

Turning Point in the Treatment of Mantle Cell Lymphoma

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ABSTRACT

Mantle cell lymphoma (MCL) is an incurable type of B-cell lymphoma. It is typically composed of small-to-medium-sized cleaved lymphoid cells with cyclin D1 protein expression due to the chromosomal translocation t(11;14)(q13;q32). Even with the development of rituximab, an anti-CD20 antibody drug, the long-term outcome of patients with MCL has not improved. Recently, new agents have been used in clinical settings, and the outcome of patients with MCL is expected to improve. The treatment of MCL may be at a turning point from intensive chemotherapy to chemotherapy-free treatment. In this study, a recent progress in the diagnosis and treatment of MCL is reviewed.

Key words bendamustine; bortezomib; ibrutinib; lymphoma; mantle-cell

Mantle cell lymphoma (MCL) is a mature B-cell neoplasm accounting for 2%–6% of non-Hodgkin lymphomas.^{1,2} Until 1991, the following names for lymphoma were used to refer to MCL: centrocytic lymphoma, intermediate lymphocytic lymphoma, mantle-zone lymphoma, lymphocytic lymphoma of intermediate differentiation, multiple lymphomatous polyposis, and mantle cell-derived lymphoma. Their association with a specific chromosomal abnormality (t(11;14)(q13;q32))³ and the identification of a novel cyclin gene at the breakpoint locus⁴ lead to the identification of MCL.⁵ In most patients with MCL, the cyclin D1 gene *CCND1* on 11q13 is relocated adjacent to the immunoglobulin heavy chain gene *IGH* on 14q32 due to chromosomal translocation t(11;14)(q13;q32), and this results in the overexpression of cyclin D1 protein in the nucleus (Fig. 1).⁶

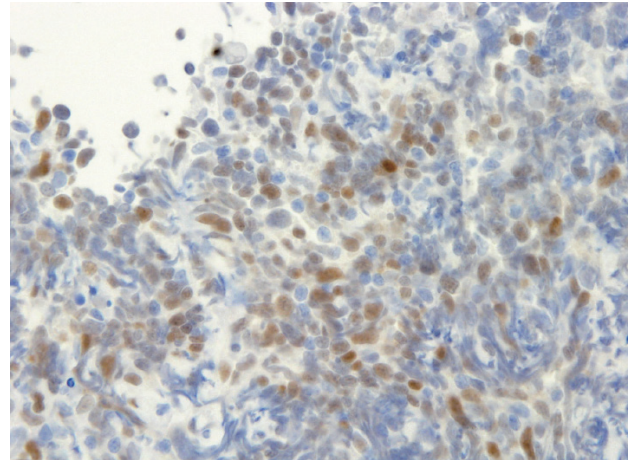


Fig. 1. Immunohistochemistry of cyclin D1 protein. Cyclin D1 protein was positive in the nuclei of mantle cell lymphoma cells.

Despite its small-to-medium-sized cells and indolent clinical behavior, patients with MCL frequently experience relapse and have a poor prognosis even after intensive chemotherapy. With the development of novel agents, the outcomes of patients with MCL substantially improved even in actual clinical settings.⁷ This review discussed the recent progress in the diagnosis and treatment of MCL particularly focusing on the novel agents available in Japan, which include bendamustine, bortezomib, and ibrutinib.

DIAGNOSIS

Typical MCL

MCL is commonly composed of small-to-medium-sized cleaved lymphoid cells, which are proliferating diffusely or vaguely in the nodules. Immunohistochemistry of lymphoma cells shows positivity for CD5, CD10, CD19, CD20, CD79a, and cyclin D1. Cyclin D1 positivity in the nucleus due to typical chromosomal translocation t(11;14)(q13;q32) supports the diagnosis, although cyclin D1 is also overexpressed in patients with multiple myeloma with the same chromosome aberration and hairy cell leukemia without any translocation, both of which are readily differentiated by the typical characteristics of their morphology and clinical presentation. MCL is usually in advanced stage when diagnosed, and extranodal involvement is common. The clinical course is

