, in the rituximab era together with high-dose cytarabine induction regimen, whether ASCT in first remission is still necessary or not remains questionable.

In the absence of ASCT, an alternative rituximab-based regimen (R-HCVAD-AM) utilizing high-dose methotrexate-cytarabine (AM) alternating with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) has been investigated by Romaguera et al in a phase II trial. Among the 97 assessable patients, the response (CR/uCR) rate was 89% in patients ≤65 years with three-year Failure-Free Survival (FFS) and Event-Free survival (EFS) rates of 73 and 86%, respectively.[37] With a median follow-up of 10 years, the median time to treatment failure (TTF) was 5.9 years and the median OS time had not been reached yet.[38] This regimen is one of the most commonly used in the USA.

In a multicenter trial setting with a comparable regimen, the Italian group Gruppo Italiano Studio Linfomi (GISL) reported an overall response rate (ORR) of 83% with a CR of 72% and, after a median follow-up of 46 months, a five-year PFS and OS rates of 61 and 73%, respectively.[39] When considering only patients assessable for response after R-HCVAD-AM, the CR rate was 83% and the estimated PFS and OS rates were 60 and 74%, respectively. Owing to different aspects (multicenter trial, no systematic use of G-CSF), these results appear less favorable than those reported by Romaguera et al, but they confirm the high efficiency of this regimen in achieving a high response rate. However, these two studies failed to demonstrate prolonged response duration with a continuous pattern of relapses.

In addition, the SWOG 02–03 phase II study[40] evaluating the efficacy of this alternating high-dose cytarabine and methotrexate regimen in 49 MCL untreated patients has recently been reported. The response rate (CR/Cru) was 55% and, with a median follow-up of 4.8 years, the median PFS was 4.8 years with a median OS of 6.8 years for the whole group. When considering only patients ≤65 years (86% of patients), the median PFS was 5.5 years with a five-year PFS and OS of 53 and 69%, respectively. The authors conclude that their results compare favorably to those reported by Romaguera et al. Altogether, these three studies demonstrate a high efficiency with a five-year PFS >50%. However, this regimen was consistently associated with a high toxicity rate, limiting its use to younger and fit patients.

Lastly, the role of rituximab maintenance in the first-line therapy for young patients in not known. In this setting, the results of the LYMA trial that randomized patients between rituximab maintenance versus no maintenance after four courses of R-DHAP followed by ASCT are awaited. Thus, until mature results are available, rituximab maintenance in young patients with MCL after ASCT cannot be recommended.[24,41] Interestingly, some results support the use of rituximab as pre-emptive therapy for patients with molecular relapse.[42,43]

Salvage therapy. Despite significant improvements in the management of MCL, most patients will relapse and eventually develop chemorefractory diseases.[44] Moreover, most patients, if not all, will relapse after having received rituximab and high-dose cytarabine-based regimens as well as ASCT consolidation. A retrospective study of the European Group for Blood and Marrow Transplantation (EBMT) reviewed 360 patients with MCL relapsing after ASCT.[45] With a median follow-up of 40 months, the median OS after relapse was 19 months. They reported that primary refractory disease, short interval between ASCT and relapse, and prior high-dose cytarabine treatment negatively impacted the outcome. Consequently, the management of relapses in young patients must take into account many considerations such as response duration, stage, age and ECOG at relapse, as well as eligibility to allogeneic stem cell transplantation (Allo-SCT).

Salvage chemotherapy regimens. There is no consensual salvage therapy for MCL. Several phase II studies, using monotherapy or combination schedules, have been reported, and some drugs seem to be promising.[4]

Bortezomib is the first drug that was approved by the Food and Drug Administration (FDA) for relapsed MCL. This was based on the results of the phase II multicenter study (PINNACLE trial),[46,47] showing an ORR of 33% (including 8% CR), a median time to progression of 6.7 months (not reached for patients in CR/Cru), and a median OS of 23.5 months. The European MCL Network is currently enrolling patients in a multicenter randomized phase III trial, assessing the role of bortezomib in association with high-dose cytarabine in patients with relapsed or refractory disease (ClinicalTrials.gov identifier NCT01449344).

