Comprehensive Review

Mantle Cell Lymphoma: New Treatments Targeted to the Biology

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Abstract

Mantle cell lymphoma (MCL) represents a distinct lymphoma subtype. The prognosis of patients with MCL is the poorest among lymphoma patients and the response to conventional treatments is inadequate. New approaches targeted to the biology of MCL and the genetics underlying the disease are being studied. Monoclonal antibodies directed at molecules expressed on MCL cells are already used in the clinical setting. This article reviews the literature on these and other new possible treatment modalities.

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Introduction

Mantle cell lymphoma (MCL) represents approximately 6% of all non-Hodgkin's lymphomas.[1] Despite being previously considered a low-grade and indolent lymphoma, it appears to have the worst characteristics of both low- and high-grade lymphomas: incurability and rapid growth.[2] Mantle cell lymphoma patients have a median age of > 60 years, are predominantly male, and often have disseminated disease at diagnosis. Mantle cell lymphoma median time to progression and survival are the shortest among all lymphoma subtypes.[1]

Mantle cell lymphoma comprises a group of lymphoma subtypes previously classified as centrocytic lymphoma, lymphocytic lymphoma of intermediate differentiation, intermediate cell lymphoma, or diffuse small cleaved–cell lymphoma.[2-7] Two main cytologic subtypes, typical and blastoid (blastic) variant, are recognized in the new World Health Organization classification.[8] Mantle cell lymphoma seems to derive from a subset of antigen-naive pregerminal center B cells localized in primary follicles or in the mantle region of secondary follicles. Mantle cell lymphoma cells express moderate to strong IgM and/or IgD surface immunoglobulins and pan B-cell antigens (CD19, CD20, CD22, CD24).[2,4,5,7,9] They are positive for CD79a, CD5, CD43, and cyclin D1, but are negative for CD23 and CD10. The genetics of MCL are characterized by the presence of the t(11;14)(q13;q32) translocation that determines cyclin D1/*Bcl-1* deregulation, in association with other molecular abnormalities mainly involving the cell cycle.[4] A series of prognostic factors have been associated with worse outcome: blastoid variant, high mitotic index, high International Prognostic Index, blood involvement, male sex, high serum β_2-microglobulin levels, P53 inactivation, loss of P27 expression, and karyotype complexity.

Many of the published papers on MCL treatment are retrospective studies, and data regarding MCL have often been extrapolated from series including other lymphoma subtypes together with untreated and treated patients in the prospective studies. Currently, there is no convincing evidence that any conventional chemotherapy regimen is curative.[2,7,10,11] Doxorubicin-containing regimens appear more effective than those without doxorubicin. Studies to date fail to demonstrate a plateau in the survival curve, which normally indicates a potential for cure.[12-19] In response to the failure of MCL to conventional chemotherapies, high-dose regimens with autologous or allogenic bone marrow transplantation (BMT) have been performed in younger MCL patients.[20-27] The published studies of intensive chemotherapy associated with total-body irradiation, followed by autologous stem cell transplant or purged BMT yielded mixed, and generally rather disappointing, results.[28,29] A retrospective analysis of the European Group for Blood and Marrow Transplantation database, comprising 150 evaluable patients with MCL treated with autologous BMT, underlined that there is no plateau of the overall survival (OS) curve.[30] The inclusion of high-dose methotrexate or cytarabine in preconsolidation regimens improved outcome and may be an advance in therapy.[29,31,32] In this article, the current literature regarding therapeutic strategies related to the biology and genetics underlying MCL is reviewed (Table 1).

Monoclonal Antibodies

Mantle cell lymphoma cells express the pan B-cell antigen CD20. This antigen is normally expressed on the surface of B cells from the early pre-B stage to the mature B stage, but is ab-

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sent on immunoglobulin-secreting plasma cells. The CD20 has 4 predicted membrane-spanning domains with both C and N termini located in the cytoplasm; only a small portion of the molecule is on the external cell surface. The molecule is neither shed nor secreted and is not internalized after binding with different monoclonal antibodies (B1, 1F5, C2B8) recognizing different epitopes of this surface fragment (Table 2).