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Abbreviations: CR, complete response rate; HCVAD/MA, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine; MCL, mantle cell lymphoma; MIPI, mantle cell lymphoma international prognostic index; OR, overall response rate; PFS, progression-free survival; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

indolent, and relapse frequently occurs after the standard chemotherapy for non-Hodgkin lymphoma. The MCL international prognostic index (MIPI) was elaborated with 455 patients with advanced stage MCL.⁸ The index was composed of age, Eastern Cooperative Oncology Group performance status, lactate dehydrogenase level, and white blood cell count, and it was modified with the incorporation of Ki-67 positivity.⁹ Furthermore, tumor cells can be detected using polymerase chain reaction in the peripheral blood and/or bone marrow in 90% of patients with advanced MCL upon diagnosis, and minimal residual disease assessment at the level of 10⁻⁵ has an impact on predicting prognosis.¹⁰ In addition, cyclin D1-negative MCL exist with cyclin D2 or cyclin D3 overexpression, which may substitute cyclin D1.¹¹ Cyclin D1 negativity is associated with better prognosis independent from other risk factors.¹²

Leukemic non-nodal MCL

t(11;14)(q13;q32) with complex cytogenetics expressing cyclin D1 mRNA was observed in a patient with prolymphocytic leukemia.¹³ Then, the leukemic variants of MCL were repeatedly reported.¹⁴ Among them, the indolent subtype of leukemic MCL was considered as leukemic non-nodal MCL, which developed through a pathway different from that of typical MCL.^{15, 16} This subtype is notably lacking in the expression of SOX11 protein, which is highly expressed in typical MCL.¹⁶

Blastoid and pleomorphic variant of MCL

The acquisition of *TP53* mutations and other oncogenic abnormalities leads to the blastoid and pleomorphic variants of MCL that have poor prognosis.^{17, 18} These cases often have tetraploid DNA contents.¹⁹ The emergence of tetraploids can be recapitulated with mouse fibroblasts transduced with *TP53* mutation that are selected under *K* condition.²⁰ In evolutionary biology, *K*-selection was initially used to describe species evolution in isolated islands; *K* is the carrying capacity of the environment, i.e., the number of individuals in a population of a given species at the population equilibrium. Thus, the development of these variants may be associated with *K* selection during the evolution of MCL cells.

In-situ mantle cell neoplasia

Cells with cyclin D1 protein overexpression may be incidentally found in the mantle zone of lymphoid follicles in otherwise reactive lymph nodes. These cells may be the precursors of MCL; however, a low risk of developing overt MCL was observed.¹⁶

TREATMENT

Rituximab-based intensive chemotherapy

With the development of rituximab, anti-CD20 antibody drug, immunochemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) has substantially improved the outcome of patients with aggressive B-cell lymphomas. However, the long-term outcome of patients with MCL has not improved with the R-CHOP regimen. Intensive immunochemotherapy regimens, such as rituximab-based hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose methotrexate and cytarabine (R-HCVAD/MA), and MCL2 protocols conducted by the Nordic Lymphoma Group have significantly improved the outcomes of younger patients with MCL in general (median overall survival [OS]: 11-13 years), which impressed the efficacy of high-dose cytarabine as the frontline treatment of MCL (Table 1).^{21, 22} Furthermore, rituximab-based chemotherapy with high-dose cytarabine followed by autologous stem cell transplantation and rituximab maintenance was a better approach for younger patients with MCL in randomized studies.^{23, 24} Even after the introduction of intensive chemotherapy, MIPI can still discriminate risk groups and identify patients with poor prognosis.²⁵ Recently, Eskelund et al. have evaluated the prognostic value of recurrent genetic aberrations in MCL and found that *TP53* mutations but not deletions retained the prognostic impact for OS in multivariate analyses.²⁶ *TP53*-mutated MCL cells may not be eradicated by intensive therapy, and patients with *TP53*-mutated MCL still have a dismal outcome with a median OS of 1.8 years.²⁶ Thus, new treatment strategy using novel agents other than intensive chemotherapy should be explored for patients with *TP53* mutations. Intriguingly, MIPI loses the potency of risk discrimination in patients without *TP53* mutations, and this indicated the need for a new prognostic model other than MIPI.