Bendamustine is another drug that has been evaluated in relapsed patients either in monotherapy or in combination

with rituximab. Ogura and colleagues[48] treated 69 patients with bendamustine alone in a phase II study. They reported an ORR and a CR rate of 100 and 73%, respectively. A phase III study compared bendamustine plus rituximab versus fludarabine plus rituximab in B-cell NHL, including MCL.[49] The combination of bendamustine plus rituximab produced a better ORR (83.5 vs. 52.5%; $P < 0.001$), a better PFS (30 vs. 11 months; $P < 0.001$), and a higher CR rate (38.5 vs. 16.2%; $P < 0.001$).

Autologous stem cell transplantation. Consolidation with ASCT could be an option for the rare patients not transplanted in the first response. However, the outcome of patients remains poor with a median duration of response around two years and a continuous pattern of relapses.[5] A study of 195 patients from the EBMT registries showed a five-year PFS and OS of 33 and 50%, respectively.[50] The incorporation of radioimmunotherapy into the conditioning regimen seems to improve the response rate and the response duration with an ORR between 91 and 100% and a three-year PFS between 89 and 93%, respectively.[51,52]

Allogeneic stem cell transplantation. For young and fit patients with an HLA-identical donor relapsing after ASCT, Allo-SCT after reduced-intensity conditioning (RIC) regimen is an interesting approach with a curative potential together with an acceptable transplant-related mortality (TRM).[25,53] Thus, the evidence for a graft-versus-lymphoma effect in MCL could yield to a prolonged and sustained response. In the two largest trials published to date, the TRM at two and five years was 24 and 21%, respectively, and the PFS and OS at two and five years were 60 and 14%, and 65 and 37%, respectively.[54,55] A retrospective EBMT study of 279 patients who underwent RIC Allo-SCT between 1998 and 2007 reported a one- and three-year PFS of 49 and 29%, respectively, and OS of 60 and 43%, respectively.[56] More recently, another survey from the EBMT registry evaluated the outcome of patients with MCL relapsing after ASCT. Among the 360 patients included in the study, 80 received an Allo-SCT. With a median follow-up of 32 months, the two- and five-year survival rates were 46 and 34%, respectively, compared to 37 and 16% in patients without Allo-SCT.[45] In conclusion, even if Allo-SCT is a high-risk procedure with an excessive early post-transplant mortality, it offers a real opportunity to cure patients with relapsed MCL with a plateau approximately two years after transplant compared to the continuing risk of relapse after ASCT as illustrated in Figure 1.[57]

Treatment for elderly patients (>65 years). With a median age at diagnosis of 68 years, MCL is a disease of the elderly. In addition, the frequency of comorbidities and the health concerns often observed with age will inevitably confer to these patients a high MIPI score. As a consequence, treating elderly patients with MCL represents a real challenge. Furthermore, it has been shown that the achievement of a molecular response is correlated with long response duration, emphasizing the need to obtain a CR.[34]

First-line strategy. Several chemotherapy regimens have been used to treat elderly patients. CR rates range between 40 and 70% and median PFS between 16 and 21 months.[4] Since the results of the German Low-Grade Lymphoma Study Group phase III trial, the addition of rituximab to CHOP is considered as the standard of care for these patients. In this study, the addition of rituximab improved the CR rate (34 vs. 7%, $P = 0.0002$), ORR (94 vs. 75%, $P = 0.0054$), and median PFS time (21 vs. 14 months, $P = 0.0131$).[26] A recent phase III trial from the European MCL Network randomized 532 patients between six cycles of R-CHOP or six cycles of rituximab plus fludarabine and cyclophosphamide (R-FC). Patients who achieved at least partial response were subsequently randomized to maintenance treatment with either