Rituximab

Rituximab (Rituxan®, IDEC-C2B8, Genentech Inc, South San Francisco, CA, and IDEC Pharmaceutical Corporation, San Diego, CA; MabThera®, Hoffman-La Roche, Basel, Switzerland) is the anti-CD20 compound most commonly used in the clinical setting. It is commercially available for relapsed or refractory indolent lymphomas in Europe and in the United States.[33-35]

Clinical Development of Rituximab. The function of the CD20 molecule and the actual mechanism of action of anti-CD20 monoclonal antibodies are still unclear. The effect of anti-CD20 ligands seems to depend heavily on the nature of the CD20 epitopes recognized by the antibodies, the differentiation stage of the lymphoma cell, and the presence of potential cosignals. The effects are broad, spanning from increased proliferation to growth arrest, and from inhibition to induction of apoptosis. The cascade of events following CD20 binding by antibodies comprise the activation of the Src family kinases p56/53^{lyn}, p56^{lck}, and p59^{fyn}, with tyrosine phosphorylation of phospholipase C-γ1 and C-γ2, a calcium influx, and caspase-3 activation.[36] The precise order of these events is not fully elucidated. CD20 itself, with its 4 transmembrane domains, may be a calcium-ion channel[36] or, alternatively, could induce calcium influx via the protein tyrosine kinase activity.[37] CD20–mediated apoptosis requires kinase activation, calcium influx, and caspase activation.[37-39] Different mechanisms seem to cooperate in the anti-CD20–mediated cell killing, and probably depend on the clonal neoplastic cell biology (Table 3). Anti-CD20 antibodies alone induce only weak growth arrest and apoptosis on lymphoma cell lines.[38,40-42] The in vitro direct growth arrest and proapoptotic effect is increased when rituximab is used as a homodimer or cross-linked with goat antimouse IgG,[37,40,43,44] causing a clustering of CD20 molecules. The same effect can also be obtained using rituximab in the presence of Fc receptor–expressing cells.[43]

Potential Mechanism of Action. The main mechanisms of action of rituximab are antibody-dependent cytotoxicity and complement-mediated cytotoxicity (CDC), by a caspase-independent mechanism.[41,42,45,46] The effect of the latter is regulated by the possible presence on the cell surface of complement inhibitors such as CD35, CD55, and CD59.[42,45,47] Anti-CD59 strongly increases in vitro CDC, suggesting that the combination of anti-CD20 and anti-CD59 monoclonal antibodies could result in better antitumor activity.[42,45,47] However, a later study failed to confirm this and did not show any correlation between the levels of CD55 and CD59 expressed on MCL cells and their in vivo and in vitro response rate to rituximab.[48] The alternative caspase-dependent killing mechanism[37,39,44] suggests the combination with agents modulating the apoptotic machinery.[49,50]

Table 1 New Possible Therapies in Mantle Cell Lymphoma

Therapeutic Approach	Stage of Development
Monoclonal antibodies	Clinical use/Clinical trials
Cyclin-dependent kinase inhibitors	Clinical trials
Proteasome inhibitors	Clinical trials
DNA vaccines	Clinical trials
Modulation of polyamine synthesis	Clinical trials

An alternative mechanism of action has been reported in acquired immune deficiency syndrome–related lymphoma cell lines.[50] Rituximab downregulates interleukin-10 (IL-10) expression, with subsequent downregulation of *bcl-2,* an IL-10 target gene, sensitizing the cells to chemotherapy-induced apoptosis. As IL-10 seems to play an important role in MCL proliferation,[51] it will be interesting to see if a similar effect can be seen in MCL.