Bendamustine

Bendamustine is composed of two chemical structures. One is that of alkylating agents and the other is that of purine analogues. It was developed in East Germany in the Cold War era and found to be effective for non-Hodgkin lymphoma in the 21st century. Bendamustine plus rituximab is the first regimen that is non-inferior to the R-CHOP regimen for the treatment of untreated indolent lymphoma and MCL in the randomized clinical trial (Table 2).^{27, 28} Because of fewer toxic effects, bendamustine is a preferred substitute for all 4 drugs of the CHOP regimen. Compared with the R-HCVAD/MA regimen

Table 1. Selective studies of intensive immunochemotherapy for untreated MCL

Phase	Treatment	<i>n</i>	Median age, years (range)	OR, % (CR)	Survival	TRM	Reference
II single-center	R-HCVAD/MA	97	61 (41–80)	97 (87)	median FFS: 4.8 years, OS: 10.7 years, 5-years FFS: 49%, OS: 67%, 10-year FFS: 26%, OS: 52% 15-year FFS: 22%, OS: 33%	4%	Chihara et al. 2016 ²¹
II multicenter	R-Maxi-CHOP + HDA + ASCT (MCL2)	159	56 (32–65)	96 (82)	median PFS: 8.5 years, OS: 12.7 years	5%	Eskelund et al. 2016 ²²
III randomized	R-CHOP + dexamethasone/BEAM/TC-ASCT vs R-CHOP/R-DHAP + TAM-ASCT	234 vs 232	55 (IQR: 49–60)	97 (76) vs 98 (83)	5-year TTF: 40% vs 65%, OS: 68% vs 76% median TTF: 3.9 years vs 9.1 years, OS: NR vs 9.8 years	3.4% vs 3.4%	Hermine et al. 2016 ²³
III randomized	R-DHAP + ASCT + none vs Rm	299 (120 vs 120)*	57 (27–65)	83 (77)	4-year PFS: 68%, OS: 78% 4-year EFS: 61% vs 79%, OS: 80% vs 89%*	4%	Le Gouill et al. 2017 ²⁴
II multicenter	R-High-CHOP/CHASER + LEED-ASCT	45	59 (35–65)	96 (82)	median PFS 3.7 years, 2-year PFS 77% 5-year PFS: 52%, OS: 71%	0%	Ogura et al. 2018 ⁴⁷

*after transplantation.

ASCT, autologous stem cell transplantation; CHASER, cyclophosphamide, high-dose cytarabine, dexamethasone, etoposide, and rituximab; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response rate; dexamethasone, carmustine, etoposide, cytarabine, and melphalan/total body irradiation and cyclophosphamide; DHAP, dexamethasone, high-dose cytarabine, and cisplatin; EFS, event-free survival; FFS, failure-free survival; HCVAD/MA, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose cytarabine and methotrexate; HDA, high-dose cytarabine; IQR, interquartile range; LEED, melphalan, cyclophosphamide, etoposide, and dexamethasone; MCL, mantle cell lymphoma; *n*, number of patients; NR, not reached; OR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; Rm, rituximab maintenance; TAM, total body irradiation, high dose cytarabine, and melphalan; TRM, treatment-related mortality; TTF, time-to-treatment failure.

Table 2. Selective studies of bendamustine-based therapy for untreated MCL

Phase	Treatment	<i>n</i>	Median age, years (range)	OR, % (CR)	Survival	TRM	Reference
III randomized	R-Bendamustine vs R-CHOP	46 vs 48	70 (65–74)	93 (40)* vs 91 (30)*	median PFS: 35.4 months vs 22.1 months	0.4%* vs 2.0%*	Rummel et al. 2013 ²⁷
III randomized	R-Bendamustine vs R-CHOP/R-CVP	34 vs 33	60 (28–84)* vs 58 (25–86)*	94 (50) vs 85 (27)	NA	0.5%* vs 0.5%*	Flinn et al. 2014 ²⁸
II two-center	R-Bendamustine + HDA + ASCT	23	57 (42–69)	96 (96)	1-year PFS: 96%, OS: 96%	0%	Armand et al. 2016 ³⁰
II randomized, closed prematurely	R-HCVAD/MA + ASCT vs R-Bendamustine + ASCT	17 vs 35	59 (44–66) vs 57 (33–64)	94 (35) vs 83 (40)	2-year PFS: 82% vs. 81%, OS: 88% vs. 87%	NA	Chen et al. 2017 ²⁹
II multicenter	R-Bendamustine + low-dose cytarabine (RBAC500)	57	71 (61–79)	91 (91)	2-year PFS: 81%, OS: 86%	0%	Visco et al. 2017 ³¹

*not restricted to MCL.

ASCT, autologous stem cell transplantation; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response rate; CVP, cyclophosphamide, vincristine, and prednisone; HDA, high-dose cytarabine; HCVAD/MA, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with high-dose cytarabine and methotrexate; MCL, mantle cell lymphoma; *n*, number of patients; NA, not available; OR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; TRM, treatment-related mortality.