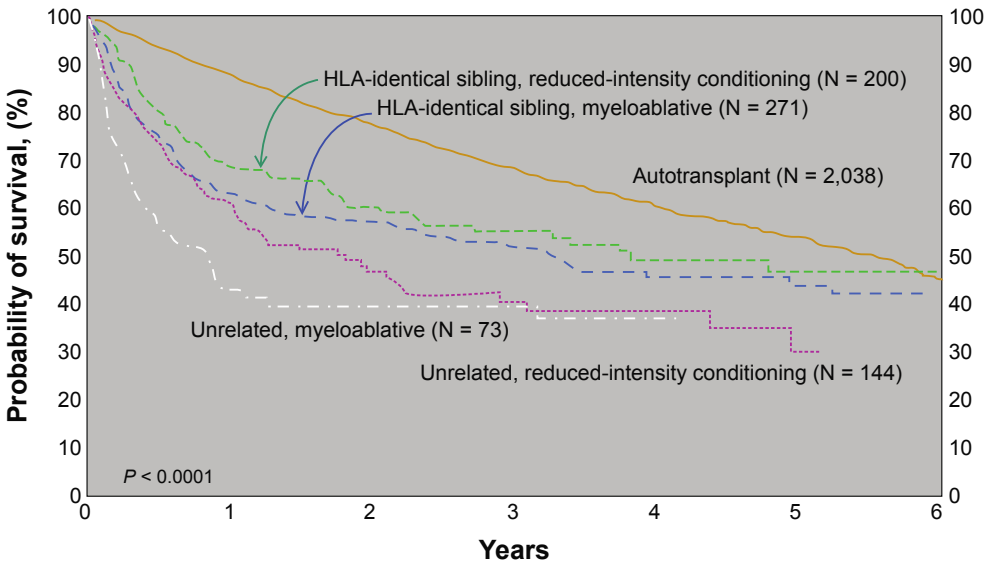

Figure 1. Probability of survival after transplants for MCL, 1998–2007 by donor type and conditioning regimen.[57]

rituximab or interferon-α. Despite similar CR and PFS rates after induction therapy between the two groups (34 vs. 40% and 28 vs. 26 months), the four-year OS was significantly better in the R-CHOP group (62 vs. 47%, $P = 0.005$) because of a higher incidence of deaths during remission in the R-FC group (10 vs. 4%).[58]

For some patients, however, the treatment with anthracycline-based regimens is not feasible because of the cardiotoxicity of this drug, mainly in the aged population with cardiovascular risk factors. Hence, it is essential to use alternative drugs with an acceptable toxicity profile and efficacy. Bendamustine has proved its efficacy in relapsed patients.[48,49] A recent phase III trial assessed the efficacy and safety profile of bendamustine in combination with rituximab (R-Benda) compared to R-CHOP in newly diagnosed patients with MCL.[59] The R-Benda group had a better median PFS rate compared to the R-CHOP group (35.4 vs. 22.1 months), although no statistical difference in OS was reported. A recent phase II trial combining bendamustine with rituximab, bortezomib, and dexamethasone was reported by the French Lymphoma Study Association (LYSA) group.[60] Although preliminary, this regimen showed a high response rate after six cycles with 75.5% of CR and 82% of molecular response. With a median follow-up of 17 months, the PFS at 15 months was 73%. An international phase III trial is currently ongoing to evaluate the safety and efficacy of Bruton's tyrosine kinase (BTK) inhibitor (ibrutinib) in association with rituximab and bendamustine in newly diagnosed MCL patients >65 years (see Table 2).

Bortezomib has also been used in first-line treatment for elderly MCL patients in a phase II study published by the French GOELAMS (Groupe Ouest-Est des Leucémies Aigues et Maladies du Sang) group.[61] Bortezomib was delivered at the standard dose of 1.3 mg/m^2/day on days 1, 4, 8, and 11 in association with rituximab (375 mg/m^2/day on day 1 (and day 8 on cycle 1)), doxorubicin (9 mg/m^2 as a continuous infusion from day 1 to 4), dexamethasone (20 twice daily from day 1 to 4), and chlorambucil (12 mg/day from day 20 to 29). The response rate was 76% (60% of CR) with a median PFS of 21 months. A randomized phase III study comparing R-CHOP to the same regimen where bortezomib replaced vincristine (VR-CAP) has been recently reported in newly diagnosed MCL patients not eligible for ASCT. With a median follow-up of 40 months, the median PFS was significantly longer in the bortezomib arm (24.7 vs. 14.4 months, $P < 0.001$), demonstrating the role of bortezomib in MCL.[62]