Multicenter Phase II Trials. Few clinical studies have been published on rituximab (Table 4). In a multicenter phase II trial from Europe and Australia, the overall response (OR) to rituximab was 33% (4 out of 12 evaluable MCL patients).[52] The response rate was similar to that observed in the diffuse large B-cell lymphoma subgroup (11 out of 30, 37%). Sixty-seven assessable MCL patients were treated with rituximab (a standard dose of 375 mg/m^2/week × 4) within a European multicenter phase II study.[53] The OR was the same in treated and untreated patients: 38% (12 out of 32) and 37% (13 out of 35), respectively. However, the complete remission (CR) rates were only 16% (5 out of 32) and 14% (5 out of 35) in the 2 groups, with a median duration of response of 1.2 years. Elevated lactate dehydrogenase at the time of therapy, and prior therapy with alkylating agents were associated with a significantly lower

Table 2 Anti-CD20 Monoclonal Antibodies Used in the Clinical Setting

Monoclonal Antibody	Origin	Commercial Name
Rituximab; IDEC-C2B8	chimeric	Rituxan®, MabThera®
^{90}Y-Ibritumomab tiuxetan; IDEC-Y2B8	murine	Zevalin™
Tositumomab/^{131}I-Tositumomab; anti-B1	murine	Bexxar®
^{131}I-IDEC-C2B8	chimeric	–
^{111}In-Ibritumomab tiuxetan; IDEC-In2B8	murine	*

*Used for imaging and dosimetry before IDEC-Y2B8

Table 3 Anti-Lymphoma Mechanisms of Anti-CD20 Monoclonal Antibodies

Antibody-dependent cytotoxicity
Complement-mediated cytotoxicity
Growth arrest
Induction of apoptosis
Chemosensitization

OR.[54] In another small study, 2 of 10 MCL patients (20%) had a partial response with rituximab.[55] In the Swiss Group for Clinical Cancer Research (SAKK) protocol 35/98, MCL patients were randomized between the standard rituximab scheme with or without 4 additional rituximab courses, at 2-month intervals.[56] Preliminary results on the first 36 MCL cases showed an OR of 22% with no CR at 12 weeks, in comparison to an OR of 52% in follicular lymphomas.

Rituximab and Combination Chemotherapy. In vitro data suggest that anti-CD20 antibodies sensitize cells to antineoplastic drugs and to toxins.[40,44,57-60] Clinical trials combining rituximab with chemotherapy regimens are open for MCL patients. The CHOP (cyclophosphamide/doxorubicin/vincristine/prednisone) regimen combined with rituximab has already shown encouraging results in follicular and diffuse large B-cell lymphomas.[61-63] A phase II trial of CHOP plus concomitant rituximab showed a 48% CR rate in untreated MCL patients, but none of the responses lasted longer than 36 months.[64] The German Low-Grade Lymphoma Study Group randomized 27 MCL patients to FCM (fludarabine/cyclophosphamide/mitoxantrone) with or without rituximab; the OR rate was 77% versus 27%, respectively with no apparent increase in toxicity.[65] Concurrent rituximab has been added to the highly effective HCVAD (hyper-cyclophosphamide, vincristine, doxorubicin, dexamethasone, high dose of cytarabine and methotrexate with leucovorin rescue therapy) regimen,[19,32] replacing BMT in untreated patients achieving CR after chemotherapy.[19,66] The CR rate was 92% (54 out of 59) with a similar response rate among patients > 65 years of age (21 out of 23, 91%) and ≤ 65 years of age (33 out of 36, 92%; Table 5).[66] With a median follow-up of 14 months, the addition of rituximab to the HCVAD (R-HCVAD) suggested that BMT is unnecessary for patients ≤ 65 years of age and appeared to improve the prognosis in the older subset of patients (Table 5).

Table 4 Results Obtained with Rituximab as a Single Agent in Patients with Mantle Cell Lymphoma

Study	No. of Patients	Overall Response Rate	Complete Remission Rate
Coiffier et al[52]	12	33%	0%
Foran et al[54]	87	34%	14%
Nguyen et al[55]	10	20%	0%
Ghielmini et al[56]	36	22%	0%