Table 3. Selective studies of bortezomib-based therapy for untreated MCL

Phase	Treatment	<i>n</i>	Median age, years (range)	OR, % (CR)	Survival	TRM	Reference
II multicenter	RiPAD + C	39	72 (65–80)	79 (59)	median PFS: 26 months, OS: NR	5%	Houot et al. 2012 ³⁵
III randomized	R-CHOP vs VR-CAP	244 vs 243	66 (26–88)	89 (42) vs 92 (53)	median PFS: 14.4 months vs 24.7 months, OS: 56.3 months vs NR	3% vs 2%	Robak et al. 2015 ³²
II two-center	Bortezomib + R + HCVAD/MA	95	61 (38–75)	100 (82)	median TTF: 55 months	4%	Romaguera et al. 2018 ³⁶
II four-center	Bortezomib + R + modified HCVAD + Rm	30	61 (48–74)	90 (77)	median PFS: 8.1 years, 6-year PFS: 53%, OS: 70%	3%*	Chang et al. 2018 ⁴⁸

*following allogeneic stem cell transplant.

CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CR, complete response rate; HCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MA, high-dose cytarabine and methotrexate; MCL, mantle cell lymphoma; *n*, number of patients; NR, not reached; OR, overall response rate; OS, overall survival; PFS, progression-free survival; R, rituximab; RiPAD + C, rituximab, bortezomib, doxorubicin, dexamethasone, and chlorambucil; Rm, rituximab maintenance; TRM, treatment-related mortality; TTF, time-to-treatment failure; VR-CAP, bortezomib, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Table 4. Selective studies of chemotherapy-free treatment for MCL

Phase	Treatment	<i>n</i> *	Median age, years (range)	OR, % (CR)	Survival	TRM	Reference
II multicenter	Ibrutinib	111	68 (40–84)	68 (21)	median PFS: 13.9 months, 18-month OS: 58%	1%	Wang et al. 2013 ³⁸
II multicenter	Ibrutinib	16	72 (55–83)	88 (13)	6-month PFS: 88%	0%	Maruyama et al. 2016 ⁴⁹
III randomized	Ibrutinib vs temsirolimus	280	68 (IQR: 13)	72 (19) vs 40 (1)	median PFS: 14.6 months vs 6.2 months, 1-year OS: 68% vs 61%	6% vs 8%	Dreyling et al. 2016 ³⁹
II single-center	Ibrutinib and rituximab	50	67 (45–86)	88 (44)	1-year PFS: 75%, OS: 86%	2%	Wang et al. 2016 ⁴³
II multicenter	Lenalidomide and rituximab	38 [†]	65 (42–86)	92 (64)	3-year PFS: 80%, OS: 90%, 5-year PFS: 64%, OS: 77%	0%	Ruan et al. 2018 ⁴⁵
II two-center	Ibrutinib and venetoclax	24 [‡]	68 (47–81)	71 (71)	1-year PFS: 75%, OS: 79%	8%	Tam et al. 2018 ⁴⁶

*relapsed or refractory MCL if not otherwise described. [†]untreated MCL. [‡]not restricted to relapsed or refractory MCL.

CR, complete response rate; IQR, interquartile range; MCL, mantle cell lymphoma; *n*, number of patients; OR, overall response rate; OS, overall survival; PFS, progression-free survival; TRM, treatment-related mortality.

as a pre-transplant induction regimen for younger patients, bendamustine plus rituximab showed a similar efficacy, and it can achieve a deep remission with a better mobilization success.²⁹ Furthermore, the phase 2 study of immunochemotherapy followed by autologous stem cell transplantation for transplant-eligible patients with MCL using bendamustine plus rituximab and then high-dose cytarabine plus rituximab showed a promising result and must be further assessed in comparative studies.³⁰ In addition, low-dose cytarabine instead of high-dose one may have a role in the treatment of MCL and must be studied in randomized trials.³¹