High-dose cytarabine has demonstrated its efficacy not only in the treatment of young patients but also in the treatment of elderly patients, achieving a high response rate but an unacceptable toxicity.[38] In an attempt to reduce the toxicity, cytarabine at a dose of 800 mg/m^2 was given in association with rituximab and bendamustine, showing an impressive ORR of 100% together with manageable toxicity.[63]

Intensive consolidation with high-dose chemotherapy and ASCT is usually not recommended for elderly patients over 65 years of age. However, for a minority of highly selected patients, it could be an acceptable option.[64]

Finally, the role of maintenance therapy in elderly patients with MCL has been assessed in the European MCL Network trial.[58] Patients allocated to maintenance therapy with rituximab exhibited a higher remission duration compared to the interferon-α group (75 vs. 27 months, respectively, $P < 0.001$). This difference was highly significant in the group of patients assigned to the R-CHOP induction regimen (median remission duration not reached vs. 23 months, $P < 0.001$) with a better OS ($P = 0.005$). Similarly, the effectiveness of radioimmunotherapy with 90-yttrium ibritumomab tiuxetan as the consolidation regimen has also been reported to improve the overall and CR rates after R-CHOP induction regimen.[65]

Salvage therapy. Until recently, salvage therapeutic options for elderly relapsed or refractory MCL patients and for younger patients not eligible to transplantation were limited. The role of bendamustine given alone or in combination has been discussed earlier.

Among the four drugs that have been approved, bortezomib monotherapy was the first drug to demonstrate its clinical activity for the treatment of relapsed/refractory MCL, leading to its approval by the FDA in 2006. The main results reported with bortezomib alone or in combination have been discussed previously.

Lenalidomide. Lenalidomide, the second-generation immunomodulatory compound, is another therapeutic approach that combines distinctive and synergistic effects.[66–68] There are some interesting data available with lenalidomide in the setting of relapsed MCL. As a single agent at a dose of 20–25 mg/day from day 1 to 21, ORR ranged between 28 and 53% with a median duration of response ranging from 13.7 to 22.2 months.[69–72] Lenalidomide has also been combined to rituximab, dexamethasone, or

Table 2. Main open studies of ibrutinib in combination with other drugs for MCL.

TRIAL	DRUGS' COMBINATION	PHASE	CONDITION
NCT01776840	Ibrutinib in combination with Rituximab and Bendamustine	III	MCL (front-line therapy)
NCT02159755	Ibrutinib in combination with Palbociclib Isethionate	I	MCL (previously treated)
NCT02269085	Ibrutinib in combination with Carfilzomib	I/II	MCL (R/R)
NCT01955499	Ibrutinib in combination with Lenalidomide	I	MCL (R/R)

Abbreviations: MCL, mantle cell lymphoma; R/R, relapsed/refractory.

bortezomib in phase I/II studies, achieving an ORR between 40 and 82% and a median response duration about 18 months.[73–75] Given these results, the FDA recently approved lenalidomide for the treatment of relapsed/refractory MCL.

Temsirolimus. Temsirolimus is an mTOR inhibitor with antiproliferative and antiangiogenic effects. It blocks the PI3K cascade signaling pathway, leading to cell cycle arrest and apoptosis.[76] Based on encouraging phase II trials demonstrating the efficacy of temsirolimus in the treatment of MCL patients,[77,78] a phase III trial has been conducted in patients with relapsed or refractory MCL, leading to the approval of temsirolimus by the European Medicines Agency (EMA). In this study, temsirolimus was randomly given according to two different schedules (175 mg weekly for three weeks, followed by either 75 or 25 mg weekly) and compared to investigator's choice of monotherapy that was in most cases gemcitabine (42%) or fludarabine (27%). The 175/75 mg group was associated with the best response rate (22 vs. 2%) and a prolonged OS (12.8 vs. 9.7 months) over the investigator's choice group.[79]

Temsirolimus has also been investigated in combination with other drugs. In a phase II study reported by Ansell and colleagues, 69 patients with relapsed or refractory MCL were treated with rituximab (375 mg/m^2/week) and temsirolimus (25 mg/week). The ORR was 59%, including a CR in 19% of patients, and 63% in rituximab-sensitive patients.[80] A LYSA phase 1b trial evaluating the combination of temsirolimus with R-CHOP, R-FC, or R-cytarabine is still ongoing (ClinicalTrials.gov identifier NCT01389427).