Rituximab in In Vivo Purging of Neoplastic Cells. The lack of benefit in terms of survival after autologous BMT and the low rate of patients achieving a molecular remission might be partially explained by the presence of neoplastic cell contamination of the harvested peripheral-blood stem cells.[7] Rituximab could be used as in vivo purging to overcome this contamination.[67] Rituximab alone induces a clearance of circulating lymphomatous cells;[56,64] within the SAKK 35/98 trial, 42% of the patients with initial circulating neoplastic cells, as evaluated with t(11;14) polymerase chain reaction (PCR) assay, achieved a conversion to a negative status, despite a lack of response on lymph node and bone marrow sites.[56] At the National Cancer Institute in Milan, 10 untreated MCL patients underwent sequential high-dose chemotherapy followed by autologous BMT.[31] In vivo purging with rituximab (2 doses after high-dose cyclophosphamide, 2 doses after high-dose cytarabine, and 2 doses after myeloablative mitoxantrone and melphalan) induced eradication of contaminating neoplastic cells in 7 of 7 patients in comparison to 2 of 3 patients who had ex vivo purging. Six of the 7 patients maintained a CR at a median follow-up of 14 months. Twenty-six of the 28 patients treated with the same schedule remained disease free after a median follow-up of 22 months; all the leukaphareses were PCR negative.[68] Another trial exploring the role of rituximab in the BMT setting has been recently published.[69] Twelve untreated MCL patients underwent debulking chemotherapy with CHOP, followed by myeloablative chemotherapy with cyclophosphamde/carmustine/etoposide, after stem cell mobilization with granulocyte colony-stimulating factor (G-CSF) plus rituximab. Eight of the 12 patients received 8 post-transplant ritixumab consolidative treatments, while 4 patients had only the first post-transplant rituximab. After a median post-transplant follow-up of approximately 8 months, all 12 patients were alive and in CR.

Ibritumomab Tiuxetan

Anti-CD20 antibodies have been conjugated to radionuclides in order to exploit the radiosensitivity of lymphoma cells.[29,70-72] In comparison with their cold counterparts, an advantage of radiolabeled monoclonal antibodies is their ability to kill lymphoma cells even devoid of the CD20 molecule, but within close proximity of those actually targeted. Ibritumomab (IDEC-Y2B8, Zevalin™; IDEC Pharmaceuticals, San Diego, CA) is a mouse monoclonal antibody that recognizes the same rituximab epitope and is linked through tiuxetan to yttrium 90, a pure β emitter. Given on an outpatient basis, it induced an OR of 67% in MCL and 80% in low-grade lymphomas, with half of cases already resistant to rituximab.[73-76] A randomized comparison of rituximab and ^{90}Y-ibritumomab in patients with follicular or transformed lymphomas revealed a response rate of 80% in the ibritumomab arm compared to 55% with rituximab (P = 0.002), with a CR/unconfirmed CR rate of 34% versus 20%, respectively.[77]

Tositumomab/^{131}I-Tositumomab

Tositumomab/iodine 131-tositumomab (Bexxar®; Coulter Pharmaceuticals, Inc, South San Francisco, CA) is an ^{131}I-radiolabeled anti-CD20 B1 antibody. Up to 34% and 79% of CRs following nonmyeloablative and myeloablative doses of tositu-

Table 5 Results Obtained with R-HCVAD Regimen in Previously Untreated Patients with Mantle Cell Lymphoma[66]

Regimen	No. of Patients	Complete Remission Rate	2-Year Overall Survival
Patients ≤ 65 Years of Age			
R-HCVAD	36	92%	87%*
HCVAD	26	100%	96%*
Patients > 65 Years of Age			
R-HCVAD	23	90%	96%*
HCVAD	22	70%	77%*

*$P > 0.05$

Abbreviations: HCVAD = hyper-cyclophosphamide, vincristine, doxorubicin, dexamethasone, high dose of cytarabine and methotrexate with leucovorin rescue therapy; R = rituximab

momab/^{131}I-tositumomab, respectively, have been reported in relapsed, refractory, or transformed low-grade lymphomas.[78-82] Sixteen MCL patients were treated in two sequential phase I/II trials with ^{131}I-tositumomab/etoposide/cyclophosphamide followed by BMT.[83,84] The estimated 3-year overall and progression-free survival rates were 93% and 61%, respectively, after a median follow-up of 19 months.

^{131}I-Labeled Rituximab

Seven patients, all previously relapsed after high-dose chemotherapy and BMT, underwent myeloablative treatment with ^{131}I-labeled rituximab.[85] Six patients obtained CR and 5 were in continuous CR after a median follow-up of 25 months.