Bortezomib

Bortezomib is the first proteasome inhibitor used in clinical practice. The use of bortezomib rather than vincristine in the standard R-CHOP regimen (VR-CAP) had a better efficacy than the R-CHOP regimen for transplant-ineligible patients at the cost of increased hematologic toxicity (Table 3).³² The *post-hoc* analysis of this study showed the clear relationship between higher cumulative bortezomib dose and longer OS, and this result indicates the role of bortezomib in the treatment strategy for elderly patients with MCL in the condition of improved supportive care and optimization of bortezomib dose.³³ Notably, bortezomib-based therapy is associated with a high incidence of painful peripheral

neuropathy and herpes zoster, which requires dose adjustment and antiviral prophylaxis particularly in elderly patients.³⁴⁻³⁶

Ibrutinib

Ibrutinib is a first-in-class drug taken once daily via oral route, and it is a covalent inhibitor of Bruton tyrosine kinase, which is important for signaling via B-cell receptors and other B-cell surface receptors. Ibrutinib binds covalently to the kinase and inhibits B-cell receptor signaling leading to downstream mitigation of cell growth, proliferation, survival, adhesion, and migration. Bruton tyrosine kinase is commonly overexpressed in MCL, and its inhibition by ibrutinib induces apoptosis.³⁷ A phase 2 study of ibrutinib involving patients with relapsed or refractory MCL had the best overall response rate (OR) of 68%, a complete response rate (CR) of 21%, and a median progression-free survival (PFS) of 13.9 months,³⁸ and a phase 3 trial had an OR of 72%, a CR of 19%, and a median PFS of 14.6 months (Table 4).³⁹ Interestingly, as observed in patients with chronic lymphoid leukemia, ibrutinib dose-dependently inhibits the adhesion and migration of MCL cells, resulting in transient lymphocytosis in patients with MCL who experience bone marrow involvement.^{40, 41} The common or serious side effects of ibrutinib include bleeding due to platelet dysfunction,⁴² diarrhea, rash, and atrial fibrillation.^{38, 39}

Moving towards chemotherapy-free treatment

Immunochemotherapy recommended for young fit patients with MCL, which is usually combined with autologous stem cell transplantation, is rarely performed in frail patients with comorbidities and elderly patients. If the risk among patients with MCL is low based on MIPI, the “watch and wait” strategy is an option particularly for elderly patients. However, novel agents without severe adverse effects are available and are given in outpatient clinics. Among them, the single use of bendamustine or in combination with rituximab is effective. Alternatively, chemotherapy-free regimens are preferred for elderly patients because it causes less severe hematologic toxicity. Ibrutinib can be administered orally, and the dose is adjusted for each patient. In addition, the combination of ibrutinib and rituximab showed favorable results for the treatment of relapsed MCL in the single-center phase 2 trial (Table 4).⁴³ Although ibrutinib antagonized the rituximab anti-lymphoma effect in a mouse model partly via the off-target inhibition of interleukin-2-inducible tyrosine kinase in natural killer cells,⁴⁴ a randomized trial of ibrutinib with rituximab against standard immunochemotherapy as first-line therapy is being conducted

(EudraCT Number: 2015-000832-13).

Furthermore, lenalidomide, a second-generation immunomodulatory compound, is an emerging new player in the treatment of lymphoma, and it was approved for the treatment of patients with relapsed or refractory MCL by the Food and Drug Administration in the United States in 2013. It has been approved in Japan for adult T-cell leukemia/lymphoma. A long-term follow-up in the phase 2 study of the R-squared regimen, i.e., lenalidomide and rituximab, for untreated MCL had 5-year PFS of 64% and OS of 77%; The OR was 92% and CR was 64%.⁴⁵ A randomized phase 3 trial on lenalidomide compared with placebo in combination with rituximab is being conducted for the treatment of relapsed or refractory indolent lymphoma (ClinicalTrials Number: NCT01938001), and favorable results were observed. Another emerging compound is venetoclax, a BCL-2 inhibitor, which has been approved by the Food and Drug Administration for the treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma. The combination of venetoclax and ibrutinib improved the outcome of patients with MCL who had been predicted to have poor outcomes with current therapy.⁴⁶

CONCLUSION

For young fit patients with MCL, intensive immunochemotherapy with autologous stem cell transplantation is still recommended. However, novel approaches should be examined for a high-risk subgroup of patients with *TP53* mutations. In addition, less intensive regimens using new agents should be compared with intensive approaches, and the establishment of frontline chemotherapy-free treatment is eagerly awaited. We should focus on the progress of clinical trials on new agents since we are at a turning point from intensive immunochemotherapy to less toxic chemotherapy-free treatment. In the near future, the outcome of patients with MCL is expected to be further improved.

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