Ibrutinib. Among the BCR signaling cascade, the BTK is an essential downstream mediator that is activated through the antigen binding and oligomerization of B-cell receptors.[81] The constitutive activation of the components of this pathway contributes to tumor proliferation and survival.[82] Ibrutinib, a selective and irreversible BTK inhibitor, was the first compound to be tested in B-cell malignancies. After the promising results of a phase I study showing an ORR of 54%,[83] a multicenter phase II trial in heavily pretreated elderly relapsed/refractory MCL patients showed an ORR of 68% (21% CR) among the 111 evaluable patients and a median PFS of 13.9 months with an increasing response over time.[84] A phase III study evaluating ibrutinib versus temsirolimus has recently achieved the expected recruitment, and the results are awaited (ClinicalTrials.gov identifier NCT01646021). The main studies with ibrutinib in combination with other drugs currently opened for recruitment are summarized in Table 2.

Ibrutinib is now approved by FDA for MCL patients in second-line treatment since November 2013 and has just been approved by the EMA (October 2014) for the treatment of patients with relapsed/refractory MCL.

New-targeted Therapies for MCL

Phosphatidylinositol 3-kinase (PI3K) inhibitors. The PI3K/AKT pathway has been shown to play a key role in cell proliferation and survival and represents a potential target in MCL.[85] PI3K inhibitors are effective in PI3K-driven tumors.[86] Two class I PI3K isoform inhibitors have been tested in the setting of relapsed MCL, the oral isoform-selective inhibitor PI3Kδ (CAL-101/GS-1101, idelalisib), which blocks survival signals, induces apoptosis, and disrupts signals from the tumor microenvironment to B-cell malignancies,[87–89] and the more pleiotropic PI3Kα-δ (copanlisib, BAY 80-6946), which exhibits preferential inhibition of AKT phosphorylation, superior antitumor activity, and potent apoptosis activity to induce apoptosis.[90] A phase I trial of idelalisib in heavily pretreated patients with MCL confirmed the activity of this compound with an ORR of 40% (5% CR) and a one-year PFS rate of 22%.[91] Copanlisib, which is administered intravenously, has been evaluated in a phase II study in patients with different lymphoma subtypes, including seven patients with MCL. The ORR was 71% (one uCR and four Partial Response (PR).[92]

Other BTK inhibitors. Apart from ibrutinib, there are several BTK inhibitors that are in clinical or preclinical development for various B-cell malignancies.[82]

Other drugs. Some other new drugs still under investigation, either alone or in combination, display an interesting panel of activity with objective responses in phase I or II trials. Among these new compounds, inhibitors of the cyclin-dependent kinase (CDK) complex,[93–95] ABT-199, a second-generation BCL-2-specific BH3 mimetic,[96] and abexinostat, a pan histone deacetylase inhibitor,[97] are the most promising drugs at this time.

Conclusions

During the last decades, significant improvements in the pathogenesis and the treatment of MCL have been made, contributing to prolonged survivals and better outcomes. Intensive chemotherapy with autologous stem cell support in young patients as well as maintenance treatment with rituximab in the elderly have permitted a better disease control. Molecular remission achievement has been demonstrated to be of major importance for long-lasting remissions. However, most patients will eventually relapse and die from the disease. The identification of multiple signaling pathways in the development of the disease, together with the availability of new-targeted therapeutic compounds, offers a novel and innovative era of opportunities with promising results. The incorporation of these new agents into the first-line regimens will perhaps change the landscape of MCL in the near future.

Author Contributions

Concieved and designed the experiments: KB. Analyzed the data: KB. Wrote the first draft of the manuscript: KB. Contributed to the writing of the manuscript: KB. Agree with manuscript results and conclusions: KB, NM. Jointly developed the structure and arguments for the paper: KB, NM. Made critical revisions and approved final version: KB, NM. Both authors reviewed and approved of the final manuscript.

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