Interferon-α

Interferon-α has small advantages as maintenance or consolidation therapy in patients with MCL responding to first-line therapy.[7,18,86] The European MCL Intergroup enrolled 180 patients in a randomized trial comparing BMT (DexaBEAM, total body irradiation and cyclophosphamide) versus interferon-α as consolidation treatment after CHOP.[87] An interim analysis of the first 76 patients showed relapses in 6 of 36 patients (17%) treated with BMT and in 21 of 40 patients (53%) treated with interferon-α, which correlates with a statistically significant reduction of relapses with the BMT arm ($P < 0.05$) but with no difference in terms of OS.

In vitro data and some early clinical trials suggest that cotreatment with cytokines, such as interferon-α, can increase the CD20 expression on neoplastic cells or the binding affinity of rituximab to the molecule.[88-91] The combination of rituximab and interferon-α has been reported in 2 studies of small lymphocytic and follicular lymphomas with promising results.[88,92]

Cyclin-Dependent Kinase Inhibitors

A number of new agents have been developed to target molecules involved in cell cycle regulation. Since deregulation of the cell cycle is relevant in MCL, such drugs might play a role in the treatment of this lymphoma subtype. Cyclin-dependent kinase inhibitors, such as flavopiridol and 7-hydroxy-staurosporine (UCN-01), are undergoing preclinical and clinical evaluation as single agents and in combination with chemotherapy.[93-96] Their mechanism of action might have a broad spectrum involving other cellular pathways besides cyclin-dependent kinases. The results of the first phase I/II studies are disappointing, particularly for flavopiridol in solid tumors.[97-99] However, it is still too early to draw any conclusion, as the scheduling has not yet been fully defined.

Proteasome Inhibitors

The proteasome pathway is crucial for intracellular protein degradation. The increased degradation of the P27 protein, an inhibitor of both cyclins D and E, in MCL,[100] might suggest a role for proteasome inhibitors in this lymphoma subtype. The proteasome inhibitor PS-341 gave promising results in a mouse model of MCL.[101] Clinical trials with the proteasome inhibitor PS-341 are underway,[19,96,102-104] but there are not yet any available data.

DNA Vaccines

Immunoglobulins are expressed on the cell surface of MCL cells and they do not undergo the process of intraclonal somatic mutations. They might be good targets for vaccines, with autologous tumor-derived immunoglobulin idiotypes[105] or with DNA vaccines encoding the tumor immunoglobulin idiotypes.[106-108] However, vaccines require a low burden of disease to be active, eradicating subclinical tumor cells and prolonging the disease-free status. Since the CR rate in MCL is very low with current available therapies, vaccination trials are combined with other experimental treatments, including consolidation after high-dose chemotherapy supported by BMT. A pilot study of 5 cycles of the EPOCH-R (doxorubicin/etoposide/cyclophosphamide/vincristine/prednisone/rituximab) regimen followed by 5 cycles of idiotype-KLH vaccine is presently ongoing at the Bethesda National Cancer Institute for untreated MCL patients; the CR rate was 93% after chemotherapy in the first 14 of 21 evaluable patients.[109]

Methylthioadenosine Phosphorylase

The housekeeping enzyme methylthioadenosine phosphorylase (MTAP) is important for the salvage of adenine nucleotides and methionine consumed in polyamine synthesis. The *MTAP* gene is located at 9p21, close to the p16^{c}/p14 locus, a region that is deleted in 15%-30% of MCL cases. Treatment approaches involving inhibition of adenine nucleotide synthesis with L-alanosine, followed by rescue with methylthioadenosine or depletion of plasma methionine by bacterial methiolase, with methylthioadenosine rescue of normal cells, could be feasible,[110] as shown in vitro on T-cell acute lymphoblastic leukemia cells.[111]

Conclusion

No standard treatment is available for patients with MCL, and, whenever feasible, patients should be treated within clinical trials. Up to now, monoclonal antibodies are the only widely used targeted treatments for MCL. Trials aimed at better

defining their role, both as single agents and in combination with conventional or myeloablative chemotherapy regimens, are ongoing. Other specific therapeutic tools are part of preclinical and clinical studies. Time will tell whether these novel therapeutic approaches can change the particularly poor outcome of this disease, and certainly, they deserve thorough evaluation.

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